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DIENST GENEESKUNDIGE VERZORGING
Comité voor de evalutie van de medische praktijk inzake geneesmiddelen

THE RATIONAL USE OF THE GLP-1 RECEPTOR AGONISTS IN TYPE 2 DIABETES

Systematic literature review: full report

Consensus conference
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Abbreviations

AACE/ACE: American Association of Clinical Endocrinologists
ACE: American College of Endocrinology
ACS: acute coronary syndrome
AD: antidiabetic drugs
ADA: American Diabetes Association
AE: adverse events
AHRQ: Agency for Healthcare Research and Quality
ALT: alanine aminotransferase
ANCOVA: analysis of covariance (a statistical model)
AP: alkaline phosphatase
ARR: absolute risk reduction
AST: aspartate aminotransferase
Bid: twice a day
BMI: body mass index
CDA: Canadian Diabetes Association
CDSR: Cochrane Database of Systematic Reviews
CI: confidence interval
CKD: chronic kidney disease
CO: crossover RCT
CV: cardiovascular
CVD: cardiovascular disease
DARE: Database of abstracts of reviews of effects
DB: double blind
DM2: diabetes mellitus type 2
DMII: diabetes mellitus type 2
DPP-4: Dipeptidyl peptidase-4
EASD: European Association for the Study of Diabetes
eGFR: estimated glomerular filtration rate
ERBP: European Renal Best Practice
ESC: European Society of Cardiology
FAS: functional analysis set
FPG: fasting plasma glucose
GGT: gamma glutamyl transpeptidase
GI: gastrointestinal
GLA: glucose lowering agents
GLP-1 Glucagon-like peptide-1
GLP-1 RA Glucagon-like peptide-1 receptor agonist
GOR: grade of recommendation
HbA1c : Hemoglobin A1c
HR: hazard ratio
IBD: inflammatory bowel disease

IGT: impaired glucose tolerance
ISR: injection site reactions
ITT: intention-to-treat analysis
IU: International units
LOCF: last observation carried forward
LOE: level of evidence
MA: meta-analysis
MET: metformin
MI :Myocardial infarction
MMRM: mixed model for repeated measures
n: number of patients
NA: not applicable
NICE: National institute for health and care excellence
NNH: number needed to harm
NNT: number needed to treat
NR: not reported
NS: not statistically significant
NT: no statistical test
OAD: oral antidiabetic drug
OHA: oral hypoglycemic agents
OL: open label
OR: Odds ratio
PG: parallel group RCT
Pla: placebo
PO: primary outcome
PP: per protocol
PPG: postprandial glucose
Py (person years)
Qd: once a day
Qw: once weekly
RCT: Randomized controlled trial
RR: Relative risk
RRR: relative risk reduction
SB: single blind
SGLT2: sodium/glucose cotransporter 2
SO: secondary outcome
SU: sulfonylurea
TNR: statistical test not reported
TSH: thyroid stimulating hormone
TZD: thiazolidinediones

1 Methodology

1.1 Introduction and scope

This systematic literature review was conducted in preparation of the consensus conference on 'The rational use of GLP-1 receptor agonists in type 2 diabetes' which will take place on the 17th of November 2016.

1.1.1 Questions to the jury

The questions to the jury, as they were phrased by the organising committee of the RIZIV/INAMI are

Incrétinomimétiques = analogues du GLP-1 = agonistes du récepteur du GLP-1
Incretinemimetica = GLP-1-analogen= GLP-1 receptoragonisten

***1.** Quels sont les objectifs généraux d'un traitement d'un patient adulte présentant un diabète de type 2 et quelles approches sont-elles à prendre en compte ?*
Wat zijn de algemene doelstellingen van een behandeling bij een volwassen patiënt met type 2-diabetes en hoe kunnen deze doelstellingen bereikt worden?

***2.** Les objectifs thérapeutiques métaboliques (HbA1c, poids, pression artérielle, profil lipidique) doivent-ils être modulés selon les caractéristiques du patient individuel, notamment en fonction de*
Moeten de metabole therapeutische doelen (HbA1c, gewicht, bloeddruk, lipidenprofiel) worden aangepast in functie van de individuele eigenschappen van de patiënt, meer bepaald
- *son âge et/ou sa fragilité*
  zijn leeftijd en/of frailty (kwetsbaarheid)
- *la durée de son diabète (fonction de la cellule ß)*
  hoe lang de diabetes al aanwezig is (β-celfunctie)
- *la présence de comorbidités (pathologie cardiovasculaire ou haut risque cardiovasculaire, …)*
  de aanwezigheid van comorbiditeiten (cardiovasculaire aandoening, verhoogd cardiovasculair risico,...)
- *l'altération de la fonction rénale*
  beperkte nierfunctie
- *la présence d'un surpoids ?*
  overgewicht?

Note
L'objectif précis selon le médicament sera précisé dans une autre question (plus précisément la question 3).
Nota
De precieze doelstellingen voor elk geneesmiddel afzonderlijk zullen in een andere vraag (meer bepaald vraag 3) worden gepreciseerd.

3. *Pour chacun des agonistes du récepteur du GLP-1suivants :*
Voor elk van de volgende GLP-1 receptoragonisten:

- *albiglutide* / albiglutide
- *dulaglutide* / dulaglutide
- *exénatide* / exenatide
- *exénatide à libération prolongée* / exenatide met verlengde afgifte
- *liraglutide* / liraglutide
- *lixisénatide* / lixisenatide

- quel est, versus autres traitements antidiabétiques (y compris les insulines)
wat is, in vergelijking met de andere antidiabetica (inclusief de insulines),

- *son efficacité sur le contrôle de la glycémie ?*
  zijn doeltreffendheid op het vlak van de controle van de glycemie?
- *son effet sur le poids corporel ?*
  zijn effect op het lichaamsgewicht?
- *son effet sur la pression artérielle ?*
  zijn effect op de bloeddruk?
- *son effet sur les évènements cliniques (cardiovasculaires, autres) ?*
  zijn effect op de klinische events (cardiovasculaire events en andere)?
- *sa sécurité (hypoglycémies, autres effets indésirables) ?*
  zijn veiligheidsprofiel (hypoglycemieën, andere ongewenste effecten)?

- quelles sont les associations rationnelles avec d'autres médicaments antidiabétiques ?
welke rationele combinaties zijn mogelijk met andere antidiabetica?

- quel est la population cible ?
voor welke doelpopulatie zijn ze bestemd?

- comment suivre l'efficacité thérapeutique de ces médicaments ?
hoe moet de therapeutische doeltreffendheid van deze geneesmiddelen opgevolgd worden?

4. *Quelle est la place des différents agonistes du récepteur du GLP-1 dans une stratégie rationnelle de prise en charge du diabète de type 2 ?*
Wat is de plaats van de verschillende GLP-1 receptoragonisten in een rationele strategie voor de aanpak van type 2-diabetes?

1.1.2 Research task of the literature group

The organising committee has specified the research task for the literature review as follows:

- To discuss selected guidelines regarding the following jury questions:
  - *2, 3, 4 (question 1 will be answered by an expert-speaker at the consensus conference)*

- To search for systematic reviews, meta-analyses, RCTs for the following populations, comparisons and endpoints:

1.1.2.1 *Populations*

The following population is to be evaluated:
Adults (≥ 18y) with type 2 diabetes.

Excluded from the literature search are:

- Children and adolescents
- Pregnant women

The following subgroups or patient characteristics will be of special interest:
- Age/frailty
- Duration of the diabetes (bèta cell function)
- Comorbidity (high cardiovascular risk or cardiovascular disease)
- Decreased kidney function (GFR <60ml/min and <30 ml/min)
- Obesity

1.1.2.2 *Interventions and comparisons*

This literature review is focused on GLP-1 receptor agonists. Only products that are currently (May 2nd) registered in Belgium will be considered (see table 1).

The GLP-1 receptor agonists will be compared to placebo or to other antidiabetic drug treatments that are currently available in Belgium (May 2nd 2016) (table 2).

GLP-1 receptor agonist
Albiglutide
Dulaglutide
Exenatide
Exenatide extended release
Lixisenatide
Liraglutide

Table 1. GLP-1 agonists to be included in this literature review

Comparators	
Placebo	
Other antidiabetic drugs	
• Metformin	
• Sulphonylurea	Glibenclamide Gliclazide Glimepiride Glipizide Gliquidon
• Thiazolidinediones	Pioglitazone
• DPP-4 inhibitors	Alogliptine

	Linagliptine Saxagliptine Sitagliptine Vildagliptine
• Other GLP-1 receptor agonists	(within-class comparisons)
• SGLT2 - inhibitors	Canagliflozine Empagliflozine
• Insulin	Basal insulin (insulin NPH, glargine, detemir) or Basal-bolus insulin or 2-3x/d (pre)mixed insulin

Table 2. Antidiabetic drugs to be included in this review

We will study these drugs in monotherapy or as add-on to an existing antidiabetic drug treatment in case of insufficient glycaemic control.

We will report comparisons with each GLP-1 receptor agonist individually whenever possible.

Information on all these drug comparisons will be obtained from RCTs.

1.1.2.3 *Endpoints*

In order to be selected for review, studies need to report at least one of the following outcomes as a primary endpoint:

Hard, clinical outcomes

- Total mortality
- Cardiovascular /cerebrovascular morbidity and mortality (macrovascular disease)
- Microvascular disease

Intermediate outcomes

- HbA1c
- Weight
- Blood pressure

Safety endpoints

- (Serious) hypoglycaemia[a]
- Congestive heart failure
- Pancreatitis
- Gastro-intestinal adverse events
- Other relevant safety outcomes will also be reported from the selected studies

[a] Since the definition of (serious) hypoglycaemia can differ considerably between studies, we will always include the study definition of the hypoglycaemic outcomes

- Rare adverse events will also be reported from large cohort studies (when no information from RCTs is available)

We will not study or report outcomes about patient quality of life or patient preferences, because a lot of the RCTs are unblinded, which can lead to considerable bias of the results.

1.1.2.4 *Study criteria*

To be included in our review, the selected studies need to meet certain criteria.

Meta-analyses and systematic reviews

- Research question matches research question for this literature review
- Systematic search in multiple databases
- Systematic reporting of results
- Inclusion of randomised controlled trials
- Reporting of clinically relevant outcomes (that match our selected outcomes)
- Only direct comparisons (no network meta-analyses)

RCT's

- Blinded studies are preferred, but we will not exclude unblinded trials
- Duration: minimum duration of 24 weeks is required
- Minimum number of participants: 40 per study-arm. For studies with multiple treatment arms, we will look at the number of participants in comparisons relevant to our search.
- Phase III trials (no phase II trials)
- Subgroup analyses will be reported if they were prespecified and if they are relevant to our research questions. We will not consider post hoc evaluations.
- RCTs in a 100% Asian population will not be included, because of low applicability of these results on our Belgian population. In most Asian studies, the dose of the GLP-1 receptor agonist liraglutide (max 0.9mg/d) is lower than standard European practice. Also, the monotherapy comparisons that are studied and the concomitant oral antidiabetic drugs that are used do not reflect the European standard clinical practice.

Observational studies (to evaluate rare safety outcomes)

- Large cohort studies (>1000 participants)

Other sources for safety and dosing

- Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI), Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG), European Medicines Agency (EMA), Meyler's Side Effects of Drugs (15th edition),-Folia Pharmacotherapeutica
- We decided to consult the SPC (Summary of Product Characteristics) for information, after we found that Meyler's had insufficient information on these relatively new drugs.

Some publications will be excluded for practical reasons:

- Publications unavailable in Belgian libraries
- Publications in languages other than Dutch, French, German and English
- Unpublished studies

1.1.2.5 *Guidelines*

Guidelines were selected and agreed upon through discussion with the organising committee, based on relevance for the Belgian situation and certain quality criteria:

- Publication date: only guidelines from 2011 onwards are to be selected.
- Quality assessment: Only guidelines that report levels of evidence/recommendation are to be selected.
- Systematic review: the guideline needs to be based on a good systematic search and review of the literature.

Note: some of the guidelines that were included in this review, do not fulfil all these selection criteria (either there was an incomplete search or no levels of evidence were reported). These guidelines are included because they are considered to be an important international reference (eg. EASD/ADA postion statement) or have a national relevance (eg. Domus Medica).

In order to make an assessment on the rigour of development of the guidelines, guidelines will be scored according to Agree II score, for the domain "Rigour of development". More information can be found on http://www.agreetrust.org/. [1]

Table 1 gives an overview of the items assessed in this domain according to the Agree II score.[1]

No.	**Description of the item**
7	Systematic methods were used to search for evidence
8	The criteria for selecting the evidence are clearly described
9	The strengths and limitations of the body of evidence are clearly described
10	The methods for formulating the recommendations are clearly described
11	Health benefits, side effects, and risks have been considered in formulating the recommendations.
12	There is an explicit link between the recommendations and the supporting evidence.
13	The guideline has been externally reviewed by experts prior to its publication
14	A procedure for updating the guideline is provided

Table 3. Items assessed by the domain "Rigour of development" in AgreeII score.

Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain. The domain score "Rigour of development" can be used to assess the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them, though be careful with the interpretation because this scoring is also subjective and the resulting scores can thus be disputable.

In the section about the guidelines, the Domain scores as assessed by the literature group, are given for each guideline.

The literature group will also report whether the guideline was developed together with other stakeholders (other healthcare professionals: pharmacists, nurses,… or patient representatives) and whether these guidelines are also targeting these groups.

Similarities and discrepancies between guidelines are to be reported.

1.2 Search strategy

1.2.1 Principles of systematic search

*Relevant RCTs, meta-analyses and systematic review*s were searched in a stepwise approach.

- As a start we have searched for large systematic reviews from reliable EBM-producers (NICE, AHRQ, the Cochrane library) that answer some or all of our research questions. One or more systematic reviews were selected as our basic source. From these sources, all references of relevant publications were screened manually.
- In a second step, we conducted a systematic search for randomised controlled trials (RCTs), meta-analyses and smaller systematic reviews that were published after the search date of our selected systematic reviews.

The following electronic databases have been searched

- Medline (PubMed)
- Cochrane Library (CDSR and DARE)

A number of other sources were consulted additionally: relevant publications, indices of magazines available in the library of vzw Farmaka asbl: mainly independent magazines that are a member of the International Society of Drug Bulletins (ISDB) such as Geneesmiddelenbulletin (The Netherlands), Folia Pharmacotherapeutica (Belgium), La Revue Prescrire (France), Drug & Therapeutics Bulletin (UK), Therapeutics Letter (Canada), Geneesmiddelenbrief (Belgium), Arzneimittelbrief (Germany),…

Guidelines were searched through the link “evidence-based guidelines” on the website of vzw Farmaka asbl (www.farmaka.be) and on the website of CEBAM (www.cebam.be). These contain links to the national and most frequently consulted international guidelines, as well as links to ‘guideline search engines’, like National Guideline Clearinghouse and G-I-N.

1.2.2 Search strategy details

As a source document and starting point to find relevant publications, the following systematic review was selected:

Shyangdan DS, Royle P, Clar C, et al. Glucagon-like peptide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev 2011:Cd006423. DOI: 10.1002/14651858.CD006423.pub2.

A search strategy was then developed in Pubmed to find relevant RCTs that appeared after the search date of the above publication (http://www.ncbi.nlm.nih.gov/pubmed/).

An additional source document was selected to find relevant cohort studies :

Bolen S, Tseng E, Hutfless S, et al. AHRQ Comparative Effectiveness Reviews. Diabetes Medications for Adults With Type 2 Diabetes: An Update 2016

Here also we developed a search strategy in Pubmed to find relevant cohort studies that appeared after the search date of the above publication.

The details of the search strategy can be found in appendix I.

1.3 Selection procedure

Selection of relevant references was conducted by two researchers independently. Differences of opinion were resolved through discussion. A first selection of references was done based on title and abstract. When title and abstract were insufficient to reach a decision, the full article was read to decide on inclusion or exclusion.

In– and exclusion criteria of the different types of studies are found in chapter 1.1.2 with relevant populations, interventions, endpoints and study criteria.

1.4 Assessing the quality of available evidence

To evaluate the quality of the available evidence, the GRADE system was used. In other systems that use 'levels of evidence', a meta-analysis is often regarded as the highest level of evidence. In the GRADE system, however, only the quality of the original studies is assessed. Whether the results of original studies were pooled in a meta-analysis is of no influence to the quality of the evidence.
The GRADE-system is outcome-centric. This means that quality of evidence is assessed for each endpoint, across studies.

The GRADE system assesses the following items:

Study design		+ 4	RCT
		+ 2	Observational
		+ 1	Expert opinion
Study quality		- 1	Serious limitation to study quality
		- 2	Very serious limitation to study quality
Consistency		- 1	Important inconsistency
Directness		- 1	Some uncertainty about directness
		- 2	Major uncertainty about directness
Imprecision		- 1	Imprecise or sparse data
Publication bias		- 1	High probability of publication bias
For observational studies	Evidence of association	+ 1	Strong evidence of association (RR of >2 or <0.5)
		+ 2	Very strong evidence of association (RR of >5 or <0.2)
	Dose response gradient	+ 1	Evidence of a dose response gradient (+1)
	Confounders	+ 1	All plausible confounders would have reduced the effect
SUM		4	HIGH quality of evidence
		3	MODERATE quality of evidence
		2	LOW quality of evidence
		1	VERY LOW quality of evidence

Table 4. Items assessed by the GRADE system

In this literature review the criteria 'publication bias' has not been assessed.

In assessing the different criteria, we have applied the following rules:

Study design

In this literature review RCT's and observational studies are included. RCTs start out as high quality of evidence (4 points), observational studies start out as low quality of evidence (2 points). Points can be deducted for items that are assessed as having a high risk of bias.

Study quality

To assess the methodological quality of RCT's, we considered the following criteria:

- **Randomization**: If the method of generating the randomization sequence was described, was it adequate (table of random numbers, computer-generated, coin tossing, etc.) or inadequate (alternating, date of birth, hospital number, etc.)?
- **Allocation concealment:** If the method of allocation was described, was it adequately concealed (central allocation, …) or inadequate (open schedule, unsealed envelopes, etc.)?
- **Blinding**: Who was blinded? Participants/personnel/assessors. If the method of blinding was described, was it adequate (identical placebo, active placebo, etc.) or inadequate (comparison of tablet vs injection with no double dummy)?
- **Missing outcome data:** Follow-up, description of exclusions and drop-outs, ITT
- **Selective outcome reporting**

If a meta-analysis or a systematic review is used, quality of included studies was assessed. It is not the quality of the meta-analysis or systematic review that is considered in GRADE assessment, but only the quality of RCTs that were included in the meta-analysis/systematic review.

Application in GRADE:

Points were deducted if one of the above criteria was considered to generate a high risk of bias for a specific endpoint.

For example:

- Not blinding participants will not decrease validity of the results when considering the endpoint 'mortality', but will decrease validity when considering a subjective endpoint such as pain, so for the endpoint pain, one point will be deducted.
- A low follow-up when no ITT analysis is done, will increase risk of bias, so one point will be deducted in this case.

Consistency

Good "consistency" means that several studies have a comparable or consistent result. If only one study is available, consistency cannot be judged. This will be mentioned in the synthesis report as "NA" (not applicable).

Consistency is judged by the literature group and the reading committee based on the total of available studies, whilst taking into account

- Statistical significance
- Direction of the effect if no statistical significance is reached. E.g. if a statistically significant effect was reached in 3 studies and not reached in 2 others, but with a non-significant result in the same direction as the other studies, these results are considered consistent.
- Clinical relevance: if 3 studies find a non-significant result, whilst a 4th study does find a statistically significant result, that has no clinical relevance, these results are considered consistent.
- For meta-analyses: Statistical heterogeneity.

Directness

Directness addresses the extent in which we can generalise the data from a study to the real population (external validity). If the study population, the studied intervention and the control group or studied endpoint are not relevant, points can be deducted here. When indirect comparisons are made, a point is also deducted.

Imprecision

A point can be deducted for imprecision if the 95%-confidence interval crosses both the point of appreciable harm AND the point of appreciable benefit (e.g. RR 95%CI ≤0.5 to ≥1.5).

Additional considerations for observational studies

For observational studies, when no points are deducted for risk of bias in one of the above categories, a point can be added if there is a large magnitude of effect (high odds ratio), if there is evidence of a dose-response gradient or (very rarely) when all plausible confounders or other biases increase our confidence in the estimated effect.

Application of GRADE when there are many studies for 1 endpoint:

Points are only deducted if the methodological problems have an important impact on the result. If 1 smaller study of poor quality confirms the results of 2 large good quality studies, no points are deducted.

More information on the GRADE Working Group website: http://www.gradeworkinggroup.org

1.5 Synopsis of study results

The complete report contains per research question

- (Comprehensive) summary of selected guidelines
- Evidence tables (English) of systematic reviews or RCTs on which the answers to the study questions are based
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system (English)

The synopsis report contains per research question

- (Brief) summary of selected guidelines
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system.

The conclusions have been discussed and adjusted through discussions between the authors of the literature search and the reading committee of the literature group.

References

1. Clinical Evidence. A compendium of the best available evidence for effective health care. Website: http://clinicalevidence.bmj.com
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3. GRADE working group. http://www.gradeworkinggroup.org
4. GRADE working group. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
5. Guyatt G, Oxman A, Kunz R et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6

2 Critical reflections of the reading committee and the literature group

2.1 Guidelines

Not all of the selected guidelines were based on a formal systematic review of the literature. They were included in our report because of their international importance. The Agree scores of the guidelines will provide an estimate of the rigour of development of each guideline.
Because GLP-1 receptor agonists are relatively new drugs, information about their efficacy, safety and use is not always up to date in the selected guidelines. New information will emerge after the search date and publication date of the guideline. This is important to keep in mind.

For jury question 2 about therapeutic targets, we only searched for answers in the selected guidelines. No further literature search was done, to limit the workload and to be able to focus more fully on the GLP-1 receptor agonists.
It is perhaps unfortunate that guidelines about potentially 'inflammatory' topics (like statin use) are not accompanied by a critical review of the literature. However, previous Consensus Conferences have addressed some of the questions regarding targets. We therefor recommend to consult the following jury reports :

- The rational use of drugs in hypertension (nov 5th 2015)
- The rational use of lipid-lowering drugs (may 22nd 2014)
- The efficient drug management of type 2 diabetes in primary care (nov 29th 2012)

All these can be found at http://www.inami.fgov.be/nl/publicaties/Paginas/consensusvergaderingen-juryrapport.aspx#.V9bS1Xp8vFC
If some recommendations in the current selected guidelines differ from the recommendations in the previous jury reports, the expert speakers will be able to comment whether the statements in the current guidelines are based on new evidence, or whether they reflect a different opinion based on the same evidence.

2.2 Populations

The trials about GLP-1 receptor agonists often excluded patients with comorbidities and high risk of complications, such as renal disease, liver disease and cardiovascular disease. This limits the applicability of the study results to the total population with type 2 diabetes. This is also one of the main reasons why we have almost no information on the subgroups that were of specific interest.

2.2.1 Subgroup - age

Although the inclusion age in most trials was usually up to 75 or 80 years, included patients were often middle-aged: mean age 50-60y. Diabetes is a chronic condition and the prevalence increases with age. There is insufficient information on antidiabetic drugs in the eldery (> 75 years). There is no information in frail eldery.

2.2.2 Subgroup – weight

The mean BMI in the trials was always > 30 kg/m^2. Usually, no stratification was done according to BMI category, and few subgroup analysis for patients with a certain BMI exist. In some trials (mostly with exenatide and liraglutide) a BMI > 25kg/m^2 was a criterion for inclusion. In most trials, a BMI > 45kg/m^2 was a criterion for exclusion.
We can conclude that GLP-1 receptor agonists were studied mainly in an overweight and obese population, but cannot make any other definite statement.

2.2.3 Subgroup – high cardiovascular risk

Most trials that evaluated HbA1c excluded patients with a 'clinically relevant' cardiac disease or with a recent cardiac event. When included, the number of patients with a previous cardiac event was not always reported. When reported, the number of patients with a previous cardiovascular disease in the trials was low.
Only LEADER and ELIXA specifically included patients with cardiovascular morbidity or high cardiovascular risk.

2.2.4 Subgroup – renal impairment

In some trials, mild or even moderate renal impairment was allowed, but no information was provided as to how many patients in the trial actually had renal impairment. We have little information on the use of GLP-1 receptor agonists in patients with renal impairment.

2.2.5 Subgroup – duration of diabetes

The mean duration of diabetes is described in every trial. (prespecified) subgroup analyses are rare.

2.3 Trial duration

Trial duration is often relatively short (6 months). Type 2 diabetes is a chronic condition usually resulting in the lifelong use of antidiabetic (and other) drugs.
When a GLP-1 receptor agonist is found to be non-inferior or superior to another antidiabetic agent at 6 months, we often have no information about how they compare after a longer period of time. It is therefore difficult to make any strong statements about comparative efficacy, even more so if you also consider other risk of bias in the available trials.

Some adverse events may take years to develop. Information on hard endpoints or long-term safety can only be established through longer follow-up (see also: Outcomes – rare safety).

2.4 Outcomes

2.4.1 Efficacy

The vast majority of studies was designed to detect differences in glycaemic control. Most often HbA1c changes were the primary outcome.
The studies also report other glycemic endpoints, weight change, blood pressure… These surrogate endpoints do not necessarily reflect a change in clinically meaningful, hard outcome measures.

Information on hard endpoints (e.g. mortality, cardiovascular disease) is very rare: only 2 of all included trials report hard endpoints as primary outcome (i.e. a composite of cardiovascular mortality and certain cardiovascular diseases) . These trials (ELIXA for lixisenatide and LEADER for liraglutide) were specifically designed (due to FDA requirements) to establish that these GLP-1 RA do not increase cardiovascular risk. Their findings and possible pitfalls are extensively discussed in the conclusions section.

2.4.2 Safety

Safety endpoints were often reported as adverse events without statistical analysis, limiting somewhat the information obtained for safety.

2.4.3 Rare safety endpoints

There are serious limitations for assessing rare adverse events and long-term safety. GLP-1 receptor agonists are relatively new drugs. This means that the follow-up time to confidently assess long-term safety is as yet too short. Most RCTs are too small and too short-term to assess rare and long-term safety. Observational studies are starting to emerge, but here also, follow-up time is limited to a couple of years and the number of patients in these studies is relatively low.

2.5 Methodological problems – Trial quality

- Practically all studies were industry sponsored.
- Studies that compared GPL-1 receptor agonists to insulin were open label. This is understandable due to the nature of the interventions but decreases the methodological quality of the studies (high risk of bias).
- All the trials use a run-in period (placebo or titration/stabilisation of active drug). This avoids enrolling patients with poor adherence and/or tries to makes sure that patients in a trial have a comparable baseline antidiabetic treatment. A run-in period may decrease the applicability of the results to a real-life population.
- A lot of the RCTs use a non-inferiority design (see under – Some methodological issues explained) but often the analyses are incompletely reported (for example they only report an analysis of the ITT population, or the authors planned a sensitivity analysis but did not report the results).
- For some GLP-1 receptor agonists, an inappropriate method of dealing with missing values was used (see under- Some methodological issues explained).

2.6 GRADE

GRADE is a method that is usually applied to the result of a meta-analysis, or to a 'body of evidence', consisting of multiple studies for a certain comparison. Our review focusses on each GLP-1 receptor agonist separately, in comparison to other drugs. Because of this, we usually have only 1 study for each comparison. It is more difficult to make firm conclusions about the benefit or harm of a drug (in a certain combination) based on 1 study.

The GRADE process requires not only an evaluation of the methodological problems in a study, but also an estimate on whether a specific methodological problem in a study is likely to create a relevant bias. Only when there is high risk of bias, the GRADE score is lowered.

2.7 Statistically significant versus clinically relevant

A study may show non-inferiority of a certain drug, or superiority, when compared to another treatment. A point estimate and a confidence interval around this estimate are usually provided. The confidence interval gives us an idea of the (im)precision of our estimate and of the range in which the true effect plausibly lies (1). It is important to realize that the true effect can be anywhere whitin this confidence interval.
The GRADE score reflects how certain we are that this estimate is close to the true effect.
This is how the results in this document are reported.
Whether a difference found in a study is also clinically relevant (i.e. will make a noticeable difference to the patient), is another matter. Some authors have tried to propose thresholds for clinical relevance. The point estimate, as well as the upper and lower boundary of the confidence interval are then examined in relation to this threshold.
- for hard endpoints, usually a relative risk reduction of 25% is proposed.
- for intermediate endpoints such as HbA1c or weight, this is more difficult. The AHRQ report proposes a HbA1c difference of 0.3% as a 'minimally important clinical difference'. For weight, they propose 1 kg. These differences were suggested by clinical experts and are, according to AHRQ, partly supported in the literature.

It will be up to the jury to consider the results of the trials in this report in the light of clinical relevance.
So the jury will need to decide, based on the results presented in this document, and based on the comments of the experts in the field, whether the body of evidence is sufficient, whether a difference between two treatments is large enough and whether our confidence in the results is large enough, to make a recommendation for or against a certain treatment. All this, while considering patient-related factors, our local healthcare situation and off course the cost to the patient and to society.

2.8 Some methodological issues explained

2.8.1 Primary endpoint – secondary endpoint

Studies are designed around a primary endpoint. Secondary endpoint can be considered as supportive evidence of the primary outcome, if the result of the primary outcome is statistically significant. When there is a large number of secondary outcomes, there is a higher risk that some secondary outcomes become false positive, due to chance. In a trial design, adjustments should be made for dealing with multiple comparisons. This was not the case for LEADER and ELIXA.

2.8.2 Number needed to treat

A number needed to treat is always specific to a study. The number is affected by the initial risk of the study population and by the study duration. As a general rule, NNTs from different studies should not be compared. A correct presentation of the NNT should also include the confidence interval for this NNT.

2.8.3 Non-inferiority trials

Non-inferiority trials are constructed to test whether the newer drug is 'not inferior' (i.e. not unacceptably worse) than an active 'conventional' treatment. To test this, a margin of non-inferiority is chosen: a threshold below which it can be established that the new drug is not (markedly) worse than its comparator.

Conducting and reporting of non-inferiority trials should be according to certain standards (2, 3).

- The **comparator** treatment should have a proven efficacy in the population that is studied. In the non-inferiority trial, this comparator should be used in the same fashion as in the historical trials in which its efficacy versus placebo was established.
- The choice of the non-inferiority **margin** is important: a very wide margin will prove statistical non-inferiority more easily but casts doubt on the actual efficacy and clinical benefit. A valid choice of margin should be based on previous placebo-controlled trials of the comparator.

The margins for the treatment difference for HbA1c that are chosen in the included trials are usually 0.3% or 0.4%. (i.e we accept that the new drug causes a 0.3% or 0.4% less HbA1c decrease than the control drug).

-The **statistical analysis** is also a matter of consideration and subject to debate. It is often advised to perform a per-protocol analysis as well as an intent-to treat (ITT) analysis. This is because it is assumed that non-inferiority is more easily proven in an ITT analysis because of the dilution of the treatment effect due to non-compliance, treatment cross-over, drop out etc. (see also below: 2.8.4 Missing values in non-inferiority trials)

In a lot of the non-inferiority trials in this review, one or more of these standards have been violated (e.g. dose of the comparator, follow-up of the comparator treatment, failing to do an appropriate statistical analysis….). This is unfortunate, because '*The less rigorously conducted the trial, the easier it can be to show non-inferiority*' (3).

2.8.4 Missing values in non-inferiority trials

A related problem are the missing values in a (non-inferiority) trial. The way these values are treated, may influence the results and can possibly bias towards a decision of non-inferiority(4-6). Two main approaches for dealing with missing values can be found in the trials that were included in this report: last observation carried forward (LOCF) and MMRM (mixed model for repeated measures).

The LOCF method is considered to have a higher risk of bias because it treats an earlier measurement as the final one. Often, this method will underestimate the treatment effects, but, depending on the treatment effect over time and the pattern of drop-out, bias could go either way. Secondly, when LOCF is used, confidence intervals tend to be smaller and type I error (false positive results) can increase (4-6).

The MMRM method is a complex statistical model that does not use a simple imputation, but uses all available data to arrive at an estimate of the mean treatment effect. It is claimed that this analysis is

less likely to cause biased estimates than the LOCF method, without inflating type 1 error too much(4-6).

Dealing with missing values (in non-inferiority trials as well as in superiority trials) is a complex business, still subject to much debate. No single statistical method is able to deal with bias arising from all the different types/reasons of missing values. It is therefore important that sensitivity analysis are planned and reported, to check the robustness of the results.

3 Guidelines

3.1 General information on selected guidelines

3.1.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in the table below.

Abbreviation	Guideline
AACE/ACE 2015(7)	Handelsman et al.: American association of clinical endocrinologists and American college of endocrinology – Clinical Practice Guidelines for developing a diabetes mellitus comprehensive care plan. 2015.
ADA 2016(8)	American Diabetes Association. Standards of medical care in diabetes - 2016
CDA 2013(9)	Canadian Diabetes Association clinical practice guidelines for the prevention and management of diabetes in Canada - 2013
Domus Medica 2015(10)	Domus Medica -Diabetes mellitus type 2. Richtlijn voor goede medische praktijkvoering. 2015.
EASD/ADA 2015(11)	Inzucchi et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes.2015.
ESC/EASD 2013(12)	The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. 2013.
NICE 2015(13)	Type 2 diabetes in adults: management. Clinical guideline update (NG28). 2015.
ERBP 2015(14)*	European Renal Best Practice: Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). 2015.

Table 5: Selected guidelines and their abbreviations as used in this report.

*As the ERBP 2015 guideline makes recommendations specifically for the diabetic population with CKD stage 3b or higher, and is not applicable to all type 2 diabetics, the recommendations of this guideline will be summarized separately.

3.1.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in the tables below.

AACE/ACE 2015		
Grades of recommendation	A	Strong
	B	Intermediate
	C	Weak
	D	Not evidence based
Levels of evidence	EL 1	Strong
	EL 2	Intermediate
	EL 3	Weak
	EL 4	None

Table 6: Levels of evidence of the AACE/ACE 2015 guideline

ADA 2016		
Levels of evidence	A	• Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered; • Or compelling nonexperimental evidence, i.e., "all or none" rule developed by the Centre for Evidence-Based Medicine at the University of Oxford; • Or supportive evidence from well-conducted randomized controlled trials that are adequately powered
	B	Supportive evidence from well-conducted cohort studies or from a well-conducted case-control study.
	C	• Supportive evidence from poorly controlled or uncontrolled studies; • Or conflicting evidence with the weight of evidence supporting the recommendation.
	E	Expert consensus or clinical experience.

Table 7: Levels of evidence of the ADA 2016 guideline

CDA 2013		
Grades of recommendation	A	The best evidence was at Level 1
	B	The best evidence was at Level 2
	C	The best evidence was at Level 3
	D	The best evidence was at Level 4 or consensus
Levels of evidence	1A	Systematic overview or meta- analysis of high quality RCTs OR Appropriately designed RCT with adequate power to answer the question posed by the investigators
	1B	Nonrandomized clinical trial or cohort study with indisputable results
	2	RCT or systematic overview that does not meet Level 1 criteria
	3	Nonrandomized clinical trial or cohort study; systematic overview or meta-analysis of level 3 studies
	4	Other

Table 8: Grades of recommendation and Levels of evidence of the CDA 2013 guideline for studies of treatment and prevention

Domus Medica 2015		
Grades of recommendation	1	Strong recommendation
	2	Weak recommendation
Levels of evidence	A	High level of evidence
	B	Moderate level of evidence
	C	Low level of evidence
	GPP	Good Practice Point/ Recommendation based on consensus

Table 9: Grades of recommendation and Levels of evidence of the Domus Medica 2015 guideline.

EASD/ADA 2015
The EASD/ADE 2015 guideline did not attribute levels of evidence or grades of recommendation to its recommendations, nor to the underlying evidence.

Table 10: Levels of evidence of the EASD/ADA 2015 guideline

ESC/EASD 2013		
Grades of recommendation	I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective
	II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure
	IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
	IIb	Usefulness/efficacy is less well established by evidence/opinion.
	III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.
Levels of evidence	A	Data derived from multiple randomized clinical trials or meta-analyses.
	B	Data derived from a single randomized clinical trial or large non-randomized studies.
	C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Table 11: Levels of evidence of the ESC/EASD 2013 guideline

NICE 2015		
The quality of evidence is assessed by using the GRADE approach, but where GRADE allocates labels or symbols to represent the strength of a recommendation, NICE does not do this. Instead, the concept of strength is reflected in the wording of the recommendation (see section 9.3.3 in the NICE guidelines manual 2012).		
Recommendations that must be used	There is a legal duty to apply the recommendation / intervention	Use “must” or “must not” Use the passive voice: “intervention x must be used”

Recommendations that should be used	The intervention will do more good than harm and will be cost-effective	Use direct instructions Prefer " (do not) offer, refer, advise, discuss" to "should"
Recommendations that could be used	The intervention will do more good than harm for most patients and will be cost-effective Other options may be similarly cost-effective Some patients may opt for a less effective but cheaper intervention Results of the intervention are more likely to vary	Use direct instructions Prefer "(do not) consider" to "could" Other options depending on phrasing: "think about, assess".

Table 12: Grades of recommendation and Levels of evidence of the NICE 2015 guideline.

ERBP 2015		
Grades of recommendation	1	Strong
	2	Weak
Levels of evidence	A	High
	B	Moderate
	C	Low
	D	Very Low

Table 13: Levels of evidence of the ERBP 2015 guideline

3.1.3 Agree II score

Information about the Agree II score can be found in the section "Methodology".

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in the table below. The total domain score is also reported in this table.

Rigour of development item	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Total**	**Domain score**
CDA 2013	5	3	5	4	6	7	6	7	**43**	**77%**
NICE 2015	7	7	7	4	6	7	5	5	**48**	**86%**
Domus Medica 2015	4	4	5	5	7	7	6	7	**45**	**80%**
ADA 2016	4	4	5	3	7	7	5	6	**41**	**73%**
EASD/ADA 2015	1	1	1	1	7	4	2	3	**20**	**36%**
ERBP 2015	7	7	7	6	7	7	5	7	**53**	**95%**
AACE/ACE 2015	1	1	6	1	7	7	4	5	**32**	**57%**
ESC/EASD 2013	3	3	6	3	7	7	4	5	**38**	**68%**

Table 14: AGREE score of selected guidelines on item "Rigour of development"

3.1.4 Included populations – interventions – main outcomes

In the tables below, the populations, interventions and main outcomes considered in the selected guidelines are represented.

AACE/ACE 2015	
Population	Diabetes mellitus patients (type I and II)
Interventions	Screening, diagnosis, treatment goals, management, management of complications, hospital care, glucose monitoring, insulin pump therapy, vaccinations, pregnancy, children
Outcomes	Not specified.

Table 15: Included population, intervention and main outcomes of the AACE/ACE 2015 guideline.

ADA 2016	
Population	All diabetic patients
Interventions	Screening, diagnostic and therapeutic actions
Outcomes	Not specified.

Table 16: Included population, intervention and main outcomes of the ADA 2016 guideline.

CDA 2013	
Population	The full guideline makes recommendations for type 1 and type 2 diabetes. Specific populations are defined at the beginning of each chapter (e.g.: type 2 diabetes in the elderly). Two chapters outline specific aspects of care for a pediatric population.
Interventions	Detection, prognosis, prevention or management of diabetes and its sequelae
Outcomes	Health benefits, risks and side effects of interventions

Table 17: Included population, intervention and main outcomes of the CDA 2013 guideline.

Domus Medica 2015	
Population	All patients with type 2 diabetes
Interventions	Screening, diagnosis, non-pharmacological treatment, self-care, psychosocial interventions, management of cardiovascular risk, glycemic control, pharmacological treatment, bariatric surgery, diagnosing and treating diabetic complications
Outcomes	Not specified

Table 18: Included population, intervention and main outcomes of the Domus Medica 2015 guideline.

EASD/ADA 2015	
Population	Patients with type 2 diabetes
Interventions	Therapeutic options for glycemic control
Outcomes	Not specified

Table 19: Included population, intervention and main outcomes of the EASD/ADA 2015 guideline.

ESC/EASD 2013	
Population	Patients with diabetes or pre-diabetes; with or without cardiovascular disease
Interventions	Prevention of cardiovascular disease, management of coronary artery disease, revascularization, management of heart failure and diabetes, management of arrhythmias and diabetes, management of peripheral and cerebrovascular disease, management of microvascular disease.
Outcomes	Not specified

Table 20: Included population, intervention and main outcomes of the ESC/EASD 2013 guideline.

NICE 2015	
Population	Adults with type 2 diabetes. Specific subgroups: adults aged 65 years and older, people with renal impairment, people in specific ethnic groups, people in specific cardiovascular groups.
Interventions	Patient education, lifestyle and non-pharmacological management, blood pressure therapy, antiplatelet therapy for primary prevention of CVD, blood glucose management, management of complications
Outcomes	Those that reflect treatment objectives in the management of type 2 diabetes: change in blood glucose levels, cardiovascular risk, diabetes-related complications, adverse events (e.g. hypoglycaemia, change in body weight)

Table 21: Included population, intervention and main outcomes of the NICE 2015 guideline.

ERBP 2015	
Population	Adult individuals with diabetes mellitus and CKD stage 3b or higher (eGFR <45 mL/min) in primary, secondary and tertiary healthcare settings
Interventions	(i) selection of renal replacement modality; (ii) management of glycaemic control; (iii) management and prevention of cardiovascular comorbidity
Outcomes	Critically important outcomes • Survival/mortality • Progression to end-stage kidney disease/Deterioration of residual renal • function • Hospital admissions: Highly important • Qol/patient satisfaction • Major morbid events: • Myocardial infarction • Stroke • Amputation • Loss of vision Highly important outcomes • Hypoglycaemia • Delayed wound healing • Infection • Visual disturbances • Pain • Functional status Moderately important outcomes (surrogate outcomes) • Hyperglycaemia • Glycaemic control • Glycated haemoglobin • Point of care (measure)

Table 22: Included population, intervention and main outcomes of the ERBP 2015 guideline.

3.1.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in the tables below.

AACE/ACE 2015

Development group	AACE members who are credentialed experts in the field of DM care
Target audience	Clinical endocrinologists and other clinicians who care for patients with DM

Table 23: Members of the development group and target audience of the AACE/ACE 2015 guideline.

ADA 2016	
Development group	Multidisciplinary expert committee comprised of physicians, diabetes educators, registered dietitians, and others who have expertise in a range of areas, including adult and pediatric endocrinology, epidemiology, public health, lipid research, hypertension, preconception planning, and pregnancy care.
Target audience	Intended for clinicians, patients, researchers, payers, and other interested individuals.

Table 24: Members of the development group and target audience of the ADA 2016 guideline.

CDA 2013	
Development group	Health professionals from family medicine, endocrinology, internal medicine, infectious disease, neurology, nephrology, cardiology, urology, psychology, obstetrics, ophthalmology, pediatrics, nursing, dietetics, pharmacy, exercise physiology and others, as well as people with diabetes, participated in the guideline development process. Each recommendation was reviewed by a panel of 6 methodologists.
Target audience	Primary care physicians and other healthcare professionals who care for people with diabetes or those at risk of diabetes

Table 25: Members of the development group and target audience of the CDA 2013 guideline.

Domus Medica 2015	
Development group	General practitioners and endocrinologists
Target audience	General practitioners

Table 26: Members of the development group and target audience of the Domus Medica 2015 guideline.

EASD/ADA 2015	
Development group	Endocrinologists, diabetologists.
Target audience	Not specified.

Table 27: Members of the development group and target audience of the EASD/ADA 2015 guideline.

ESC/EASD 2013	
Development group	Cardiologists, diabetologists, interventional cardiologists, nurse, pharmacologist, epidemiologist
Target audience	Clinicians and other healthcare workers

Table 28: Members of the development group and target audience of the ESC/EASD 2013 guideline.

NICE 2015	
Development group	Psychiatrists, diabetologists, pharmacists, cardiologists, expert in behavioural medicine, general practitioners, diabetes nurses, nephrologists, patients and carers
Target audience	Primary and secondary care

Table 29: Members of the development group and target audience of the NICE 2015 guideline.

ERBP 2015	
Development group	Nephrologists, endocrinologists, cardiologists, experts in epidemiology and systematic review methodology
Target audience	Any health care professional caring for patients with diabetes and CKD stage 3b or higher (general practitioners, internists, surgeons, and other physicians, in both an out-patient and in-hospital setting).

Table 30: Members of the development group and target audience of the ERBP 2015 guideline.

3.1.6 Conflicts of interest

3.1.6.1 *AACE/ACE 2015*

Cochairpersons

- Dr. Yehuda Handelsman reports that he has received consultant/speaker fees and research grant support from Boehringer Ingelheim GmbH, GlaxoSmithKline plc, and Novo Nordisk A/S; consultant fees and research grant support from Amgen Inc, Gilead, Merck & Co, Inc, and sanofi-aventis U.S. LLC; research grant support from Intarcia Therapeutics, Inc, Lexicon Pharmaceuticals, Inc, and Takeda Pharmaceutical Company Limited; consultant fees from Halozyme, Inc; and consultant/speaker fees from Amarin Corporation, Amylin Pharmaceuticals, LLC, Janssen Pharmaceuticals, Inc, and Vivus, Inc.
- Dr. Zachary Bloomgarden reports that he has received speaker honoraria from Merck & Co, Inc and Santarus, Inc; consultant honoraria from Bristol-Myers Squibb Company/AstraZeneca and Boehringer Ingelheim GmbH; speaker/consultant honoraria from Johnson & Johnson Services, Inc and Novo Nordisk A/S; stockholder earnings from Abbott Laboratories, Covidien, F. Hoffman-La Roche Ltd, Hospira Inc, Pfizer Inc, St. Jude Medical, Inc, and Zoetis; and stockholder earnings and consultant honoraria from Novartis AG.
- Dr. George Grunberger reports that he has received speaker honoraria and research support for his role as investigator from Bristol-Myers Squibb Company, Eli Lilly and Company, and Novo Nordisk A/S; speaker honoraria from Amarin Corporation, Janssen Pharmaceuticals, Inc, Merck & Co, Inc, sanofi-aventis U.S. LLC, Santarus, Inc, Takeda Pharmaceutical Company Limited, and Valeritas, Inc.
- Dr. Guillermo Umpierrez reports that he has received consultant honoraria and research grant support from Boehringer Ingelheim GmbH, Merck & Co, Inc, Novo Nordisk A/S, sanofi-aventis U.S. LLC, and Regeneron.
- Dr. Robert S. Zimmerman reports that he has received speaker honoraria from Janssen Pharmaceuticals, Inc, Johnson & Johnson Services, Inc, Merck & Co, Inc, and Santarus, Inc; and research grant support from Novo Nordisk A/S.

Authors and/or Task Force Members

- Dr. Timothy Bailey reports that he has received speaker/consultant honoraria and research support from Novo Nordisk A/S; consultant honoraria and research support from Bayer AG, BD, Medtronic, Inc, and sanofi-aventis U.S. LLC; and research support from Abbott Laboratories, ACON Laboratories, Inc, Alere, Animas Corporation, Cebix Incorporated, Bristol-Myers Squibb Company, Dexcom, Inc, Eli Lilly and Company, GlaxoSmithKline plc, Halozyme, Inc, Insulet Corporation, LifeScan, Inc, MannKind Corporation, Merck & Co, Inc, Orexigen Therapeutics, Inc, and Tandem Diabetes Care.
- Dr. Lawrence Blonde reports that he has received speaker/consultant honoraria and research grant support to Ochsner Medical Center for his role as investigator from Novo Nordisk A/S and sanofi-aventis U.S. LLC; research grant support to Ochsner Medical Center for his role as investigator from Eli Lilly and Company; speaker honoraria from Amylin Pharmaceuticals, LLC; speaker/ consultant honoraria from AstraZeneca, Bristol-Myers Squibb Company, Janssen Pharmaceuticals, Inc, and Merck & Co, Inc; and consultant honoraria from Eisai Inc, GlaxoSmithKline plc, and Quest Diagnostics Incorporated.
- Dr. George Bray reports that he has received speaker honoraria from Herbalife International of America, Inc and advisor honoraria from Medifast, Inc.
- Dr. Alan J. Cohen reports that he has received speaker honoraria from AstraZeneca, sanofi-aventis U.S. LLC, and Takeda Pharmaceutical Company Limited; and speaker honoraria and research funding from Boehringer Ingelheim GmbH/Eli Lilly and Company, Merck & Co, Inc, and Novo Nordisk A/S.
- Dr. Samuel Dagogo-Jack reports that he has received fees for his role as diabetes expert legal consultant from Sidley Austin LLP and Adams and Reese LLP; consultant honoraria from Janssen Pharmaceuticals, Inc, Merck & Co, Inc, and Santarus, Inc; consultant honoraria and research support for his role as principal investigator from Novo Nordisk A/S; and research support for his role as principal investigator from AstraZeneca and Boehringer Ingelheim GmbH.
- Dr. Jaime Davidson reports that he has received consultant honoraria from Aspire Bariatrics and GlaxoSmithKline plc; advisory board honoraria from Amgen Inc and Eli Lilly and Company; advisory board/ speaker honoraria from AstraZeneca/Bristol-Myers Squibb Company and Novo Nordisk A/S; and advisory board/ speaker bureau honoraria from Janssen Pharmaceuticals, Inc.
- Dr. Daniel Einhorn reports that he has received consultant honoraria from Bristol-Myers Squibb Company/ AstraZeneca; consultant honoraria and research grant support from Eli Lilly and Company and Novo Nordisk A/S; consultant honoraria and shareholdings from Freedom Meditech, Inc, GlySens Incorporated, and Halozyme, Inc; consultant/speaker honoraria and research grant support from Janssen Pharmaceuticals, Inc; and research grant support from AstraZeneca, MannKind Corporation, sanofiaventis U.S. LLC, and Takeda Pharmaceutical Company Limited.
- Dr. Om Ganda reports that he has received advisory board honoraria from Amgen Inc. and sanofi-aventis U.S. LLC and research grant support from Amarin Corporation.
- Dr. Alan J. Garber reports that he has received advisory board/consultant/speaker's bureau honoraria from Janssen Pharmaceuticals, Inc., Merck & Co., Inc., Novo Nordisk A/S, and Vivus, Inc; consultant/speaker's bureau honoraria from Salix Pharmaceuticals, Inc./Santarus, Inc; advisory board/consultant honoraria from Bayer AG; advisory board honoraria from

Halozyme Therapeutics, Inc and GlaxoSmithKline plc; speaker's bureau honoraria from Eisai Inc; and consultant honoraria from Lexicon Pharmaceuticals, Inc and Viking Therapeutics.

- Dr. W. Timothy Garvey reports that he has received research support from Amylin Pharmaceuticals, Inc, Merck & Co, Inc, sanofi-aventis U.S. LLC, and Weight Watchers International, Inc; research support and advisory board honoraria from Eisai Inc; and advisory board honoraria from Alkermes plc, AstraZeneca, Bristol-Myers Squibb Company, Daiichi Sankyo Company, Limited, Janssen Pharmaceuticals, Inc, LipoScience, Inc, Novo Nordisk A/S, Takeda Pharmaceutical Company Limited, and Vivus, Inc.
- Dr. Robert R. Henry reports that he has received research grant support from Hitachi Ltd. and sanofi-aventis U.S. LLC; consultant/advisory board honoraria from Alere, ClinMet, Eisai Inc, and Isis Pharmaceuticals, Inc; speaker honoraria from Amgen Inc, Daiichi Sankyo Company, Limited, Elcelyx Therapeutics, Inc, Merck & Co., Inc, and Vivus, Inc; consultant/advisory board/speaker honoraria from Boehringer Ingelheim GmbH, F. Hoffman-La Roche Ltd/Genentech Inc, Gilead, Intarcia Therapeutics, Inc, Johnson & Johnson Services, Inc/Janssen Pharmaceuticals, Inc, and Novo Nordisk A/S; and consultant/advisory board/ speaker honoraria and research grant support from Eli Lilly and Company.
- Dr. Irl B. Hirsch reports that he has received research grant support for his role as principal investigator from Halozyme, Inc and sanofi-aventis U.S. LLC; and consultant honoraria from Abbott Laboratories, BD, and F. Hoffman-La Roche Ltd.
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- Dr. Paul S. Jellinger reports that he has received speaker honoraria from Amarin Corporation, Boehringer Ingelheim GmbH, Bristol-Myers Squibb Company/ AstraZeneca, Janssen Pharmaceuticals, Inc, and Novo Nordisk A/S.
- Dr. Lois Jovanovič reports that she does not have any relevant financial relationships with any commercial interests.
- Dr. Harold E. Lebovitz reports that he has received scientific advisory board honoraria from Biocon, Intarcia Therapeutics, Inc, MetaCure, and Poxel SA; consultant honoraria from AstraZeneca, Janssen Pharmaceuticals, Inc, and sanofi-aventis U.S. LLC; and stock dividends from AbbVie, Inc and Merck & Co, Inc.
- Dr. Derek LeRoith reports that he has received consultant honoraria from Bristol-Myers Squibb Company/ AstraZeneca, Janssen Pharmaceuticals, Inc, Merck & Co, Inc, Novo Nordisk A/S, and sanofi-aventis U.S. LLC.
- Dr. Philip Levy reports that he has received speaker honoraria from Boehringer Ingelheim GmbH, Daiichi Sankyo Company, Limited, Janssen Pharmaceuticals, Inc, and Novo Nordisk A/S.
- Dr. Janet B. McGill reports that she has received speaker's bureau/consultant honoraria from Janssen Pharmaceuticals, Inc and Merck & Co, Inc; consultant honoraria and research grant support to Washington University School of Medicine from MannKind Corporation, Novo Nordisk A/S, and sanofi-aventis U.S. LLC; consultant honoraria from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim GmbH, Eli Lilly and Company, and McNEIL-PPC, Inc; and

research grant support to Washington University School of Medicine from Andromeda Biotech Ltd, Intarcia Therapeutics, Inc, Novartis AG, and Takeda Pharmaceutical Company Limited.

- Dr. Jeffrey I. Mechanick reports that he has received honoraria for lectures and program development by Abbott Nutrition.
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- Dr. Eric Orzeck reports that he does not have any relevant financial relationships with any commercial interests.
- Dr. Rachel Pessah-Pollack reports that she does not have any relevant financial relationships with any commercial interests.
- Dr. Paul D. Rosenblit reports that he has received speaker/advisory board honoraria from Amarin Corporation; speaker honoraria from Boehringer Ingelheim GmbH, Bristol-Myers Squibb Company, and Janssen Pharmaceuticals, Inc; advisory board honoraria and research grant support for his role as principal investigator from Dexcom, Inc; research grant support for his role as principal investigator from Amgen Inc, Daiichi Sankyo Company, Limited, Eli Lilly and Company, GlaxoSmithKline plc, MannKind Corporation, Novartis AG, Orexigen Therapeutics, Inc, Pfizer Inc, and sanofi aventis U.S. LLC; and speaker honoraria and research grant support for his role as principal investigator from AstraZeneca, Eisai Inc., Merck & Co, Inc, Novo Nordisk A/S, and Takeda Pharmaceutical Company Limited.
- Dr. Aaron I. Vinik reports that he has received consultant fees from Isis Pharmaceuticals, Inc, Merck & Co, Inc, and Pamlab, Inc; consultant fees and research grant support for his role as principal investigator from Pfizer Inc; and research grant support for his role as principal investigator from Impeto Medical, Intarcia Therapeutics, Inc, Tercica, Inc, and ViroMed Laboratories Inc.
- Dr. Kathleen Wyne reports that she has received speaker honoraria from AbbVie, Inc, Novo Nordisk A/S, and Salix Pharmaceuticals, Inc.
- Dr. Farhad Zangeneh reports that he has received consultant/speaker's bureau honoraria from Abbott Laboratories, AbbVie, Inc, Amarin Corporation, AstraZeneca, Auxilium, Boehringer Ingelheim GmbH, Bristol-Myers Squibb Company, Daiichi Sankyo Company, Limited, Eisai Inc, Eli Lilly and Company, Forest Laboratories, Inc, GlaxoSmithKline plc, Janssen Pharmaceuticals, Inc, Novo Nordisk A/S, Salix Pharmaceuticals, Inc, Takeda Pharmaceutical Company Limited, and Vivus, Inc.

Medical Writer

- Ms. Amanda M. Justice reports that she has received consulting fees for writing/editorial support from AsahiKasei Corporation and sanofi-aventis U.S. LLC.

3.1.6.2 *ADA 2016*

Committee members disclosed the following financial or other conflicts of interest covering the period of 12 months before December 2015

Member	Employment	Industry-sponsored research grant	Other research support
William H. Herman, MD, MPH (Chair)	University of Michigan, Ann Arbor, MI	None	None
Thomas W. Donner, MD	Johns Hopkins University School of Medicine, Baltimore, MD	Novo Nordisk*#	None
R. James Dudl, MD	Kaiser Permanente, Bonita, CA	None	None
Hermes J. Florez, MD, PhD, MPH	University of Miami and GRECC-Miami VA Healthcare System, Miami, FL	None	None
Judith E. Fradkin, MD	National Institutes of Health, Bethesda, MD	None	None
Charlotte A. Hayes, MMSc, MS, RD, CDE, ACSM CCEP	Private practices: $(NF)^2$ Nutrition and Fitness Consulting, Atlanta, GA	None	None
Rita Rastogi Kalyani, MD, MHS, FACP	Johns Hopkins University, Baltimore, MD	None	None
Suneil Koliwad, MD, PhD	University of California, San Francisco, San Francisco, CA	None	None
Joseph A. Stankaitis, MD, MPH	Monroe Plan for Medical Care, Pittsford, NY; YourCare Health Plan, Buffalo, NY	None	None
Tracey H. Taveira, PharmD, CDOE, CVDOE	University of Rhode Island College of Pharmacy, Kingston, RI; Providence VA Medical Center, Warren Alpert Medical School of Brown University, Providence, RI	None	None
Deborah J. Wexler, MD, MSc	Massachusetts General Hospital, Boston, MA	U01DK098246—GRADE R18DK102737—REAL HEALTH-Diabetes	None
Joseph Wolfsdorf, MB, BCh	Boston Children's Hospital, Boston, MA	None	None
Jane L. Chiang, MD (Staff)	American Diabetes Association, Alexandria, VA	None	None
Erika Gebel Berg, PhD (Staff)	American Diabetes Association, Alexandria, VA	None	None
Allison T. McElvaine, PhD (Staff)	American Diabetes Association, Alexandria, VA	None	None

DSMB, Data and Safety Monitoring Board; GRECC, Geriatric Research Education and Clinical Center; MEDCAC, Medicare Evidence Development & Coverage Advisory Committee.
*≥$10,000 per year from company to individual.
#Grant or contract is to university or other employer.

3.1.6.3 *CDA 2013*

Committee members were volunteers and received no remuneration or honoraria for their participation. Members of all

committees signed an annual duality of interest form listing all financial interests or relationships with manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services.

Dualities of interest were discussed during deliberations where relevant. In the case of a potential duality or outright conflict of interest, committee members removed themselves from discussions.

Funding for the development of the guidelines was provided from the general funds of the Canadian Diabetes Association and from unrestricted educational grants from Novo Nordisk Canada Inc, Eli Lilly Canada Inc, Merck Canada Inc, Bristol-Myers Squibb and AstraZeneca, and Novartis Pharmaceuticals Canada Inc. These companies were not involved in any aspect of guideline development, literature interpretation, the decision to publish or any other aspect related to the publication of these guidelines, and they did not have access to guideline meetings, guideline drafts or committee deliberations.

3.1.6.4 *Domus Medica 2015*

Some members of the author group and some external experts have declared to have been a member of the advisory board of , or to have been paid to lecture at symposia by , or to have contributed to clinical studies of the following pharmaceutical companies : Sanofi , Novo Nordisk, Merck , Eli Lilly, Astra Zeneca , Boehringer - Ingelheim , Novartis, Merck , Bristol Myers Squibb , Janssen Pharmaceuticals, Pfizer, Medtronic, Roche and Servier .

The authors , experts and members of the Guideline Commission of Domus Medica have expressly stated that these activities at the invitation of or with funding / sponsorship of the industry had no influence on the results and use the data in the creation of this guideline . No conflicts of interest that could affect the content of this guideline were identified.

3.1.6.5 *EASD/ADA 2015*

During the past 12 months, the following relationships with companies whose products or services directly relate to the subject matter in this document are declared:

- R.M. Bergenstal: membership of scientific advisory board, consultation services or clinical research support with AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck & Co., Novo Nordisk, Roche, Sanofi, and Takeda (all under contracts with his employer). Inherited stock in Merck & Co. (previously held by family)
- J.B. Buse: research and consulting with AstraZeneca; Boehringer Ingelheim; BristolMyers Squibb Company; Eli Lilly and Company; Johnson & Johnson; Merck & Co., Inc.; Novo Nordisk; Sanofi; and Takeda (all under contracts with his employer)
- E. Ferrannini: membership on scientific advisory boards or speaking engagements for Merck Sharp & Dohme, Boehringer Ingelheim, GlaxoSmithKline, Bristol-Myers Squibb/AstraZeneca, Eli Lilly & Co., Novartis, and Sanofi. Research grant support from Eli Lilly & Co. and Boehringer Ingelheim S.E. Inzucchi: membership on scientific/research advisory boards for Boehringer Ingelheim, AstraZeneca, Intarcia, Lexicon, Merck & Co., and Novo Nordisk. Research supplies to Yale University from Takeda. Participation in medical educational projects, for which unrestricted funding from Boehringer Ingelheim, Eli Lilly, and Merck & Co. was received by Yale University D.R. Matthews: has received advisory board consulting fees or honoraria from Novo Nordisk, GlaxoSmithKline, Novartis, Johnson & Johnson, and Servier. He has research support from Johnson & Johnson. He has lectured for Novo Nordisk, Servier, and Novartis
- M. Nauck: research grants to his institution from Berlin-Chemie/Menarini, Eli Lilly,Merck Sharp & Dohme, Novartis, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Lilly Deutschland, and Novo Nordisk for participation in multicenter clinical trials. He has received consulting fees and/or honoraria for membership in advisory boards and/or honoraria for speaking from Amylin, AstraZeneca, BerlinChemie/Menarini, Boehringer Ingelheim, BristolMyers Squibb, Diartis Pharmaceuticals, Eli Lilly, F. Hoffmann-La Roche, GlaxoSmithKline, Hanmi, Intarcia Therapeutics, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, Takeda, and Versartis, including reimbursement for travel expenses

- A.L. Peters: has received lecturing fees and/or fees for ad hoc consulting from AstraZeneca, Bristol-Myers Squibb, Janssen, Eli Lilly, Novo Nordisk, Sanofi, and Takeda
- Tsapas: has received research support (to his institution) from Novo Nordisk and Boehringer Ingelheim and lecturing fees from Novartis, Eli Lilly, and Boehringer Ingelheim
- R. Wender: declares he has no duality of interest Author Contributions. All the named Writing Group authors contributed substantially to the document. All authors supplied detailed input and approved the final version. S.E. Inzucchi and D.R. Matthews directed, chaired, and coordinated the input with multiple e-mail exchanges between all participants.

3.1.6.6 *ESC/EASD 2013*

The declarations of interest of the task force members of the ESC/EASD guideline can be found on-line (http://www.escardio.org/static_file/Escardio/Guidelines/Diabetes2013_DOI.pdf ; 49 pages)

3.1.6.7 *NICE 2015*

The following members of the Guideline Development Group made declarations of interests. All other members of the Group stated that they had no interests to declare.

Member	**Interest declared**	**Type of interest**	**Decision taken**
Christine Bundy	Holds a Scientific Advisory Board position with Simple Healthcare Products for which an honorarium is received for attending approximately 3 meetings per year	Non-specific personal pecuniary	Declare and participate
Indranil Dasgrupta	Has been a member of an advisory board on a new phosphate binder for chronic kidney disease for Mitsubishi Pharma	Non-specific personal pecuniary	Declare and participate
Indranil Dasgrupta	Working department has received a research grant from Medtronic for a study of renal denervation for resistant hypertension	Non-specific, non-personal pecuniary	Declare and participate
David Edwards	Acts as a Chair and member on a number of advisory boards. Has organised, chaired and presented at local, national and international	Non-specific personal pecuniary	Declare and participate

	meetings on male and/or female sexual problems and stress. Has written guidelines, been filmed, reviewed/ written articles for both lay and medical press. These activities have been reimbursed by organisations including pharmaceutical companies in the form of transport, accommodation and sometimes honoraria. Companies that travel, accommodation and honoraria have been received from are Bayer, Eli Lilly, Schwabe and Takeda & Menarini, Pfizer, ProStrakan and Owen Mumford		
David Edwards	President of the British Society for Sexual Medicine, Member of Men's Health Expert Policy Group which aims to educate those in power especially government and key stakeholders. Travel/occasional accommodation but not time is paid for by Bayer	Non-specific personal pecuniary	Declare and participate
David Edwards	Clinical adviser to the Klinefelter's National Association. Member of an advisory board for prostate cancer management known as atypical small acinar proliferation (ASAP)	Non-specific personal pecuniary	Declare and participate
David Edwards	Participated as a medical researcher for studies undertaken by the Universities of Oxford and Southampton	Non-specific personal pecuniary	Declare and participate
David Edwards	Chief investigator in the UK for a study on low dose aspirin. The study is sponsored by Bayer	Non-specific personal pecuniary	Declare and participate
Natasha Jacques	Participation in advisory board on Management of Diabetes in Renal Disease (sponsored by Boehringer	Specific personal pecuniary	Declare and participate as in line with NICE policy, it is more than 1 year since the conflict

	Ingelheim) 17.01.12	interest	occurred and the topics this may relate to are discussed
Natasha Jacques	Speaker on 'Adherence Issues in Diabetes'– event sponsored by MSD 25.04.12	Specific personal pecuniary interest	Declare and participate as in line with NICE policy, it is more than 1 year since the conflict occurred and the topics this may relate to are discussed
Yvonne Johns	Has been asked by Diabetes UK Wales on behalf of the Welsh Medical Council to discuss and bring forward patient views on lixisenatide for the diabetes group in which she is involved. None of the patients have been asked to use the drug but were asked whether they would consider using it based in an information leaflet they received and their experiences of other GLP-1's	Personal non-pecuniary	Declare and participate
Natasha Marsland	Employed by Diabetes UK	Non-personal pecuniary	Declare and participate
Jonathan Roddick	Member of MSD advisory board for sitagliptin until appointment	Specific personal pecuniary	Able to participate as recommendations on drug treatment in type 2 diabetes were not made until 2014
Mohamed Roshan	Attended a diabetes advisory meeting. Reimbursement paid to the GP practice	Specific non-personal pecuniary	Declare and participate
Mohamed Roshan	Developer of Diabetes Education modules in Leicester which include modules on diabetes therapies between 2011 and 2013. No money was received	Personal non-pecuniary	Declare and participate

Mohamed Roshan	Developed and chaired meetings for GLP-1 educational program in Leicester for Primary Care as part of Department of Diabetes	Personal non-pecuniary	Declare and participate
Mohamed Roshan	Attends advisory committee on Lixisenatide for Sanofi and will be trained in future as speaker (last attended March 2013). Received reimbursement to cover locum fees and staff time	Specific personal pecuniary	Declare and withdraw
Mohamed Roshan	Will attend conference for discussion on saxagliptin and cardiovascular outcomes evidence recently published. Reimbursement from Astra Zeneca	Specific personal pecuniary	Declare and withdraw
Mohamed Roshan	Will be training as speaker for Bristol Myer Squibb	Specific personal pecuniary	Declare and withdraw
Mohamed Roshan	Have chaired meeting for Insulin Degludec (Tresiba) in Sept 2013. Locum expenses reimbursed by Novo Nordisk	Specific personal pecuniary	Declare and withdraw
Sailesh Sankar	Attended the International Diabetes Federation in 4th December 2011, the travel and subsistence was supported by Boehringer Ingleheim with in the ABPI regulation guidelines	Specific personal pecuniary	Able to participate as recommendations on drug treatment in type 2 diabetes were not made until 2014
Sailesh Sankar	Chaired an evening meeting on the 12th of June 2012 for GP educational session supported by Novo Nordisk	Specific personal pecuniary	Able to participate as recommendations on drug treatment in type 2 diabetes were not made until 2014
Sailesh Sankar	October 2011 – did an evening educational session for GPs	Specific personal	Able to participate as recommendations on drug treatment in type 2

	supported by Boehringer Ingelheim	pecuniary	diabetes were not made until 2014
Sailesh Sankar	Principal Investigator for Roche EXPERT study. The study recruited patient to use an EXPERT bolus advisor blood glucose monitor versus a Nano monitor. This study was in relation to feasibility of use of bolus advisor in patients with type 1 diabetes. In this study 9 patients were recruited from Feb 2012 onwards and study was completed in October 2012. This study was funded by ROCHE to meet the expenses of the overheads and running of the study at UHCW site. The UHCW Trust has invoiced the company and the funding yet to be received. The exact amount can be confirmed on receipt	Non-personal specific pecuniary	Declare and participate
Sailesh Sankar	Research nurse team was also involved in a retrospective data collection for study/audit conducted at UHCW trust in relation to use of INSULINX blood glucose monitoring in patients with type 1 diabetes. Funding was (£150.00 per patient data collected) was agreed by the trust R and D in relation to this project. This study was funded by ABBOTT diabetes care This was done over September to October 2012 period. Approximately 10 patients' data were collected for this study	Specific non-personal pecuniary	Declare and participate
Sailesh Sankar	Receiving a grant from Novo Nordisk to lead development of an education application for computer and phone devices for clinicians and medical students. The application will covering managing blood glucose levels for people with diabetes on insulin and preventing ketoacidosis. Novo Nordisk produce insulin licensed for use in people	Specific non-personal pecuniary	Declare and participate

	with type 1 and type 2 diabetes		

3.1.6.8 *ERBP 2015*

Luis Coentrão, Cécile Couchoud, Adrian Covic, Johan De Sutter, Christiane Drechsler, Kitty J. Jager, Hakan Nacak, Charlie Tomson, Steven Van Laecke declared no conflicts of interest.

Dr Henk Bilo

- grant from Novo Nordisk and Sanofi Aventis

Prof. Luigi Gnudi

- Consultant for Glaxosmithkline
- Lecture/symposia for Janssen, Boehringer-Lilly, Sanofi, AstraZeneca
- Grants from Abbvie, AstraZeneca, Janssen, Boehringer-Lilly, Sanofi, Novo Nordisk, Takeda, Chemocentrix

Prof. David Goldsmith

- Consultant for Sanofi, Keryx, Amgen, Abbott, Fresenius
- Lectures/conferences to Sanofi, Keryx, Abbott, Fresenius, S

Dr. James G. Heaf

- Grant from Fresenius
- Prof. Olof Heimburger
- Consultant for Medivir
- Lecturing for Baxter Healthcare, Fresenius, Bayer, Sandoz
- Grant from AstraZeneca

Dr. Evi Nagler

- Grant from European Renal Best Practice – Official Guideline writing body of ERA-EDTA

Dr. Maria Jose Soler Romeo

- Writing for Abbvie
- Grant from Abbvie

Prof Wim Van Biesen

- Marketing/product development for Fresenius
- Lecturing for Fresenius, Baxter, Gambro

Dr. Liesbeth Van Huffel

- Lecturing for Roche Diagnostics Belgium

Dr. Laurent Weekers

- Advice to Alexion
- Conference : Astellas, Novartis, Sandoz

Prof. Andrzej Jan Wieçek

- Advice to Boehringer Ingelheim
- Lectures for Amgen, Fresenius, Vifor
- Conference fees from Amgen, Roche, Fresenius
- Grant from National Centre of Science

3.1.7 Method of reporting of the recommendations and notes

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in **bold**.

Even though the NICE 2015 guideline did not grade its recommendations, it does appraise and determine a level of evidence for the studies leading to the recommendations. For that reason, the recommendations of the NICE 2015 guideline are also written in **bold**.

Text taken directly from the guidelines, that is not graded but provides supplemental information or a clarification of the formal recommendations, is written in *italics*.

Comments by the bibliography group are written in plain text.

3.2 Therapeutic metabolic goals

3.2.1 Goals for Glycemic control

3.2.1.1 *Summary*

All guidelines state that glycemic targets should be individualized based on patient characteristics. The following characteristics are mentioned:

Characteristic	More strict	Guideline	Less strict	Guideline
Age	/	/	**Frail elderly**	CDA 2013
Duration of diabetes	**Short**	Domus Medica 2015, ADA 2016, EASD/ADA 2015, AACE/ACE 2015, ESC/EASD 2013	**Longstanding + difficult to achieve target**	CDA 2013, Domus Medica 2015, ADA 2016, EASD/ADA 2015, AACE/ACE 2015, ESC/EASD 2013
Risk of severe hypoglycemia	**Low**	EASD/ADA 2015	**Recurrent and severe, hypoglycemia unawareness**	CDA 2013, Domus Medica 2015, ADA 2016, EASD/ADA 2015, AACE/ACE 2015, NICE 2015
Presence or absence of cardiovascular disease	**No significant**	Domus Medica 2015 , ADA 2016, AACE/ACE 2015, ESC/EASD 2013	**Extensive, high risk**	CDA 2013
Life expectancy	**Long**	Domus Medica 2015, ADA 2016, EASD/ADA 2015, ESC/EASD 2013	**Limited**	CDA 2013, Domus Medica, ADA 2016, EASD/ADA 2015, AACE/ACE 2015, NICE 2015
Level of functional dependency	/	/	**high**	CDA 2013, ESC/EASD 2013
Comorbidities	**Absent**	EASD/ADA 2015	**multiple**	CDA 2013, ADA 2016, EASD/ADA 2015, AACE/ACE 2015, NICE 2015
Microvascular or cardiovascular complications	**Absent**	EASD/ADA 2015	**extensive**	Domus Medica 2015, ADA 2016, EASD/ADA 2015, AACE/ACE 2015, ESC/EASD 2013
Intensity of treatment	**Treated with lifestyle or metformin only; or single drug not associated with hypoglycemia**	ADA 2016, NICE 2015	/	/
Patient attitude and expected treatment efforts	**Highly motivated, adherent**	EASD/ADA 2015	**Less motivated, nonadherent**	EASD/ADA 2015
Resources and support system	**Readily available**	EASD/ADA 2015	**Limited**	EASD/ADA 2105, ESC/EASD 2015

Table 31: Summary of patient characteristics on which choice of HbA1c target should be based, according to guidelines.

Most guidelines provide a glycemic target that most patients should aim for, a stricter glycemic target for some, and a more relaxed glycemic target for others (CDA 2013, Domus Medica 2015, ADA 2016, EASD/ADA 2015, ESC/EASD 2013). NICE 2015 recommends one standard HbA1c target range between 6.5% (47.5 mmol/mol) and 7% (53 mmol/mol). AACE/ACE 2015 recommends a standard target of ≤6.5% (47.5 mmol/mol), and a more relaxed target range of 7-8% (53- 63.9 mmol/mol).

Guideline	More strict	Standard target	More relaxed
CDA 2013	**≤6.5%** (≤47.5 mmol/mol)	**≤7%** (≤ 53 mmol/mol)	**7.1 – 8.5%** (54.1 – 69.4 mmol/mol)
Domus Medica 2015	**<6.5%**(<47.5 mmol/mol)	**<7%** (<53 mmol/mol)	**<8%** (< 63.9 mmol/mol)
ADA 2016	**<6.5%** (<47.5 mmol/mol)	**<7%** (<53 mmol/mol)	**<8%** (< 63.9 mmol/mol)
EASD/ADA 2015	"**more stringent"**	**7%** (53 mmol/mol)	**"less stringent"**
NICE 2015	/	**6.5%-7%** (47.5 – 53 mmol/mol)	/
ESC/EASD 2013	**6.0-6.5%** (42 -47.5 mmol/mol)	**<7%** (<53 mmol/mol)	**7.5-8.0%** (58.5 – 63.9 mmol/mol)
AACE/ACE 2015	/	**≤6.5%** (≤ 47.5 mmol/mol)	**7-8%** (53- 63.9 mmol/mol)

Table 32: Standard target, stricter and more relaxed HbA1c target, according to guidelines.

Two guidelines state that healthy elderly should aim for the same goals as other patients (CDA 2013, ADA 2016).

One guideline states that in the frail elderly, the target should be ≥8.5% (69.4 mmol/mol) (CDA 2013); in another guideline, the target depends on health status(ADA 2016).

One guideline does not recommend a tighter control for diabetics with eGFR <45mL/min. The HbA1c target of this population should be 7.0 to 8.5% (53 to 69.4 mmol/mol), depending on patient characteristics (ERBP 2015).

There were no specific recommendations concerning HbA1c target in the obese.

3.2.1.2 *AACE/ACE 2015*

R11. Glucose targets should be individualized and take into account life expectancy, disease duration, presence or absence of micro- and macrovascular complications, CVD risk factors, comorbid conditions, and risk for hypoglycemia, as well as the patient's psychological status (Grade A; BEL 1).

In general, the goal of therapy should be an A1C level ≤6.5% for most nonpregnant adults, if it can be achieved safely (Table 7) (Grade D; BEL 4).
To achieve this target A1C level, FPG may need to be <110 mg/dL, and the 2-hour PPG may need to be <140 mg/dL (Table 7) (Grade B, BEL 2).

In adults with recent onset of T2D and no clinically significant CVD, glycemic control aimed at normal (or near-normal) glycemia should be considered, with the aim of preventing the development of micro- and macrovascular complications over a lifetime, if it can be achieved without substantial hypoglycemia or other unacceptable adverse consequences (Grade A; BEL 1).

Although it is uncertain that the clinical course of established CVD is improved by strict glycemic control, the progression of microvascular complications clearly is delayed. A less stringent glucose goal should be considered (A1C 7 to 8%) in patients with history of severe hypoglycemia, limited life expectancy, advanced renal disease or macrovascular complications, extensive comorbid conditions, or long-standing DM in which the A1C goal has been difficult to attain despite intensive efforts, so long as the patient remains free of polydipsia, polyuria, polyphagia, and other hyperglycemia associated symptoms (Grade A; BEL 1).

3.2.1.3 *ADA 2016*

A reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol). A

Providers might reasonably suggest more stringent A1C goals (such as <6.5% [48 mmol/mol]) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease. C

Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. B

Elderly

Older adults who are functional and cognitively intact and have significant life expectancy may receive diabetes care with goals similar to those developed for younger adults. E

Glycemic goals for some older adults might reasonably be relaxed, using individual criteria, but hyperglycemia leading to symptoms or risk of acute hyperglycemic complications should be avoided in all patients. E

Patients with diabetes residing in long-term care facilities need careful assessment to establish a glycemic goal and to make appropriate choices of glucose-lowering agents based on their clinical and functional status. E

Table 10.1—Framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes

Patient characteristics/ health status	Rationale	Reasonable A1C goal‡	Fasting or preprandial glucose	Bedtime glucose	Blood pressure	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.5% (58 mmol/mol)	90–130 mg/dL (5.0–7.2 mmol/L)	90–150 mg/dL (5.0–8.3 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0% (64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	<8.5%† (69 mmol/mol)	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)	<150/90 mmHg	Consider likelihood of benefit with statin (secondary prevention more so than primary)

This represents a consensus framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes. The patient characteristic categories are general concepts. Not every patient will clearly fall into a particular category. Consideration of patient and caregiver preferences is an important aspect of treatment individualization. Additionally, a patient's health status and preferences may change over time. ADL, activities of daily living.
‡A lower A1C goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden.
*Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. By "multiple," we mean at least three, but many patients may have five or more (27).
**The presence of a single end-stage chronic illness, such as stage 3–4 congestive heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy.
†A1C of 8.5% (69 mmol/mol) equates to an estimated average glucose of ~200 mg/dL (11.1 mmol/L). Looser A1C targets above 8.5% (69 mmol/mol) are not recommended as they may expose patients to more frequent higher glucose values and the acute risks from glycosuria, dehydration, hyperglycemic hyperosmolar syndrome, and poor wound healing.

Figure 1: ADA 2016 treatment targets in the elderly

3.2.1.4 *CDA 2013*

Glycemic targets should be individualized based on age, duration of diabetes, risk of severe hypoglycemia, presence or absence of cardiovascular disease, and life expectancy [Grade D, Consensus].

Therapy in most individuals with type 1 or type 2 diabetes should be targeted to achieve an A1C ≤7.0% in order to reduce the risk of microvascular [Grade A, Level 1A] and, if implemented early in the course of disease, macrovascular complications [Grade B, Level 3].

An A1C ≤6.5% may be targeted in some patients with type 2 diabetes to further lower the risk of nephropathy [Grade A, Level 1] and retinopathy [Grade A, Level 1, but this must be balanced against the risk of hypoglycemia [Grade A, Level 1].

Less stringent A1C targets (7.1%-8.5% in most cases) may be appropriate in patients with type 1 or type 2 diabetes with any of the following [Grade D, Consensus]:

- **Limited life expectancy**
- **High level of functional dependency**
- **Extensive coronary artery disease at high risk of ischemic events**
- **Multiple comorbidities**
- **History of recurrent severe hypoglycemia**
- **Hypoglycemia unawareness**
- **Longstanding diabetes for whom it is difficult to achieve an A1C ≤7.0% despite effective doses of multiple antihyperglycemic agents, including intensified basal-bolus insulin therapy**

In order to achieve an A1C ≤7.0%, people with diabetes should aim for:

- **FPG or preprandial PG target of 4.0-7.0 mmol/L and a 2-hour PPG target of 5.0-10.0 mmol/L [Grade B, Level 2 for type 1; Grade B, Level 2 for type 2 diabetes].**
- **If an A1C target ≤7.0% cannot be achieved with a PPG target of 5.0-10.0 mmol/L, further PPG lowering to 5.0-8.0 mmol/L should be achieved [Grade D, Consensus, for type 1 diabetes; Grade D, Level 4 for type 2 diabetes].**

Abbreviations: A1C, glycated hemoglobin; BG, blood glucose; FPG, fasting plasma glucose; PG, plasma glucose; PPG, postprandial plasma glucose

Elderly people

Healthy elderly people with diabetes should be treated to achieve the same glycemic, blood pressure and lipid targets as younger people with diabetes [Grade D, Consensus].

In the frail elderly, while avoiding symptomatic hyperglycemia, glycemic targets should be A1C ≥8.5% and fasting plasma glucose or preprandial PG 5.0-12.0 mmol/L, depending on the level of frailty. Prevention of hypoglycemia should take priority over attainment of glycemic targets because the risks of hypoglycemia are magnified in this patient population [Grade D, Consensus].

In elderly people with cognitive impairment, strategies should be used to strictly prevent hypoglycemia, which include the choice of antihyperglycemic therapy and less stringent A1C target [Grade D, Consensus].

3.2.1.5 *DOMUS MEDICA 2015*

Individualize the target for HbA1c according to the profile of the patient (Grade 1B)

Strive generally to an HbA1c < 7% (53 mmol / mol). (Grade 1B)

Try to pursue a stricter HbA1c < 6.5% (48 mmol / mol) in some, taking into account the individual patient profile and the risk of hypoglycaemia . (Grade 1C) Patients who can pursue a stricter HbA1c are patients with short duration of diabetes , a long life expectancy and no significant cardiovascular disease.

Accept a less strict HbA1c < 8% (64 mmol / mol) in people with a history of severe hypoglycemia, limited life expectancy , extensive microvascular or cardiovascular complications or long-standing diabetes where the target is difficult to achieve . (Grade 1B)

3.2.1.6 *EASD/ADA 2015*

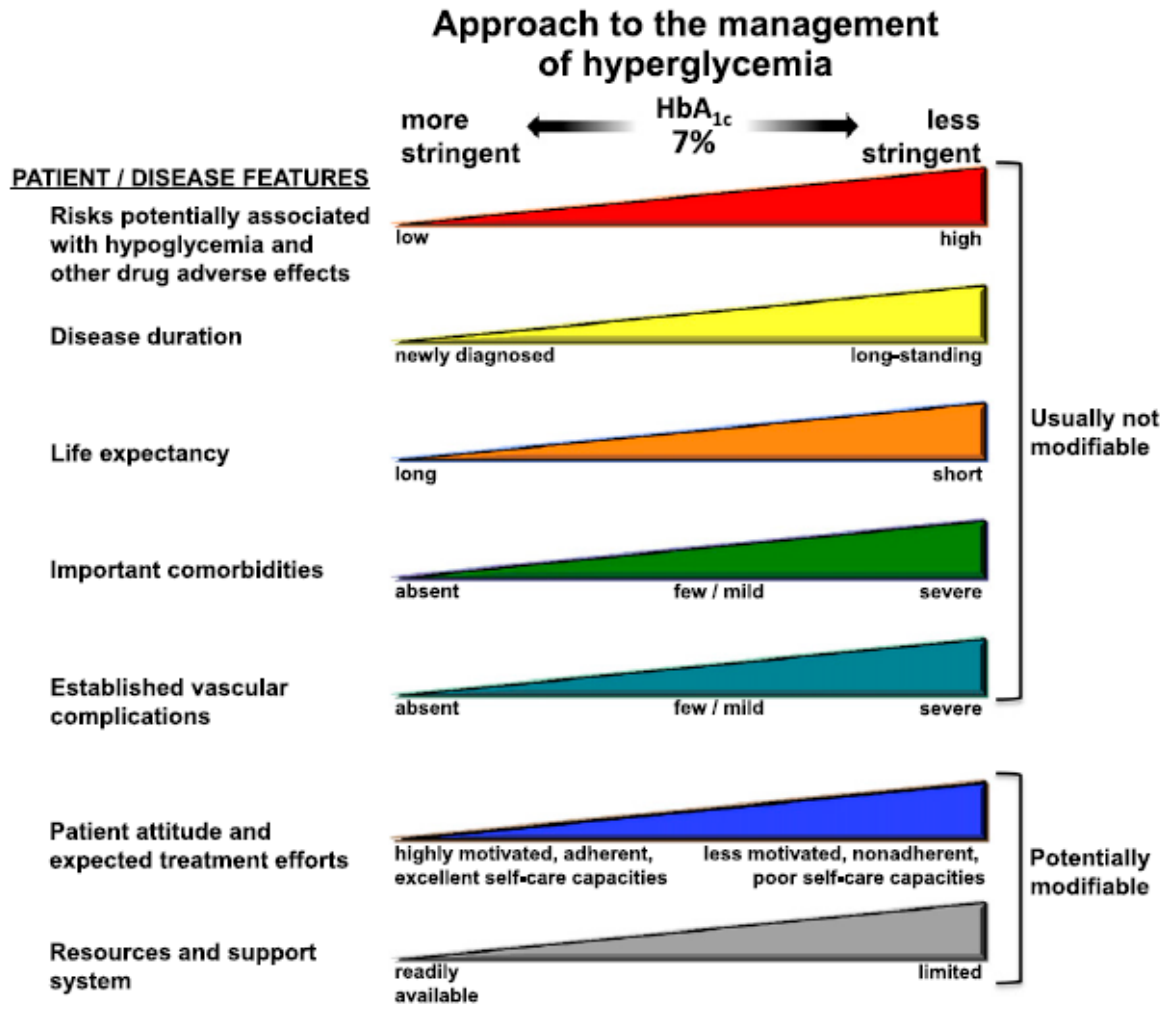


Figure 1—Modulation of the intensiveness of glucose lowering in type 2 diabetes. Depiction of patient and disease factors that may be used by the practitioner to determine optimal HbA_{1c} targets in patients with type 2 diabetes. Greater concerns regarding a particular domain are represented by increasing height of the corresponding ramp. Thus, characteristics/predicaments toward the left justify more stringent efforts to lower HbA_{1c}, whereas those toward the right suggest (indeed, sometimes mandate) less stringent efforts. Where possible, such decisions should be made with the patient, reflecting his or her preferences, needs, and values. This "scale" is not designed to be applied rigidly but to be used as a broad construct to guide clinical decision making. Based on an original figure by Ismail-Beigi et al. (59).

Figure 2: EASD/ADA 2015 targets for glycemic control

3.2.1.7 *ESC/EASD 2013*

Glycaemic control in diabetes			
Recommendations	**Class [a]**	**Level [b]**	**Ref. [c]**
It is recommended that glucose lowering is instituted in an individualized manner taking duration of DM, co-morbidities and age into account.	I	C	-
It is recommended to apply tight glucose control, targeting a near-normal HbA_{1c} (<7.0% or <53 mmol/mol) to decrease microvascular complications in T1DM and T2DM.	I	A	151–153, 155, 159
A HbA_{1c} target of ≤7.0% (≤53 mmol/mol) should be considered for the prevention of CVD in T1 and T2 DM.	IIa	C	-
Basal bolus insulin regimen, combined with frequent glucose monitoring, is recommended for optimizing glucose control in T1DM.	I	A	151, 154
Metformin should be considered as first-line therapy in subjects with T2DM following evaluation of renal function.	IIa	B	153

CVD = cardiovascular disease; DM = diabetes mellitus; HbA_{1c} = glycated haemoglobin A_{1c}; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

Figure 3: ESC/EASD 2013 targets for glycemic control

More stringent targets (e.g. HbA1c 6.0–6.5% (42–48 mmol/mol])might be considered in selected patients with short disease duration, long life expectancy and no significant CVD, if it can be achieved without hypoglycaemia or other adverse effects. As discussed above, the accumulated results from T2DM cardiovascular trials suggest that not everyone benefits from aggressive glucose management. It follows that it is important to individualize treatment targets.

Elderly people.
Older people have a higher atherosclerotic disease burden, reduced renal function and greater co-morbidity. Life expectancy is reduced, especially in the presence of long-term complications.

Glycaemic targets for elderly people with long-standing or more complicated disease should be less ambitious than for younger, healthier individuals. If lower targets cannot be achieved with simple interventions, an HbA1c of ,7.5–8.0% (,58–64 mmol/mol) may be acceptable, transitioning upwards as age increases and capacity for self-care, cognitive, psychological and economic status and support systems decline

3.2.1.8 *NICE 2015*

Involve adults with type 2 diabetes in decisions about their individual HbA1c target. Encourage them to achieve the target and maintain it unless any resulting adverse effects (including hypoglycaemia), or their efforts to achieve their target, impair their quality of life. [new 2015]

For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycaemia, support the person to aim for an HbA1c level of 48 mmol/mol (6.5%). For adults on a drug associated with hypoglycaemia, support the person to aim for an HbA1c level of 53 mmol/mol (7.0%). [new 2015]

In adults with type 2 diabetes, if HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher:

- **reinforce advice about diet, lifestyle and adherence to drug treatment and**
- **support the person to aim for an HbA1c level of 53 mmol/mol (7.0%) and**
- **intensify drug treatment. [new 2015]**

Consider relaxing the target HbA1c level (see recommendations 41–42) on a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes:

- **who are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy**
- **for whom tight blood glucose control poses a high risk of the consequences of hypoglycaemia, for example, people who are at risk of falling, people who have impaired awareness of hypoglycaemia, and people who drive or operate machinery as part of their job**
- **for whom intensive management would not be appropriate, for example, people with significant comorbidities. [new 2015]**

If adults with type 2 diabetes achieve an HbA1c level that is lower than their target and they are not experiencing hypoglycaemia, encourage them to maintain it. Be aware that there are other

possible reasons for a low HbA1c level, for example, deteriorating renal function or sudden weight loss. [new 2015]

3.2.1.9 *ERBP 2015*

We recommend against tighter glycaemic control if this results in severe hypoglycaemic episodes (1B).

We recommend vigilant attempts to tighten glycaemic control with the intention to lower HbA1C when values are >8.5% (69 mmol/mol) (1C).

We suggest vigilant attempts to tighten glycaemic control with the intention to lower HbA1C according to the flow chart in Figure 4 in all other conditions (2D).

We recommend intense self-monitoring only to avoid hypoglycaemia in patients at high risk for hypoglycaemia (2D).

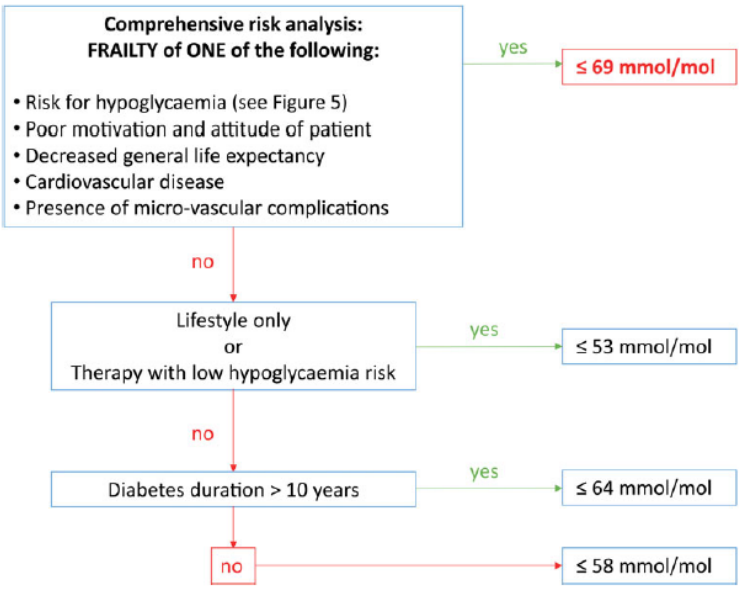


FIGURE 4: Flowchart of management targets for HbA1C in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min).

Figure 4: ERBP 2015 targets for glycemic control in patients with CKD stage 3B or higher

3.2.2 Goals for Body weight

3.2.2.1 *Summary*

Three guidelines recommend a reduction in body weight of 5-10% (DOMUS MEDICA 2015, NICE 2015, AACE/ACE 2015). One guideline recommends a 5% reduction (ADA 2016). One guideline recommends to achieve a “lower, healthy body weight”(CDA 2013).

There were no specific recommendations concerning body weight target in the elderly, in function of the duration of diabetes, in diabetics with comorbidity, or with decreased kidney function.

3.2.2.2 *AACE/ACE 2015*

Table 7
Comprehensive Diabetes Care Treatment Goals

Parameter	Treatment goal	Reference (evidence level and study design)
Glucose		
A1C, %	Individualize on the basis of age, comorbidities, duration of disease; in general ≤6.5 for most; closer to normal for healthy; less stringent for "less healthy"	(4 [EL 4; NE])
FPG, mg/dL	<110	
2-h PPG, mg/dL	<140	
Inpatient hyperglycemia: glucose, mg/dL	140-180	(5 [EL 4; consensus NE])
Blood pressure	Individualize on the basis of age, comorbidities, and duration of disease, with general target of:	(8 [EL 4; NE])
Systolic, mm Hg	~130	
Diastolic, mm Hg	~80	
Lipids		
LCL-C, mg/dL	<100, moderate risk <70, high risk	(4 [EL 4; NE])
Non-HDL-C, mg/dL	<130, moderate risk <100, high risk	
Triglycerides, mg/dL	<150	
TC/HDL-C ratio	<3.5, moderate risk <3.0, high risk	
ApoB, mg/dL	<90, moderate risk <80, high risk	
LDL particles	<1,200 moderate risk <1,000 high risk	
Weight		
Weight loss	Reduce weight by at least 5 to 10%; avoid weight gain	(4 [EL 4; NE])
Anticoagulant therapy		
Aspirin	For secondary CVD prevention or primary prevention for patients at very high risk[a]	(9 [EL 1; MRCT but small sample sizes and event rates]; 10 [EL 1; MRCT]; 11 [EL 1; MRCT]; 12 [EL 2; PCS])

Abbreviations: ApoB = apolipoprotein B; BEL = best evidence level; CVD = cardiovascular disease; DM = diabetes mellitus; EL = evidence level; FPG = fasting plasma glucose; HDL-C = high-density lipoprotein cholesterol; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; LDL = low-density lipoprotein; MRCT = meta-analysis of randomized controlled trials; NE = no evidence (theory, opinion, consensus, review, or preclinical study); PCS = prospective cohort study; PPG = postprandial glucose; TC = total cholesterol.
[a] High risk, DM without cardiovascular disease; very high risk, DM plus CVD.

Figure 5: AACE/ACE 2015 treatment targets in type 2 diabetes

3.2.2.3 *ADA 2016*

Diet, physical activity, and behavioral therapy designed to achieve 5% weight loss should be prescribed for overweight and obese patients with type 2 diabetes ready to achieve weight loss. A

3.2.2.4 *CDA 2013*

- **An interdisciplinary weight management program (including a nutritionally balanced, calorie-restricted diet; regular physical activity; education; and counselling) for overweight**

and obese people with, or at risk for, diabetes should be implemented to prevent weight gain and to achieve and maintain a lower, healthy body weight [Grade A, Level 1A].

3.2.2.5 *DOMUS MEDICA 2015*

The target for overweight or obesity is a weight reduction of at least 5 to 10% of the body weight . (Grade 1C).

3.2.2.6 *EASD/ADA 2015*

No recommendations

3.2.2.7 *ESC/EASD 2013*

No recommendations

3.2.2.8 *NICE 2015*

For adults with type 2 diabetes who are overweight, set an initial body weight loss target of 5–10%. Remember that lesser degrees of weight loss may still be of benefit, and that larger degrees of weight loss in the longer term will have advantageous metabolic impact. [2009]

3.2.2.9 *ERBP 2015*

No recommendations

3.2.3 Goals for Dyslipidemia

3.2.3.1 *Summary*

The LDL-cholesterol targets for patients with diabetes, with or without additional cardiovascular risk factors or established cardiovascular disease, as recommended by the selected guidelines, is summarized in the table below.

	Target LDL-C for DM, no additional CVD risk factor	**Target LDL-C for DM, additional CVD or CVD risk factors**
CDA 2013		≤77 mg/dL
Domus Medica 2015	<100 mg/dL	<70 mg/dL
AACE/ACE 2015	<100mg/dL	<70 mg/dL
ESC/EASD 2013	<100 mg/dL	<70 mg/dL

Table 33 LDL-C targets for diabetics with or without additional cardiovascular risk factors, according to guidelines.

One guideline did not recommend to treat to a certain target (ADA 2016).

This guideline recommends to treat healthy elderly to the same goals as other patients. In frail elderly, the likelihood of benefit with a statin should be considered (ADA 2016).

In patients with diabetes and an eGFR<45 mL/min, the dose of lipid-lowering medication should be adjusted to the renal function, not to the lipid levels, according to one guideline (ERBP 2015).

There were no specific recommendations concerning cholesterol targets in function of the duration of diabetes or in the obese.

3.2.3.2 *AACE/ACE 2015*

• R26. In persons with DM or prediabetes and no atherosclerotic CVD (ASCVD) or major cardiovascular risk factors (i.e., moderate CVD risk), treatment efforts should target a low-density lipoprotein cholesterol (LDL-C) goal of <100 mg/dL and a non-HDL-C goal of <130 mg/dL (Grade B; BEL 2).

In high-risk patients (those with DM and established ASCVD or at least 1 additional major ASCVD risk factor such as hypertension, family history, low HDL-C, or smoking), a statin should be started along with therapeutic lifestyle changes regardless of baseline LDL-C level (Grade A; BEL 1).

In these patients, an LDL-C level <70 mg/dL and a non-HDL-C treatment goal <100 mg/dL should be targeted (Table 7) (Grade B; BEL 2).

If the triglyceride concentration is ≥200 mg/dL, non-HDL-C may be used to predict ASCVD risk (Grade C; BEL 3).

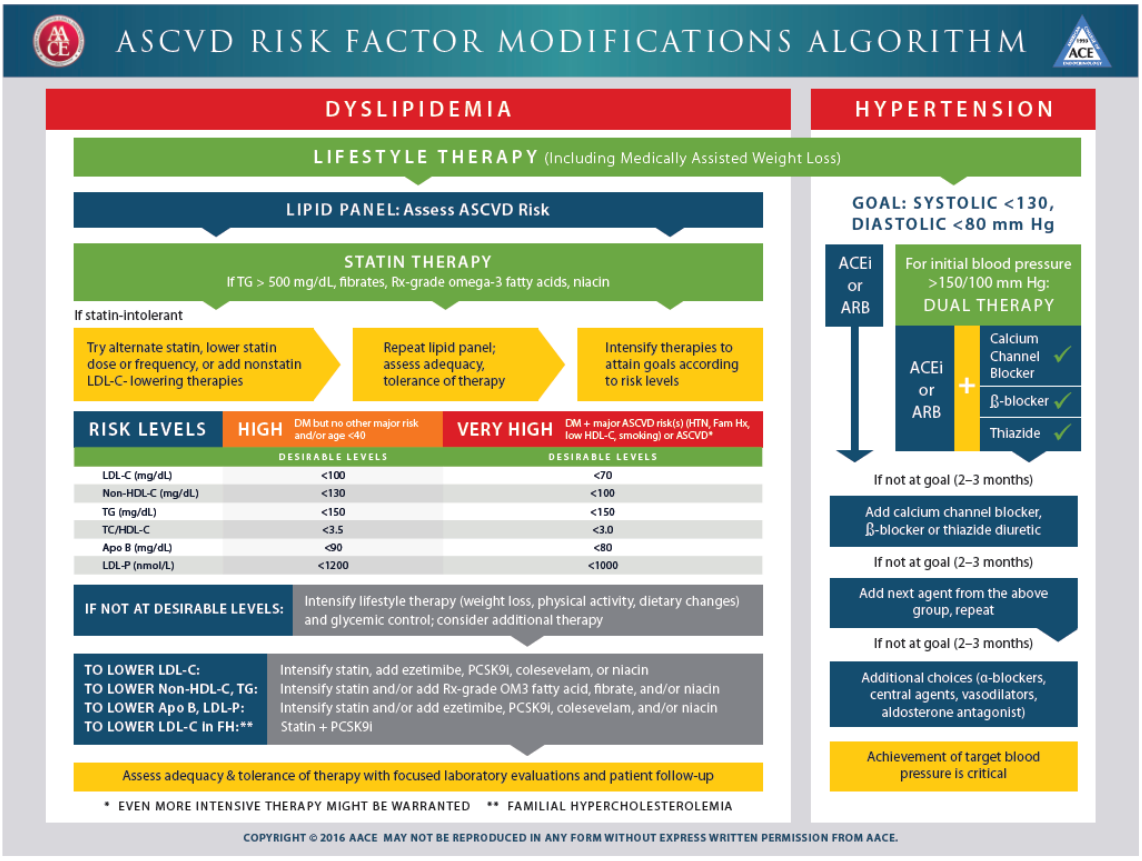
Secondary treatment goals may be considered, including apolipoprotein B (ApoB) <80 mg/dL and low-density lipoprotein particles (LDL-P) <1,000 nmol/L in patients with ASCVD or at least 1 major risk factor, and <90 mg/dL or <1,200 nmol/L in patients without ASCVD and no additional risk factors, respectively (Grade D; BEL 4).

• R27. Pharmacologic therapy should be used to achieve lipid targets unresponsive to therapeutic lifestyle changes alone (Grade A; BEL 1).

Statins are the treatment of choice in the absence of contraindications. Statin dosage should always be adjusted to achieve LDL-C and non-HDL-C goals (Table 7) unless limited by adverse effects or intolerance (Grade A; BEL 1).

Combining the statin with a bile acid sequestrant, niacin, and/or cholesterol absorption inhibitor should be considered when the desired target cannot be achieved with the statin alone; these agents may be used instead of statins in cases of statin-related adverse events or intolerance (Grade C; BEL 3).

In patients who have LDL-C levels at goal but triglyceride concentrations ≥200 mg/dL and low HDL-C (<35 mg/dL), treatment protocols including the use of fibrates, niacin, or high-dose omega-3 fatty acids may be used to achieve the non-HDL-C goal (Table 7) (Grade B; BEL 2).
High-dose omega-3 fatty acids, fibrates, or niacin may also be used to reduce triglyceride levels ≥500 mg/dL (Grade C; BEL 3).



T2D Algorithm, Executive Summary, *Endocr Pract.* 2016;22(No. 1) 111

Figure 6: AACE/ACE algorithm for treatment of cardiovascular risk factors

3.2.3.3 *ADA 2016*

For patients of all ages with diabetes and atherosclerotic cardiovascular disease, high-intensity statin therapy should be added to lifestyle therapy.A

For patients with diabetes aged <40 years with additional atherosclerotic cardiovascular disease risk factors, consider using moderate-intensity or high-intensity statin and lifestyle therapy. C

For patients with diabetes aged 40–75 years without additional atherosclerotic cardiovascular disease risk factors, consider using moderate-intensity statin and lifestyle therapy. A

For patients with diabetes aged 40–75 years with additional atherosclerotic cardiovascular disease risk factors, consider using high-intensity statin and lifestyle therapy. B

For patients with diabetes aged >75 years without additional atherosclerotic cardiovascular disease risk factors, consider using moderate-intensity statin therapy and lifestyle therapy. B

For patients with diabetes aged >75 years with additional atherosclerotic cardiovascular disease risk factors, consider using moderate-intensity or high-intensity statin therapy and lifestyle therapy. B

In clinical practice, providers may need to adjust intensity of statin therapy based on individual patient response to medication (e.g., side effects, tolerability, LDL cholesterol levels). E

The addition of ezetimibe to moderate-intensity statin therapy has been shown to provide additional cardiovascular benefit compared with moderate-intensity statin therapy alone and may be considered for patients with a recent acute coronary syndrome with LDL cholesterol ≥50 mg/dL (1.3 mmol/L) or for those patients who cannot tolerate high-intensity statin therapy. A

Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. A

However, therapy with statin and fenofibrate may be considered for men with both triglyceride level ≥204 mg/dL (2.3 mmol/L) and HDL cholesterol level ≤34 mg/dL (0.9 mmol/L). B

Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone and may increase the risk of stroke and is not generally recommended. A

Table 8.2—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy	Moderate-intensity statin therapy
Lowers LDL cholesterol by ≥50%	Lowers LDL cholesterol by 30% to <50%
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 2–4 mg

*Once-daily dosing.

Figure 7: ADA 2016 high-intensity and moderate-intensity statins

Elderly

Older adults who are functional and cognitively intact and have significant life expectancy may receive diabetes care with goals similar to those developed for younger adults. E

Other cardiovascular risk factors should be treated in older adults with consideration of the time frame of benefit and the individual patient. Treatment of hypertension is indicated in virtually all older adults, and lipid-lowering and aspirin therapy may benefit those with life expectancy at least equal to the time frame of primary or secondary prevention trials. E

When palliative care is needed in older adults with diabetes, strict blood pressure control may not be necessary, and withdrawal of therapy may be appropriate. Similarly, the intensity of lipid management can be relaxed, and withdrawal of lipid-lowering therapy may be appropriate. E

Table 10.1—Framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes

Patient characteristics/ health status	Rationale	Reasonable A1C goal‡	Fasting or preprandial glucose	Bedtime glucose	Blood pressure	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.5% (58 mmol/mol)	90–130 mg/dL (5.0–7.2 mmol/L)	90–150 mg/dL (5.0–8.3 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0% (64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	<8.5%† (69 mmol/mol)	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)	<150/90 mmHg	Consider likelihood of benefit with statin (secondary prevention more so than primary)

This represents a consensus framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes. The patient characteristic categories are general concepts. Not every patient will clearly fall into a particular category. Consideration of patient and caregiver preferences is an important aspect of treatment individualization. Additionally, a patient's health status and preferences may change over time. ADL, activities of daily living.
‡A lower A1C goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden.
*Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. By "multiple," we mean at least three, but many patients may have five or more (27).
**The presence of a single end-stage chronic illness, such as stage 3–4 congestive heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy.
†A1C of 8.5% (69 mmol/mol) equates to an estimated average glucose of ~200 mg/dL (11.1 mmol/L). Looser A1C targets above 8.5% (69 mmol/mol) are not recommended as they may expose patients to more frequent higher glucose values and the acute risks from glycosuria, dehydration, hyperglycemic hyperosmolar syndrome, and poor wound healing.

Figure 8: ADA 2016 treatment targets in the elderly

3.2.3.4 *CDA 2013*

Statin therapy should be used to reduce cardiovascular risk in adults with type 1 or type 2 diabetes with any of the following features:

- **Clinical macrovascular disease [Grade A, Level 1 (50)]**
- **Age ≥40 years [Grade A Level 1 (50,51), for type 2 diabetes; Grade D, Consensus for type 1 diabetes]**
- **Age <40 years and 1 of the following:**
  - **Diabetes duration >15 years and age >30 years [Grade D, Consensus]**
  - **Microvascular complications [Grade D, Consensus]**
  - **Warrants therapy based on the presence of other risk factors according to the 2012 Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia (53). [Grade D, Consensus]**

<u>Dyslipididemia</u>

For patients with indications for lipid-lowering therapy (see Vascular Protection chapter, p. S100), treatment should be initiated with a statin [Grade A, Level 1 (26,28), to achieve LDL-C ≤2.0 mmol/L [Grade C, Level 3 (40)].

In patients achieving goal LDL-C with statin therapy, the routine addition of fibrates or niacin for the sole purpose of further reducing CV risk should not be used [Grade A, Level 1 (54,55)].

For individuals not at LDL-C target despite statin therapy as described above, a combination of statin therapy with second-line agents may be used to achieve the LDL-C goal [Grade D, Consensus].
For those who have serum TG >10.0 mmol/L, a fibrate should be used to reduce the risk of pancreatitis (Grade D, Consensus) while also optimizing glycemic control and implementing lifestyle interventions (e.g. weight loss, optimal dietary strategies, reduction of alcohol).

Abbreviations: apo B, apolipoprotein B; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride

3.2.3.5 *DOMUS MEDICA 2015*

Aim for an LDL <100 mg / dL. (Grade 1C)

Consider a target with a lower LDL - value of < 70 mg / dl in the presence of cardiovascular diseases. (Grade 1C)

Accept a decrease of 30-40 % of the LDL - cholesterol if these target values are difficult to achieve . (GPP)

3.2.3.6 *EASD/ADA 2015*

No recommendations

3.2.3.7 *ESC/EASD 2013*

Dyslipidaemia in diabetes			
Recommendations	**Class [a]**	**Level [b]**	**Ref. [c]**
Statin therapy is recommended in patients with T1DM and T2DM at very high-risk (i.e. if combined with documented CVD, severe CKD or with one or more CV risk factors and/or target organ damage) with an LDL-C target of <1.8 mmol/L (<70 mg/dL) or at least a ≥50% LDL-C reduction if this target goal cannot be reached.	I	A	227, 234, 238
Statin therapy is recommended in patients with T2DM at high risk (without any other CV risk factor and free of target organ damage) with an LDL-C target of <2.5 mmol/L (<100 mg/dL).	I	A	227, 234
Statins may be considered in T1DM patients at high risk for cardiovascular events irrespective of the basal LDL-C concentration.	IIb	C	-
It may be considered to have a secondary goal of non–HDL-C <2.6 mmol/L (<100 mg/dL) in patients with DM at very high risk and of <3.3 mmol/L (<130 mg/dL) in patients at high risk.	IIb	C	-
Intensification of statin therapy should be considered before the introduction of combination therapy with the addition of ezetimibe.	IIa	C	-
The use of drugs that increase HDL-C to prevent CVD in T2DM is not recommended.	III	A	251, 252, 256

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

Figure 9: recommendations of ESC/EASD 2013 concerning dyslipidemia in diabetes

DM and coronary artery disease

Table 10 Summary of treatment targets for managing patients with diabetes mellitus or impaired glucose tolerance and coronary artery disease

Blood pressure (mmHg) In case of nephropathy	<140/85 Systolic <130
Glycaemic control HbA_{1c} (%)[a]	Generally <7.0 (53 mmol/mol) On an individual basis <6.5–6.9% (48–52 mmol/mol)
Lipid profile mmol/l (mg/dL) LDL-cholesterol	Very high risk patients <1.8 mmol/L (<70 mg/dL) or reduced by at least 50% High risk patients <2.5 mmol/L (<100mg/dL)
Platelet stabilization	Patients with CVD and DM ASA 75–160 mg/day
Smoking Passive smoking	Cessation obligatory None
Physical activity	Moderate to vigorous ≥150 min/week
Weight	Aim for weight stabilization in the overweight or obese DM patients based on calorie balance, and weight reduction in subjects with IGT to prevent development of T2DM
Dietary habits Fat intake (% of dietary energy) Total Saturated Monounsaturated fatty acids Dietary fibre intake	 <35% <10% >10% >40 g/day (or 20 g/1000 Kcal/day)

CVD = cardiovascular disease; DM = diabetes mellitus; HbA_{1c} = glycated haemoglobin A_{1c}; IGT = impaired glucose tolerance; LDL = low density lipoprotein; T2DM = type 2 diabetes mellitus.
[a]Diabetes Control and Complication Trial standard.

Figure 10: recommendations of ESC/EASD 2013 concerning treatment targets

Multifactorial risk management in diabetes			
Recommendations	**Class [a]**	**Level [b]**	**Ref. [c]**
Risk stratification should be considered as part of the evaluation of patients with DM and IGT.	IIa	C	-
Cardiovascular risk assessment is recommended in people with DM and IGT as a basis for multifactorial management.	I	B	156, 213
Treatment targets, as listed in Table 10, should be considered in patients with DM and IGT with CVD.	IIa	B	156, 213

CVD = cardiovascular disease; DM = diabetes mellitus; HbA_{1c} = glycated haemoglobin A1c; IGT = impaired glucose tolerance; LDL = low density lipoprotein; T2DM = type 2 diabetes mellitus.
[a]Diabetes Control and Complication Trial standard.

Figure 11: recommendations of ESC/EASD 2013 concerning multifactorial risk management

3.2.3.8 *NICE 2015*

No recommendations

3.2.3.9 *ERBP 2015*

DM and CKD (eGFR <45mL/min)

We recommend starting a statin in patients with diabetes and CKD stage 3b and 4 (1B).

We suggest a statin be considered in patients with diabetes and CKD stage 5 (2C).

We recommend against starting a statin in patients with diabetes and CKD stage 5D (1A).

There was no consensus in the guideline development group on whether or not statins should be stopped in patients with diabetes with CKD stage 5D.

We suggest fibrates can replace statins in patients with CKD stage 3b who do not tolerate statins (2B).

Doses of lipid-lowering agents should be adapted according to renal function (Table 8).

• As the doses in Table 8 should be considered maximal doses in patients with CKD, repetitive measurement of lipid levels does not add diagnostic or therapeutic value.
• For patients with CKD stage 5 or CKD stage 5D, patient preference and motivation to take another pill with its risk of side effects and limited expected benefit should guide management

Table 8. Dose recommendations of statins in patients with CKD stage 3b or higher (eGFR <45 mL/min). Adapted from Tonelli and Wanner [189].

Statin	Maximum dose when eGFR <45 mL/min
Lovastatin	No data
Fluvostatin	80 mg
Atorvastatin	20 mg
Rosuvastatin	10 mg
Simvastatin/ezetimibe	20/10 mg
Pravastatin	40 mg
Simvastatin	40 mg
Pitavastatin	2 mg

Figure 12: ERBP 2015 maximum dosage of statins in patients with CKD stage 3B or higher

3.2.4 Blood pressure Goals

3.2.4.1 *Summary*

The blood pressure targets for patients with diabetes, as recommended by the selected guidelines, is summarized in the table below.

	Systolic target value (mmHg)	Diastolic target value (mmHg)
CDA 2013	<130	<80
DOMUS MEDICA 2015	<140	<90
ADA 2016	<140	<90
	<130 (if young, albuminuria, + additional CVD risk) IF achievable without undue disease burden	<80 (if young, albuminuria, + additional CVD risk) IF achievable without undue disease burden
NICE 2015	<140	<80
	<130 (kidney, eye or cerebrovascular damage)	<80 (kidney, eye or cerebrovascular damage)
AACE/ACE 2015	130	80
	<120 Consider for some patients, provided this target can be reached safely without adverse effects	<80 Consider for some patients, provided this target can be reached safely without adverse effects
	More relaxed goals for frail patients with complicated comorbidities or those who have adverse medication effects	
ESC/EASD 2013	<140	<85

Table 34: Systolic and diastolic target values according to guidelines.

One guideline recommends to treat the healthy elderly to the same goals as other patients. However, treatment goals of <130/70 mmHg were not recommended. For elderly in very poor health, a treatment target of <150/90 mmHg was suggested (ADA 2016).

One guideline suggests against lower BP targets in diabetes patients with an eGFR <45 mL :min. The systolic blood pressure target in this population was <140 mmHg (ERBP 2015).

There were no specific recommendations concerning blood pressure targets in function of the duration of diabetes or in the obese.

3.2.4.2 *AACE/ACE 2015*

R22. The blood pressure goal for persons with DM or prediabetes should be individualized and should generally be about 130/80 mm Hg (Table 7) (Grade B; BEL 2).

A more intensive goal (e.g., <120/80 mm Hg) should be considered for some patients, provided this target can be reached safely without adverse effects from medication (Grade C; BEL 3).

More relaxed goals may be considered for frail patients with complicated comorbidities or those who have adverse medication effects (Grade D; BEL 4).

3.2.4.3 *ADA 2016*

Systolic Targets

- **People with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg. A**
- **Lower systolic targets, such as 130 mmHg, may be appropriate for certain individuals with diabetes, such as younger patients, those with albuminuria, and/or those with hypertension and one or more additional atherosclerotic cardiovascular disease risk factors, if they can be achieved without undue treatment burden. C**

Diastolic Targets c

- **Individuals with diabetes should be treated to a diastolic blood pressure goal of <90 mmHg. A**
- **Lower diastolic targets, such as <80 mmHg, may be appropriate for certain individuals with diabetes, such as younger patients, those with albuminuria, and/or those with hypertension and one or more additional atherosclerotic cardiovascular disease risk factors, if they can be achieved without undue treatment burden. B**

Treatment

In older adults, pharmacological therapy to achieve treatment goals of <130/70 mmHg is not recommended; treating to systolic blood pressure 130 mmHg has not been shown to improve cardiovascular outcomes and treating to diastolic blood pressure <70 mmHg has been associated with higher mortality. C

Elderly

Older adults who are functional and cognitively intact and have significant life expectancy may receive diabetes care with goals similar to those developed for younger adults. E

Other cardiovascular risk factors should be treated in older adults with consideration of the time frame of benefit and the individual patient. Treatment of hypertension is indicated in virtually all older adults, and lipid-lowering and aspirin therapy may benefit those with life expectancy at least equal to the time frame of primary or secondary prevention trials. E

When palliative care is needed in older adults with diabetes, strict blood pressure control may not be necessary, and withdrawal of therapy may be appropriate. Similarly, the intensity of lipid management can be relaxed, and withdrawal of lipid-lowering therapy may be appropriate. E

Table 10.1—Framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes

Patient characteristics/ health status	Rationale	Reasonable A1C goal‡	Fasting or preprandial glucose	Bedtime glucose	Blood pressure	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.5% (58 mmol/mol)	90–130 mg/dL (5.0–7.2 mmol/L)	90–150 mg/dL (5.0–8.3 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0% (64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	<8.5%† (69 mmol/mol)	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)	<150/90 mmHg	Consider likelihood of benefit with statin (secondary prevention more so than primary)

This represents a consensus framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes. The patient characteristic categories are general concepts. Not every patient will clearly fall into a particular category. Consideration of patient and caregiver preferences is an important aspect of treatment individualization. Additionally, a patient's health status and preferences may change over time. ADL, activities of daily living.
‡A lower A1C goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden.
*Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. By "multiple," we mean at least three, but many patients may have five or more (27).
**The presence of a single end-stage chronic illness, such as stage 3–4 congestive heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy.
†A1C of 8.5% (69 mmol/mol) equates to an estimated average glucose of ~200 mg/dL (11.1 mmol/L). Looser A1C targets above 8.5% (69 mmol/mol) are not recommended as they may expose patients to more frequent higher glucose values and the acute risks from glycosuria, dehydration, hyperglycemic hyperosmolar syndrome, and poor wound healing.

Figure 13: ADA 2016 treatment targets in the elderly

3.2.4.4 *CDA 2013*

Persons with diabetes mellitus should be treated to attain SBP <130 mm Hg [Grade C, Level 3 (6,7)] and DBP <80 mm Hg [Grade B, Level 1 (8)]. (These target BP levels are the same as the BP treatment thresholds). Combination therapy using 2 first-line agents may also be considered as initial treatment of hypertension [Grade C, Level 3 (9,10)] if SBP is 20 mm Hg above target or if DBP is 10 mm Hg above target. However, caution should be exercised in patients in whom a substantial fall in BP is more likely or poorly tolerated (e.g. elderly patients, patients with autonomic neuropathy).

For persons with cardiovascular or kidney disease, including microalbuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy [Grade A, Level 1A (11e14)].

For persons with diabetes and hypertension not included in the above recommendation, appropriate choices include (in alphabetical order): ACE inhibitors [Grade A, Level 1A (15)], ARBs

[Grade A, Level 1A (12)], dihydropyridine CCBs [Grade A, Level 1A (15)], and thiazide/thiazide-like diuretics [Grade A, Level 1A (15)].

If target BP levels are not achieved with standard dose monotherapy, additional antihypertensive therapy should be used [Grade D, Consensus]. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to hydrochlorothiazide [Grade A, Level 1A (16)].

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.

3.2.4.5 *DOMUS MEDICA 2015*

Aim for a systolic blood pressure < 140 mmHg and a diastolic blood pressure < 90 mm Hg in all people with diabetes . (Grade 1B)

In the pursuit of lower values, the risk of side effects such as hypotension and syncope increase. If there is an increased risk of CVA (e.g. a history of CVA or TIA), an even lower systolic blood pressure (<130 mmHg) may be targeted, provided that this can be achieved without, or with acceptable adverse effects.

3.2.4.6 *EASD/ADA 2015*

No recommendations

3.2.4.7 *ESC/EASD 2013*

Blood pressure control in diabetes			
Recommendations	**Class [a]**	**Level [b]**	**Ref. [c]**
Blood pressure control is recommended in patients with DM and hypertension to lower the risk of cardiovascular events.	I	A	189–191, 193–195
It is recommended that a patient with hypertension and DM is treated in an individualized manner, targeting a blood pressure of <140/85 mmHg.	I	A	191–193, 195
It is recommended that a combination of blood pressure lowering agents is used to achieve blood pressure control.	I	A	192–195, 205–207
A RAAS blocker (ACE-I or ARB) is recommended in the treatment of hypertension in DM, particularly in the presence of proteinuria or micro-albuminuria.	I	A	200, 205–207
Simultaneous administration of two RAAS blockers should be avoided in patients with DM.	III	B	209, 210

ACE-I = angiotensin converting enzyme-inhibitors; ARB = angiotensin receptor blockers; DM = diabetes mellitus; RAAS = renin angiotensin aldosterone system.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

Figure 14: ESC/EASD 2013 blood pressure targets

3.2.4.8 *NICE 2015*

Monitor blood pressure every 1–2 months, and intensify therapy if the person is already on antihypertensive drug treatment, until the blood pressure is consistently below 140/80 mmHg (below 130/80 mmHg if there is kidney, eye or cerebrovascular damage). [2009]

Provide lifestyle advice (see section 5.1.6 in this guideline and the lifestyle interventions section in 'Hypertension in adults' [NICE guideline CG127]) if blood pressure is confirmed as being consistently above 140/80 mmHg (or above 130/80 mmHg if there is kidney, eye or cerebrovascular damage). [2009]

Add medications if lifestyle advice does not reduce blood pressure to below 140/80 mmHg (below 130/80 mmHg if there is kidney, eye or cerebrovascular damage). [2009]

3.2.4.9 *ERBP 2015*

In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m2), should we aim at lower blood pressure targets than in the general population?

We suggest against applying lower blood pressure targets in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m2) than in the general population (2C).

We suggest that in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/ 1.73 m2) but without proteinuria, all blood pressure-lowering drugs can be used equally to lower blood pressure (2C).

Blood pressure should be carefully titrated to a target <140 mmHg SBP, while monitoring tolerance and avoiding side effects.

- *Patients with diabetes and CKD stage 3b or higher might suffer from autonomic dysfunction and are thus more prone to complications associated with sudden hypotension.*
- *A diastolic blood pressure that is too low can jeopardize coronary perfusion.*

3.3 GLP-1 receptor agonists

3.3.1 Summary

3.3.1.1 *What is the role of GLP-1 agonists?*

	CDA 2013 (LoE/GoR)	ADA 2016 EASD/ADA 2015 (LoE/GoR)	Domus Medica 2015 (LoE/GoR)	NICE 2015 (LoE/GoR)	AACE/ACE 2015 (LoE/GoR)
1st step	Metformin **(A for overweight patients; D, consensus for non-overweight patients)**	Metformin **(A)**	Metformin **(1A)**	Metformin **(no LoE/GoR)**	Metformin OR GLP-1, DPP4, SGLT2, acarbose if entry A1C <7.5% (58.5 mmol/mol) **(C, BEL 3)**
2nd step (intensification)	Choose from all other classes (**D, consensus**)	Second oral agent, GLP-1 or basal insulin **(A)**	Other oral agent **(1C)**	DPP4-i OR pioglitazone OR sulfonylurea **(no LoE/GoR)**	Immediately if HbA1c >7.5% (58.5 mmol/mol) Met + GLP-1 or SGLT2 OR DPP-4 **(C, BEL 3)**
3rd step (intensification)		Add third agent (choice between oral agents, GLP-1 or basal insulin) **(no LoE/GoR)**	Third oral drug, basal insulin, or GLP-1 **(1C)**	Met + DPP4+SU OR met+pio+SU OR met+ pio Or SU + SGLT-2 OR insulin **(no LoE/GoR)**	
4th step (intensification)		Metformin + basal insulin + prandial insulin OR GLP-1 **(no LoE/GoR)**		Met + SU + GLP-1 // GLP-1 + insulin ONLY if specialist care advice **(no LoE/GoR)**	

Table 35: Summary of 1st choice pharmacological agents for each step of diabetes treatment. In green: the steps in which a GLP-1 is a possible choice according to the guideline. LoE: level of evidence. GoR: grade of recommendation.

All selected guidelines suggest to base the choice of pharmacological agent on characteristics of the patient (comorbidities, preference, body weight, hypoglycemia risk) and the drug (effectiveness, risk of hypoglycemia, effect on body weight, adverse effects, contraindications, cost).

In one guideline, GLP-1 receptor agonists are a possible choice as monotherapy (AACE/ACE 2015).

In 3 guidelines, a GLP-1 agonist is a possible choice in duotherapy, after monotherapy with metformin (CDA 2013, ADA 2016, EASD/ADA 2015).

In one guideline, a GLP-1 agonist is only a possible therapeutic choice in triple therapy, after duotherapy with two oral agents (Domus Medica 2015).

In one guideline, a GLP-1 agonist is only a possible choice as the fourth step, after failed triple therapy (NICE 2015).

No guidelines give preference to one particular GLP-1 agonist above others.

	Glucose lowering	Hypoglycemia	Weight	Ease of use	Other endpoints	Adverse effects	Contra-indications	Cost
AACE/ACE 2015	Mild to moderate	Neutral	Loss	/	/	• GI adverse effects : Moderate • caution in perscribing information about pancreatitis	Exenatide not indicated in CrCl <30 mL/min	/
ADA 2016	Efficacy high	Low risk	Loss	• Injectable • Training requirements	Lowers some cardiovascular risk factors	• GI side effects (nausea, vomiting, diarrhea) • Elevated heart rate • ? acute pancreatitis • C-cell hyperplasia/ medullary thyroid tumors in animals	/	High
CDA 2013	1.0% expected decrease in A1c ; relative A1c lowering ↘↘ to ↘↘↘ Improved postprandial control	Negligible risk as monotherapy	Significant loss	Administration parenteral	/	• Nausea and vomiting • Rare cases of pancreatitis • Parafollicular cell hyperplasia	Contraindicated with personal/family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2	High
Domus Medica 2015	Effect on post-prandial glucose > fasting glucose	Few hypoglycemias	Loss	• Versus insulin : easy administration : less education,	• Blood pressure reduction • No data on	/	• Only when there is still endogenous beta cell activity • Not to be used in	High

				no dose titration • Versus insulin : limited need for self-monitoring	long-term effectiveness • No data on long-term safety • No data on hard endpoints/ diabetes-related complications		renal failure	
ERBP 2015	Evidence for beneficial effect	Evidence for beneficial effect	Evidence for beneficial effect	/	• All cause mortality : not investigated or insufficient data • CV events : not investigated or insufficient data	/	• Lixisenatide : dose adaptation in advanced CKD • Exenatide : avoid in advanced CKD • Liraglutide : dose adaptation in advanced CKD most likely not necessary	/

Table 36: Summary of advantages, disadvantages and considerations of GLP-1 RA

Five of the selected guidelines provided tables with a summary of the advantages, disadvantages and considerations of GLP-1 agonists (AACE/ACE 2015, ADA 2016, CDA 2013, Domus Medica 2015, ERBP 2015). None of these tables were part of a formal recommendation, so no levels of evidence or grades of recommendation were provided for these statements.

All of the 5 guidelines mentioned the effect of GLP-1 agonists on glucose lowering, hypoglycaemia, and weight as advantages.

The ease of use was mentioned in three guidelines, once as an advantage versus insulin (Domus Medica 2015), twice as a disadvantage versus oral antidiabtic medication (ADA 2016, CDA 2013).

The effect on cardiovascular risk factors (blood pressure) was mentioned as an advantage in two guidelines (ADA 2016, Domus Medica 2015). However, two guidelines cite the lack of data regarding effect on hard endpoints (CV events, mortality, diabetes-related complications) and long-term effectivity as a possible disadvantage (Domus Medica 2015, ERBP 2015).

Three guidelines discuss adverse events (AACE/ACE 2015, ADA 2016, CDA 2013). All mention GI disorders and an unsure risk of pancreatitis. Two guidelines mention thyroid disorder/cancer (ADA 2016, CDA 2013).

Three guidelines mention a contra-indication of GLP-1 agonists in renal failure (AACE/ACE 2015, Domus Medica 2015; ERBP 2015). The ERBP 2015 guideline makes a distinction between the different GLP-1 agonists (exenatide, liraglutide, and lixisenatide) regarding their use in chronic kidney disease.

Three guidelines mention the high cost of GLP-1 agonists as an disadvantage (ADA 2016, CDA 2013, Domus Medica 2015).

3.3.1.2 *What are rational combinations with other antidiabetics ?*

Two guidelines do not give preference to certain combinations with GLP-1 (CDA 2013, AACE/ACE 2015).

ADA 2016 and EASD/ADA 2015 recommend to combine metformin and a GLP-1 with an SU, a TZD or basal insulin. The combination of metformin, basal insulin and GLP-1 is also recommended (as a fourth step).

When combining GLP-1 and basal insulin, Domus Medica 2015 recommends to retain therapy with sulfonylurea and metformin.

NICE 2015 recommends the combination metformin + sulfonylurea + GLP-1. The combination GLP-1 + insulin is only recommended when specialist advice and ongoing support from a multidisciplinary team is available.

3.3.1.3 *How to monitor treatment with GLP-1 ?*

Most guidelines recommend to monitor glucose every 3-6 months, and to adjust medication if target is not reached (CDA 2015, ADA 2016, EASD/ADA 2015, AACE/ACE 2015).

NICE 2015 recommends to continue GLP-1 only if a reduction of HbA1c by at least 1% (11 mmol/mol) and a weight loss of at least 3% of initial body weight is reached within 6 months.

3.3.1.4 *Special groups – renal impairment*

For people with diabetes and CKD with a eGFR <45 mL/min, the ERBP 2015 guideline recommends metformin in a first step, in a dose adjusted to renal function (1500-850 mg per day in CKD-3, 500 mg/day in CKD-4, careful consideration in CKD-5).

As a second step, adding a drug with a low risk for hypoglycemia is recommended. This could be a GLP-1 receptor agonist.

Dose adjustments are necessary with exenatide and lixisenatide from CKD stage 2 (<90 mL/min) on. Exenatide is to be avoided from CKD stage 4 (<30 mL/min) on.

3.3.1.5 *Special groups – other*

There were no specific recommendations concerning GLP-1 agonist use in the elderly, in function of the duration of diabetes, in diabetics with comorbidity, or in the obese.

3.3.2 AACE/ACE 2015

R16. Pharmacotherapy for T2D should be prescribed based on suitability for the individual patient's characteristics (Grade D; BEL 4). As shown in Table 9, antihyperglycemic agents vary in their impact on FPG, PPG, weight, and insulin secretion or sensitivity, as well as the potential for hypoglycemia and other adverse effects. The initial choice of an agent involves comprehensive patient assessment including a glycemic profile obtained by self-monitoring of blood glucose (SMBG) and the patient's A1C, weight, and presence of comorbidities. Minimizing the risks of hypoglycemia and weight gain are priorities.

• R17. Details about the effects of and rationale for available antihyperglycemic agents can be found in the 2015 AACE Comprehensive Diabetes

Management Algorithm Consensus Statement (4). The AACE recommends initiating therapy with metformin, a glucagon-like peptide 1 (GLP1) receptor agonist, a dipeptidyl peptidase 4 (DPP-4) inhibitor, a sodium glucose cotransporter 2 (SGLT2) inhibitor, or an α-glucosidase inhibitor for patients with an entry A1C <7.5% (Grade C; BEL 3). A TZD, sulfonylurea, or glinide may be considered as alternative therapies but should be used with caution due to side-effect profiles (Grade C; BEL 3). For patients with entry A1C levels >7.5%, the AACE recommends initiating treatment with metformin (unless contraindicated) plus a second agent, with preference given to agents with a low potential for hypoglycemia that are weight neutral or associated with weight loss (Grade C; BEL 3). This includes GLP-1 receptor agonists, SGLT2 inhibitors, or DPP-4 inhibitors as the preferred second agents; TZDs and basal insulin may be considered as alternatives.

Colesevelam, bromocriptine, or an α-glucosidase inhibitor have limited glucose-lowering potential but also carry a low risk of adverse effects and may be useful for glycemic control in some situations (Grade C; BEL 3). Sulfonylureas and glinides are considered the least desirable alternatives due to the risk of hypoglycemia (Grade B; BEL 2). For patients with an entry A1C >9.0% who have symptoms of hyperglycemia, insulin therapy alone or in combination with metformin or other oral agents is recommended (Grade A; BEL 1). Pramlintide and the GLP-1 receptor agonists can be used as adjuncts to prandial insulin therapy to reduce postprandial hyperglycemia, A1C, and weight (Grade B; BEL 2). The longacting GLP-1 receptor agonists also reduce fasting glucose.

• R18. Insulin should be considered for T2D when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia (Grade A; BEL 1).

Therapy with long-acting basal insulin should be the initial choice in most cases (Grade C; BEL 3). The insulin analogs glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because analog insulins are associated with less hypoglycemia (Grade C; BEL 3). When control of postprandial hyperglycemia is needed, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or inhaled insulin) over regular human insulin because the former have a more rapid onset and offset of action and are associated with less hypoglycemia (Grade B; BEL 2).

Premixed insulin formulations (fixed combinations of shorter- and longer-acting components) of human or analog insulin may be considered for patients in whom adherence to more intensive insulin regimens is problematic; however, these preparations have reduced dosage flexibility and may increase the risk of hypoglycemia compared with basal insulin or basal-bolus regimens (Grade B; BEL 2). Basal-bolus insulin regimens are flexible and recommended for intensive insulin therapy (Grade B; BEL 3).

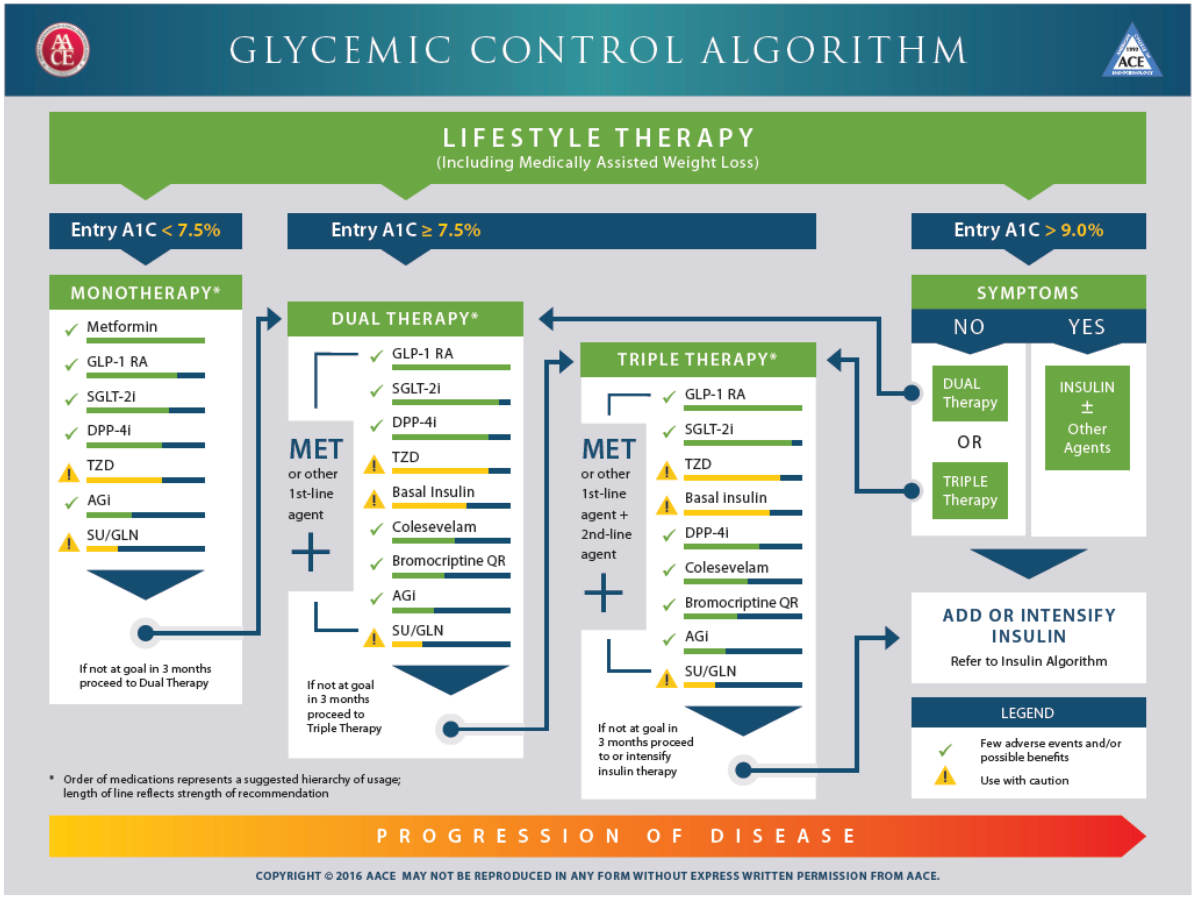
• R19. Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals (e.g., every 3 months) when treatment goals are not achieved or maintained (Grade C; BEL 3). The 2015 AACE algorithm outlines treatment choices on the basis of the A1C level (4 [EL 4; NE]).

Table 9
Effects of Diabetes Drug Action[a]

	Met	GLP1RA	SGLT2I	DPP4I	TZD	AGI	Coles	BCR-QR	SU/Glinide	Insulin	Pram
FPG lowering	**Moderate**	**Mild to moderate[b]**	**Moderate**	Mild	**Moderate**	Neutral	Mild	Neutral	**SU: moderate** Glinide: mild	**Moderate to marked (basal insulin or premixed)**	Mild
PPG lowering	Mild	**Moderate to marked**	Mild	**Moderate**	Mild	**Moderate**	Mild	Mild	**Moderate**	**Moderate to marked (short/ rapid-acting insulin or premixed)**	**Moderate to marked**
NAFLD benefit	Mild	Mild	Neutral	Neutral	**Moderate**	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
Hypoglycemia	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	*SU: moderate to severe Glinide: mild to moderate*	*Moderate to severe, especially with short/rapid-acting or premixed*	Neutral
Weight	**Slight loss**	**Loss**	**Loss**	Neutral	*Gain*	Neutral	Neutral	Neutral	*Gain*	*Gain*	**Loss**
Renal impairment/ GU	*Contraindicated in stage 3B, 4, 5 CKD*	*Exenatide not indicated in CrCl <30 mL/ min*	*GU infection risk*	Dose adjustment may be necessary (except linagliptin)	*May worsen fluid retention*	Neutral	Neutral	Neutral	*Increased hypoglycemia risk*	*Increased risks of hypoglycemia and fluid retention*	Neutral
GI adverse effects	*Moderate*	*Moderate (caution in PIs about pancreatitis)*	Neutral	Neutral *(caution in PIs about pancreatitis)*	Neutral	*Moderate*	Mild	*Moderate*	Neutral	Neutral	*Moderate*
CHF	Neutral	Neutral	Neutral	Neutral *(caution: possibly increased CHF hospitalization risk in CV safety trial)*	*Moderate*	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Possible benefit	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Safe	?	Neutral	Neutral
Bone	Neutral	Neutral	*Bone loss*	Neutral	*Moderate bone loss*	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

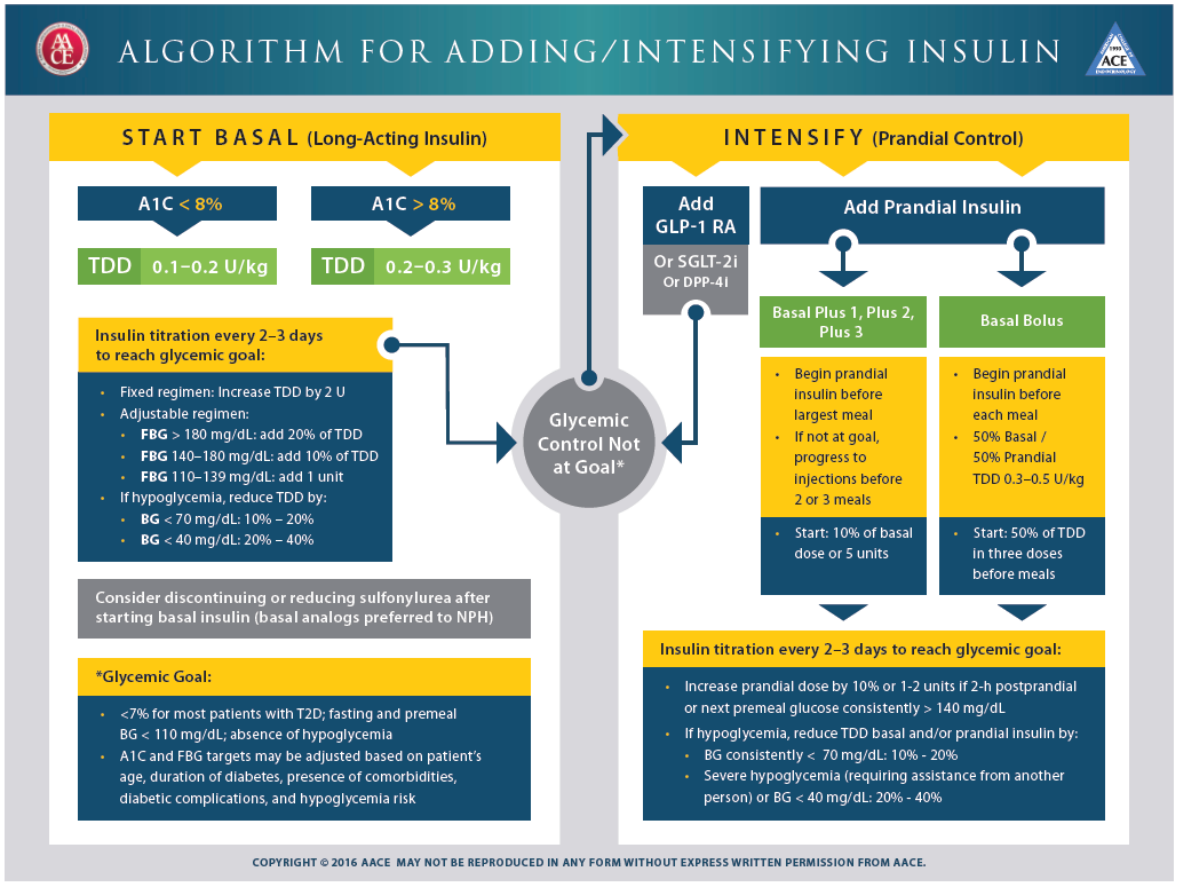
Abbreviations: AGI = α-glucosidase inhibitors; BCR-QR = bromocriptine quick release; CHF = congestive heart failure; CKD = chronic kidney disease; Coles = colesevelam; CrCl = creatinine clearance; CV = cardiovascular; DPP4I = dipeptidyl peptidase 4 inhibitors; FPG = fasting plasma glucose; GI = gastrointestinal; GLP1RA = glucagon-like peptide 1 receptor agonists; GU = genitourinary; Met = metformin; NAFLD = nonalcoholic fatty liver disease; PI = prescribing information; PPG = postprandial glucose; SGLT2I = sodium-glucose cotransporter 2 inhibitors; SU = sulfonylureas; TZD = thiazolidinediones.
[a] Boldface type highlights a benefit or potential benefit; italic type highlights adverse effects.
[b] Mild: albiglutide and exenatide; moderate: dulaglutide, exenatide extended release, and liraglutide.

Figure 15: AACE/ACE 2015 comparative table of diabetes drug action



T2D Algorithm, Executive Summary, *Endocr Pract.* 2016;22(No. 1) 109

Figure 16: AACE/ACE 2015 algorithm for glycemic control



110 T2D Algorithm, Executive Summary, *Endocr Pract.* 2016;22(No. 1)

Figure 17: AACE/ACE 2015 algorithm for adding/intensifying insulin

3.3.3 ADA 2016

Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes. A

Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes and markedly symptomatic and/or elevated blood glucose levels or A1C. E

If non-insulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target over 3 months, then add a second oral agent, a glucagon-like peptide 1 receptor agonist, or basal insulin. A

A patient-centered approach should be used to guide the choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, weight, comorbidities, hypoglycemia risk, and patient preferences. E

For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed. B

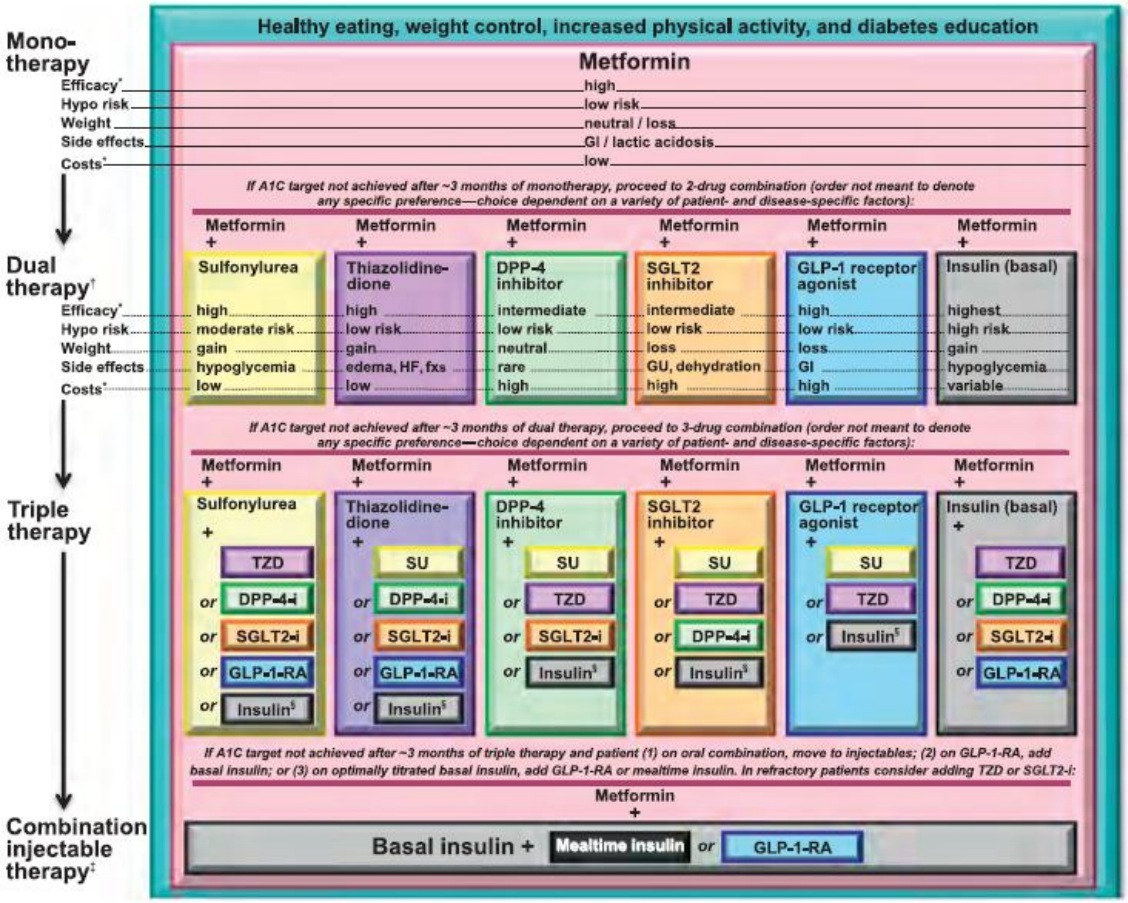


Figure 7.1—Antihyperglycemic therapy in type 2 diabetes: general recommendations (17). The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic therapy for patients with type 2 diabetes are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances). DPP-4-i, DPP-4 inhibitor; fxs, fractures; GI, gastrointestinal; GLP-1-RA, GLP-1 receptor agonist; GU, genitourinary; HF, heart failure; Hypo, hypoglycemia; SGLT2-i, SGLT2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. *See ref. 17 for description of efficacy categorization. †Consider starting at this stage when A1C is ≥9% (75 mmol/mol). ‡Consider starting at this stage when blood glucose is ≥300–350 mg/dL (16.7–19.4 mmol/L) and/or A1C is ≥10–12% (86–108 mmol/mol), especially if symptomatic or catabolic features are present, in which case basal insulin + mealtime insulin is the preferred initial regimen. §Usually a basal insulin (NPH, glargine, detemir, degludec). Adapted with permission from Inzucchi et al. (17).

Figure 18: ADA 2016 algorithm for antihyperglycemic therapy

Table 7.1—Properties of available glucose-lowering agents in the U.S. and Europe that may guide individualized treatment choices in patients with type 2 diabetes (17)

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
Biguanides	• Metformin	Activates AMP-kinase (? other)	• ↓ Hepatic glucose production	• Extensive experience • No hypoglycemia • ↓ CVD events (UKPDS)	• Gastrointestinal side effects (diarrhea, abdominal cramping) • Vitamin B_{12} deficiency • Contraindications: CKD, acidosis, hypoxia, dehydration, etc. • Lactic acidosis risk (rare)	Low
Sulfonylureas	2nd Generation • Glyburide/ glibenclamide • Glipizide • Gliclazide† • Glimepiride	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk (UKPDS)	• Hypoglycemia • ↑ Weight	Low
Meglitinides (glinides)	• Repaglinide • Nateglinide	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• ↓ Postprandial glucose excursions • Dosing flexibility	• Hypoglycemia • ↑ Weight • Frequent dosing schedule	Moderate
TZDs	• Pioglitazone‡ • Rosiglitazone§	Activates the nuclear transcription factor PPAR-γ	• ↑ Insulin sensitivity	• No hypoglycemia • Durability • ↑ HDL-C • ↓ Triglycerides (pioglitazone) • ? ↓ CVD events (PROactive, pioglitazone)	• ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosiglitazone) • ? ↑ MI (meta-analyses, rosiglitazone)	Low
α-Glucosidase inhibitors	• Acarbose • Miglitol	Inhibits intestinal α-glucosidase	• Slows intestinal carbohydrate digestion/absorption	• No hypoglycemia • ↓ Postprandial glucose excursions • ? ↓ CVD events (STOP-NIDDM) • Nonsystemic	• Generally modest A1C efficacy • Gastrointestinal side effects (flatulence, diarrhea) • Frequent dosing schedule	Low to moderate
DPP-4 inhibitors	• Sitagliptin • Vildagliptin† • Saxagliptin • Linagliptin • Alogliptin	Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations	• ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent)	• No hypoglycemia • Well tolerated	• Angioedema/urticaria and other immune-mediated dermatological effects • ? Acute pancreatitis • ? ↑ Heart failure hospitalizations	High
Bile acid sequestrants	• Colesevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production	• ? ↓ Hepatic glucose production • ? ↑ Incretin levels	• No hypoglycemia • ↓ LDL-C	• Generally modest A1C efficacy • Constipation • ↑ Triglycerides • May ↓ absorption of other medications	High
Dopamine-2 agonists	• Bromocriptine (quick release)§	Activates dopaminergic receptors	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• No hypoglycemia • ? ↓ CVD events (Cycloset Safety Trial)	• Generally modest A1C efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis	High

Continued on p. S56

Figure 19: ADA 2016 comparative table of antidiabetic drugs

Table 7.1—Continued

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
SGLT2 inhibitors	• Canagliflozin • Dapagliflozin‡ • Empagliflozin	Inhibits SGLT2 in the proximal nephron	• Blocks glucose reabsorption by the kidney, increasing glucosuria	• No hypoglycemia • ↓ Weight • ↓ Blood pressure • Effective at all stages of type 2 diabetes • Associated with lower CVD event rate and mortality in patients with CVD (EMPA-REG OUTCOME)	• Genitourinary infections • Polyuria • Volume depletion/hypotension/ dizziness • ↑ LDL-C • ↑ Creatinine (transient) • DKA, urinary tract infections leading to urosepsis, pyelonephritis	High
GLP-1 receptor agonists	• Exenatide • Exenatide extended release • Liraglutide • Albiglutide • Lixisenatide† • Dulaglutide	Activates GLP-1 receptors	• ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent) • Slows gastric emptying • ↑ Satiety	• No hypoglycemia • ↓ Weight • ↓ Postprandial glucose excursions • ↓ Some cardiovascular risk factors	• Gastrointestinal side effects (nausea/vomiting/diarrhea) • ↑ Heart rate • ? Acute pancreatitis • C-cell hyperplasia/medullary thyroid tumors in animals • Injectable • Training requirements	High
Amylin mimetics	• Pramlintide§	Activates amylin receptors	• ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety	• ↓ Postprandial glucose excursions • ↓ Weight	• Generally modest A1C efficacy • Gastrointestinal side effects (nausea/vomiting) • Hypoglycemia unless insulin dose is simultaneously reduced • Injectable • Frequent dosing schedule • Training requirements	High
Insulins	• Rapid-acting analogs - Lispro - Aspart - Glulisine - Inhaled insulin • Short-acting - Human Regular • Intermediate-acting - Human NPH • Basal insulin analogs - Glargine - Detemir - Degludec† • Premixed (several types)	Activates insulin receptors	• ↑ Glucose disposal • ↓ Hepatic glucose production • Suppresses ketogenesis	• Nearly universal response • Theoretically unlimited efficacy • ↓ Microvascular risk (UKPDS)	• Hypoglycemia • Weight gain • ? Mitogenic effects • Training requirements • Patient reluctance • Injectable (except inhaled insulin) • Pulmonary toxicity (inhaled insulin)	Moderate to high#

CKD, chronic kidney disease; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (31); GIP, glucose-dependent insulinotropic peptide; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; MI, myocardial infarction; PPAR-γ, peroxisome proliferator–activated receptor γ; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events (32); STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (33); TZD, thiazolidinedione; UKPDS, UK Prospective Diabetes Study (34,35). Cycloset trial of quick-release bromocriptine (36). *Cost is based on lowest-priced member of the class (see ref. 17). †Not licensed in the U.S. ‡Initial concerns regarding bladder cancer risk are decreasing after subsequent study. §Not licensed in Europe for type 2 diabetes. #Cost is highly dependent on type/brand (analogs > human insulins) and dosage. Adapted with permission from Inzucchi et al. (17).

Figure 20: ADA 2016 comparative table of antidiabetic drugs

3.3.4 CDA 2013

In people with type 2 diabetes, if glycemic targets are not achieved using lifestyle management within 2 to 3 months, antihyperglycemic agent therapy should be initiated [Grade A, Level 1A (3)]. Metformin may be used at the time of diagnosis, in conjunction with lifestyle management (Grade D, Consensus).

- **If A1C ≥8.5%, antihyperglycemic agents should be initiated concomitantly with lifestyle management, and consideration should be given to initiating combination therapy with 2 agents, one of which may be insulin (Grade D, Consensus).**
- **Individuals with symptomatic hyperglycemia and metabolic decompensation should receive an initial antihyperglycemic regimen containing insulin [Grade D, Consensus].**

Metformin should be the initial drug used [Grade A, Level 1A (26,80) for overweight patients; Grade D, Consensus for nonoverweight patients].

Other classes of antihyperglycemic agents, including insulin, should be added to metformin, or used in combination with each other, if glycemic targets are not met, taking into account the information in Figure 1 and Table 1 [Grade D, Consensus], and these adjustments to and/or additions of antihyperglycemic agents should be made in order to attain target A1C within 3 to 6 months [Grade D, Consensus].
Choice of pharmacological treatment agents should be individualized, taking into consideration [Grade D, Consensus]:

- **Patient characteristics:**
  - **Degree of hyperglycemia**
  - **Presence of comorbidities**
  - **Patient preference and ability to access treatments**
- **Properties of the treatment:**
  - **Effectiveness and durability of lowering BG**
  - **Risk of hypoglycemia**
  - **Effectiveness in reducing diabetes complications**
  - **Effect on body weight**
  - **Side effects**
  - **Contraindications**

When basal insulin is added to antihyperglycemic agents, long-acting analogues (detemir or glargine) may be used instead of intermediate-acting NPH to reduce the risk of nocturnal and symptomatic hypoglycemia [Grade A, Level 1A (19,78,79)].

When bolus insulin is added to antihyperglycemic agents, rapid-acting analogues may be used instead of regular insulin to improve glycemic control [Grade B, Level 2 (20)] and to reduce the risk of hypoglycemia [Grade D, Consensus)].

All individuals with type 2 diabetes currently using or starting therapy with insulin or insulin secretagogues should be counseled about the prevention, recognition and treatment of drug-induced hypoglycemia [Grade D, Consensus].

Table 1
Antihyperglycemic agents for use in type 2 diabetes

Class* and mechanism of action	Drug (brand name)	Expected† decrease in A1C	Relative† A1C lowering	Hypoglycemia	Other therapeutic considerations
Alpha-glucosidase inhibitor: inhibits pancreatic alpha-amylase and intestinal alpha-glucosidase	Acarbose (Glucobay) (7,81,82)	0.6%	↓	Negligible risk as monotherapy	• Not recommended as initial therapy in people with marked hyperglycemia (A1C ≥8.5%) • Weight neutral as monotherapy • GI side effects
Combined formulations	Avandamet (metformin + rosiglitazone)	0.8%	↓↓	Negligible risk as monotherapy	• See metformin, TZDs, DPP-4 inhibitors and sulfonylureas
	Janumet (metformin + sitagliptin) Jentadueto (metformin + linagliptin)	0.7%	↓↓		
	Avandaryl (glimepiride + rosiglitazone)	1.6%	↓↓↓	Moderate risk	
DPP-4 inhibitor: amplifies incretin pathway activation by inhibition of enzymatic breakdown of endogenous GLP-1 and GIP (45)	Sitagliptin (Januvia) Saxagliptin (Onglyza) Linagliptin (Trajenta)	0.7%	↓↓	Negligible risk as monotherapy	• Weight neutral • Improved postprandial control • Rare cases of pancreatitis
GLP-1 receptor agonist: activates incretin pathway by utilizing DPP-4 resistant analogue to GLP-1 (45–48)	Exenatide (Byetta) Liraglutide (Victoza)	1.0%	↓↓ to ↓↓↓	Negligible risk as monotherapy	• Improved postprandial control • Significant weight loss • Nausea and vomiting • Administration parenteral • Rare cases of pancreatitis • Parafollicular cell hyperplasia • Contraindicated with personal/family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2
Insulin: activates insulin receptors to regulate metabolism of carbohydrate, fat and protein (3,10,11,50,53,83–85)	**Bolus (prandial) insulins** *Rapid-acting analogues* Aspart (NovoRapid) Glulisine (Apidra) Lispro (Humalog) *Short-acting* Regular (Humulin-R, Novolin ge Toronto) **Basal insulins** *Intermediate-acting* NPH (Humulin-N, Novolin ge NPH) *Long-acting basal analogues* Detemir (Levemir) Glargine (Lantus) **Premixed insulins** Premixed Regular-NPH (Humulin 30/70; Novolin ge 30/70, 40/60, 50/50) Biphasic insulin aspart (NovoMix 30) Insulin lispro/lispro protamine suspension (Humalog Mix25, Mix50)	0.9%—1.1%	↓↓↓	Significant risk (hypoglycemia risk highest with regular and NPH insulin)	• Potentially greatest A1C reduction and no maximal dose • Numerous formulations and delivery systems (including subcutaneous-injectable) • Allows for regimen flexibility • When initiating insulin, consider adding bedtime long-acting basal analogue or intermediate-acting NPH to daytime oral antihyperglycemic agents (although other regimens can be used) • Basal-bolus regimen recommended if above fails to attain glycemic targets • Increased risk of weight gain relative to sulfonylureas and metformin

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Figure 21: CDA 2013 comparative table of antidiabetic drugs

Insulin secretagogue: activates sulfonylurea receptor on beta cell to stimulate endogenous insulin secretion	**Sulfonylureas**	0.8%	↓↓		• Relatively rapid BG-lowering response • All insulin secretagogues reduce glycemia similarly (except nateglinide, which is less effective) • Postprandial glycemia is especially reduced by meglitinides • Hypoglycemia and weight gain are especially common with glyburide • Consider using other class(es) of antihyperglycemic agents first in patients at high risk of hypoglycemia (e.g. the elderly, renal/hepatic failure) • If a sulfonylurea must be used in such individuals, gliclazide is associated with the lowest incidence of hypoglycemia (94) and glimepiride is associated with less hypoglycemia than glyburide (90)
	Glidazide (Diamicron, Diamicron MR, generic) (86,87)			Minimal/moderate risk	
	Glimepiride (Amaryl) (88–90)			Moderate risk	
	Glyburide (Diabeta, Euglucon, generic) (3)			Significant risk	
	(*Note:* Chlorpropamide and tolbutamide are still available in Canada but rarely used)				
	Meglitinides	0.7%			
	Nateglinide (Starlix) (91)		↓	Minimal/moderate risk	• Nateglinide and repaglinide are associated with less hypoglycemia than sulfonylureas due to their shorter duration of action allowing medication to be held when forgoing a meal
	Repaglinide (GlucoNorm) (92,93)		↓↓	Minimal/moderate risk	
Metformin: enhances insulin sensitivity in liver and peripheral tissues by activation of AMP-activated protein kinase	Glucophage, Glumetza, generic (52,95)	1.0%–1.5%	↓↓	Negligible risk as monotherapy	• Improved cardiovascular outcomes in overweight subjects • Contraindicated if CrCl/eGFR <30 mL/min or hepatic failure • Caution if CrCl/eGFR <60 mL/min • Weight neutral as monotherapy, promotes less weight gain when combined with other antihyperglycemic agents, including insulin • B12 deficiency (96) • GI side effects
Thiazolidinedione (TZD): enhances insulin sensitivity in peripheral tissues and liver by activation of peroxisome proliferator-activated receptor-gamma receptors (28–30,33,35,97–104)	Pioglitazone (Actos) Rosiglitazone (Avandia)	0.8%	↓↓	Negligible risk as monotherapy	• Longer duration of glycemic control with monotherapy compared to metformin or glyburide • Mild BP lowering • Between 6 and 12 weeks required to achieve full glycemic effect • Weight gain • May induce edema and/or congestive heart failure • Contraindicated in patients with known clinical heart failure or evidence of left ventricular dysfunction on echocardiogram or other heart imaging • Higher rates of heart failure when combined with insulin‡ • Rare occurrence of macular edema • Higher occurrence of fractures (29,30,33) • Possibility of increased risk of myocardial infarction with rosiglitazone (31,108) • Rare risk bladder cancer with pioglitazone (109)
Weight loss agent: inhibits lipase	Orlistat (Xenical) (105–107,110)	0.5%	↓	None	• Promote weight loss • Orlistat can cause diarrhea and other GI side effects

A1C, glycated hemoglobin; *BG*, blood glucose; *BP*, blood pressure; *CrCl*, creatinine clearance; *DPP-4*, dipeptidyl peptidase 4; *eGFR*, estimated glomerular filtration rate; *GI*, gastrointestinal; *GIP*, gastric inhibitory peptide; *GLP-1*, glucagon-like peptide 1; *AMP*, adenosine monophosphate.

Physicians should refer to the most recent edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and detailed prescribing information.

* Listed in alphabetical order.

† A1C percentage/relative reduction expected when agent from this class is added to metformin therapy (37,105,111) with exception of metformin where A1C percentage/relative reduction reflects expected monotherapy efficacy.

‡ Combining insulin with a TZD is not an approved indication in Canada.

Figure 22: CDA 2013 comparative table of antidiabetic drugs

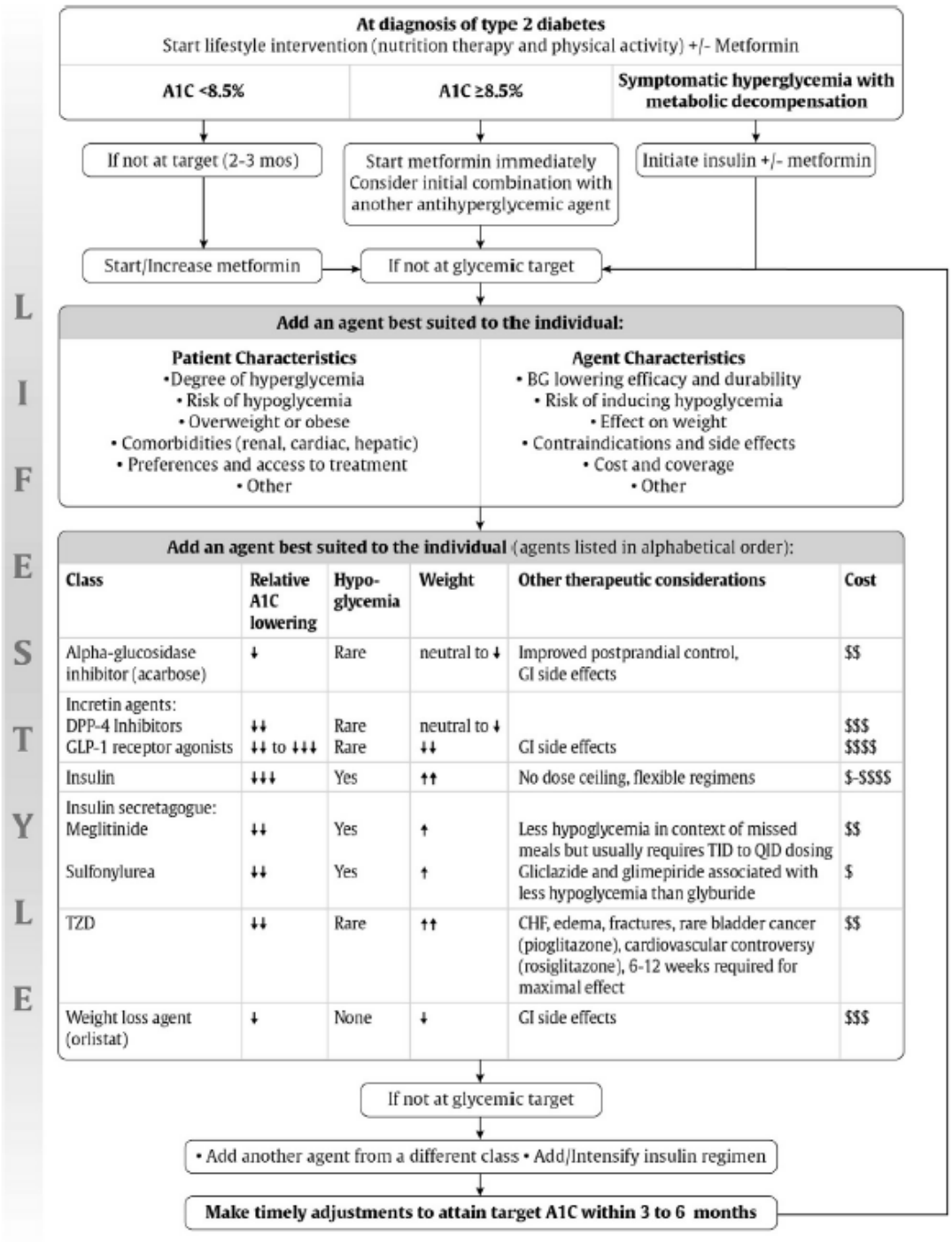


Figure 1. Management of hyperglycemia in type 2 diabetes.
Physicians should refer to the most recent edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and for detailed prescribing information.
A1C, glycated hemoglobin; *CHF*, congestive heart failure; *DPP-4*, dipeptidyl peptidase 4; *GI*, gastrointestinal; *GLP-1*, glucagon-like peptide 1; *TZD*, thiazolidinedione.

Figure 23: CDA 2013 algorithm for antihyperglycemic therapy

- **In <u>overweight or obese adults</u> with type 2 diabetes, the effect of antihyperglycemic agents on body weight should be taken into account [Grade D, Consensus].**

Elderly people

In elderly people with type 2 diabetes, sulphonylureas should be used with caution because the risk of hypoglycemia increases exponentially with age [Grade D, Level 4 (80)].

- **In general, initial doses of sulphonylureas in the elderly should be half of those used for younger people, and doses should be increased more slowly [Grade D, Consensus].**
- **Gliclazide and gliclazide MR [Grade B, Level 2 (85,87)] and glimepiride [Grade C, Level 3 (86)] should be used instead of glyburide, as they are associated with a reduced frequency of hypoglycemic events.**
- **Meglitinides may be used instead of glyburide to reduce the risk of hypoglycemia [Grade C Level 2 (92) for repaglinide; Grade C, Level 3 (93) for nateglinide], particularly in patients with irregular eating habits [Grade D Consensus].**

In elderly people, thiazolidinediones should be used with caution due to the increased risk of fractures and heart failure [Grade D Consensus].

Detemir and glargine may be used instead of NPH or human 30/70 insulin to lower the frequency of hypoglycemic events [Grade B, Level 2 (113,114)].

In elderly people, if insulin mixture is required, premixed insulins and prefilled insulin pens should be used instead of mixing insulins to reduce dosing errors and to potentially improve glycemic control [Grade B, Level 2 (100e102)].

The clock drawing test may be used to predict which elderly subjects will have difficulty learning to inject insulin [Grade D, Level 4 (99)].

3.3.5 DOMUS MEDICA 2015

Start metformin when the HbA1c target has not been reached (after a period of three months) with changes in lifestyle. (Grade 1A)

Consider starting with another antidiabetic drug orally only when there is complete intolerance or a contraindication for metformin; taking into account the profile of the patient and the antidiabetic drug. (Grade 2C)

Add a second oral antidiabetic drug (sulfonylurea / glinide, DPP4 inhibitor, glitazone or SGLT2 inhibitor) if the individual targets were not reached after a period of three months monotherapy with metformin. (Grade 1C)

Add a third oral antidiabetic drug (sulphonylurea / glinide, DPP4-inhibitor, glitazone or SGLT2 inhibitor), a basal insulin, or a GLP-1 agonist to the treatment if the individual targets were not reached after period of three months with bitherapy. (Grade 1C)

Take into account the patient's profile and antidiabetic drug (comorbidity, financial considerations, the presence of overweight or obesity, contraindications, side effects and evidence) in the choice of a particular class. (Grade 1C)

When writing the recommendation, we have also taken into account the reimbursement criteria applicable in Belgium . For example, the ADA guideline recommends a basal insulin or GLP -1 agonist as a possible therapeutic option immediately after monotherapy. In Belgium, however, reimbursement for GLP-1 agonists after metformin in monotherapy is not provided.

When and how to start with insulin / a GLP-1 agonist?

Associate insulin or a GLP-1 agonist when a combination of oral drugs at the maximal tolerated dose is insufficient to achieve the individual HbA1c target value. (Grade 1B)

Take into account the profile of the patient when choosing between a GLP-1 agonist or insulin. Consider a GLP-1 agonist in obese patients or in patients for whom hypoglycemia is a particular danger. (Grade 1C)

Choose a basal insulin (NPH) at bedtime when starting insulin therapy. (Grade 1A)

Titrate the dose of insulin based on the fasting glucose. Consider switching to long-acting insulin analogues (insulin glargine) if hypoglycemia occurs. (Grade 1C)

Provide access to specific education and self-monitoring when starting a GLP-1 agonist or insulin. (Grade 1A)

Retain only metformin and / or sulfonylurea as a treatment when starting a basal insulin or GLP-1 agonist. (Grade 1A)

Intensify the treatment, if the target values are not achieved in spite of the addition of a basal insulin or GLP-1 agonist. (Grade 1A)

Start insulin therapy immediately (without previous oral antidiabetics) when glycemia is severely dysregulated and / or in the presence of hyperglycemia-related complaints. (Grade 1C)

Initiation of GLP -1 analogues

Once or twice daily administration

Exenatide before breakfast and supper . Start with 2 x 5 µg and increase after 1 month to 2 x 10 µg.
Liraglutide once a day at a fixed time . Start with 0.6 mg , increase after 1 week to 1.2 mg/ d, if necessary to this can be increased to 1.8 mg/ d.
Lixisenatide once daily before the meal that provides the largest glycemia spike . Start with 10 µg, increase after 1 month to 20 µg/ d.

Once weekly administration

Exenatide ER . Administer 1 x per week , without regard to meals. Reduce the dose of the sulphonylurea if hypoglycaemia can be expected.

Advantages and disadvantages of GLP-1 analogues

The main advantages of GLP-1 analogues are weight reduction and a reduced risk of hypoglycaemia (unless they are combined with sulfonylurea or insulin). The main side effect of GLP-1 analogues is nausea, but this usually disappears after a few days to weeks. Moreover, it can usually be avoided by eating slowly, taking small portions and stopping immediately when satiated. The main contraindications for the initiation of a GLP-1 agonist are: renal impairment (GFR <45 ml / min) and known gastroparesis. GLP-1 analogues are expensive in comparison to insulin. Although they reduce glycemia, no studies demonstrate a reduction of diabetes-related complications in the long term. Reimbursement of GLP-1 analogues in Belgium is currently reserved for association to bitherapy with metformin / sulfonylurea or metformin / pioglitazone. Only lixisenatide is also reimbursed in combination with insulin.

Insulin	**GLP-1 agonists**
Advantages	**Advantages**

• Long known
• Main effect on fasting glucose
• Most efficient effect on HbA1c reduction
• Dose titration possible
• Studies with hard endpoints : reduction of microvascular complications
• Extra-glycemic effects :
  ○ Lowering of triglycerides
  ○ Lowering of inflammatory parameters
• Use in renal failure, liver failure, heart failure
	• Effect on post-prandial glucose > fasting glucose
	• Easy administration : less education, no dose titration
	• Few hypoglycemias
	• Extra effects :
	  ○ Weight loss
	  ○ Blood pressure reduction
	• Limited need for self-monitoring

Disadvantages	**Disadvantages**
• Risk of hypoglycemia • Weight gain • Education sometimes difficult • Co-operation of patient is necessary	• No data on long-term effectiveness • No data on long-term safety • No data on hard endpoints/diabetes-related complications • Price • Not to be used in renal failure • Only when there is still endogenous beta cell activity

Table 37: advantages and disadvantages of GLP-1 agonists and insulin

Intensifying treatment

Intensify the treatment when the HbA1c target cannot be achieved with one injection of insulin, associated with oral antidiabetics, despite an acceptable fasting glycemia. This can be done by associating prandial (before the meal) insulin (rapid-acting, or ultra-rapid-acting) or by associating a GLP-1 agonist.

When the individual glycemic target values cannot be achieved with a GLP-1 agonist in association with maximal oral drugs, an association with an intermediate or long-acting insulin (basal insulin) can be considered. In Belgium only lixisenatide is reimbursed as an add on therapy with basal insulin. Alternatively, opt for a switch to a basal-bolus insulin treatment: basal insulin (intermediate or long-acting insulin) + 3 prandial insulin injections (rapid-acting or ultra-rapid-acting insulin).

When combining GLP-1-agonists and basal insulin, sulfonylurea and metformin are preferentially retained. When a basal / prandial insulin injection scheme is used, sulfonylurea can usually be stopped. Here, too, the choice for either the combination prandial / basal insulin, or a combination of a GLP-1-agonist / basal insulin, depends on the profile of the patient. Treatment with prandial insulin requires extensive education for dose titration and dietary education (carbohydrate portions), and therefore requires more patient co-operation.

When the combination of a GLP-1 agonist with a basal insulin (on top of oral treatment) is still insufficient to reach the target values, intensification of the treatment is only possible by associating a prandial insulin (basal bolus injection system). Note that there is no long-term data on combination therapy with GLP-1 agonists with basal insulin, nor the comparison with a basal-bolus insulin regimen.

Prerequisites
When starting insulin, structured education is a minimal requirement .

This means at the least:

- *self-monitoring and adjustment of the insulin dose to reach target ,*
- *dietary advice ,*
- *treatment of hypoglycemia, management of acute fluctuations in glycemia .*

When starting a GLP -1 agonist, structured education concerning injection technique and self-monitoring is desirable as well.

3.3.6 EASD/ADA 2015

Same recommendations as ADA 2016

3.3.7 ESC/EASD 2013

"The choice of agent, the conditions of their use and the role of combination therapy is beyond the scope of this document"

Glucose lowering agents in chronic kidney disease.
Around25% of people with T2DM have chronic kidney disease (CKD)stages 3–4 (eGFR <50 mL/min). Aside from the increased CV risk associated with this condition, the use of glucose-lowering agents may need to be modified, either because a particular agent is contraindicated in CKD or because the dosage needs to be altered. Metformin, acarbose and most sulphonylureas should be avoided in stage3–4 CKD, whilst insulin therapy and pioglitazone can be used in their place as required. The DPP-4 inhibitors require dose adjustment with progressive CKD with the exception of linagliptin, which is well tolerated in these circumstances. The SGLT2 inhibitors have not been evaluated in CKD.

3.3.8 NICE 2015

Offer standard-release metformin as the initial drug treatment for adults with type 2 diabetes. [new 2015] In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment[a] with:

- **a dipeptidyl peptidase-4 (DPP-4) inhibitor or**
- **pioglitazone[b] or**
- **a sulfonylurea. [new 2015]**

a. Be aware that, if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered, that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification.

b. When prescribing pioglitazone, exercise particular caution if the person is at high risk of the adverse effects of the drug. Pioglitazone is associated with an increased risk of heart failure, bladder cancer and bone fracture. Known risk factors for these conditions, including increased age, should be carefully evaluated before treatment: see the manufacturers' summaries of product characteristics for details. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2011) advises that 'prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated'.

Algorithm for blood glucose lowering therapy

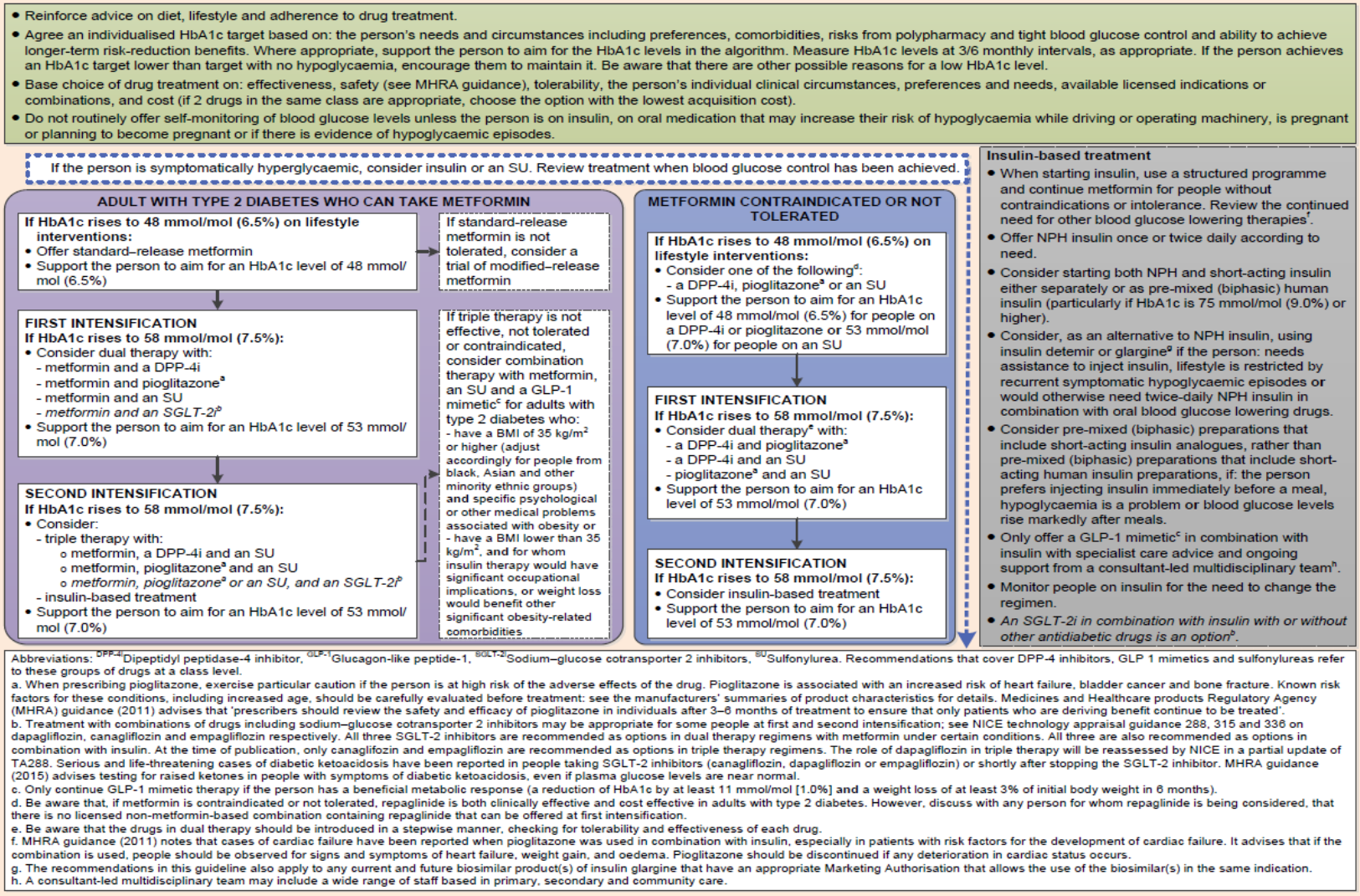


Figure 24: NICE 2015 algorithm for antihyperglycemic therapy

In adults with type 2 diabetes, do not offer or continue pioglitazoned if they have any of the following:

- **heart failure or history of heart failure**
- **hepatic impairment**
- **diabetic ketoacidosis**
- **current, or a history of, bladder cancer**
- **uninvestigated macroscopic haematuria. [new 2015]**

In adults with type 2 diabetes, if initial drug treatment with metformin has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider dual therapy with: below the person's individually agreed threshold for intensification, consider dual therapy with:

- **metformin and a DPP-4 inhibitor or**
- **metformin and pioglitazoned or**
- **metformin and a sulfonylurea. [new 2015]**

In adults with type 2 diabetes, if metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider dual therapye with:

- **a DPP-4 inhibitor and pioglitazoned or**
- **a DPP-4 inhibitor and a sulfonylurea or**
- **pioglitazoned and a sulfonylurea. [new 2015]**

In adults with type 2 diabetes, if dual therapy with metformin and another oral drug (see recommendation 59) has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider either:

- **triple therapy with:**
    - **metformin, a DPP-4 inhibitor and a sulfonylurea or**
    - **metformin, pioglitazoned and a sulfonylurea or**
- **starting insulin-based treatment (see recommendations 66–68). [new 2015]**

If triple therapy with metformin and 2 other oral drugs (see recommendation 61) is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who:

- **have a BMI of 35 kg/m2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or**
- **have a BMI lower than 35 kg/m2 AND:**
    - **for whom insulin therapy would have significant occupational implications or**
    - **weight loss would benefit other significant obesity-related comorbidities. [new 2015]**

Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months). [2015]

In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, and if dual therapy with 2 oral drugs (see recommendation 60) has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider insulin-based treatment (see recommendations 66–68). [new 2015]

In adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary teamf. [new 2015]

3.3.9 ERBP 2015

We recommend metformin in a dose adapted to renal function as a first line agent when lifestyle measures alone are insufficient to get HbA1C in the desired range according to Figure 4 (1B).

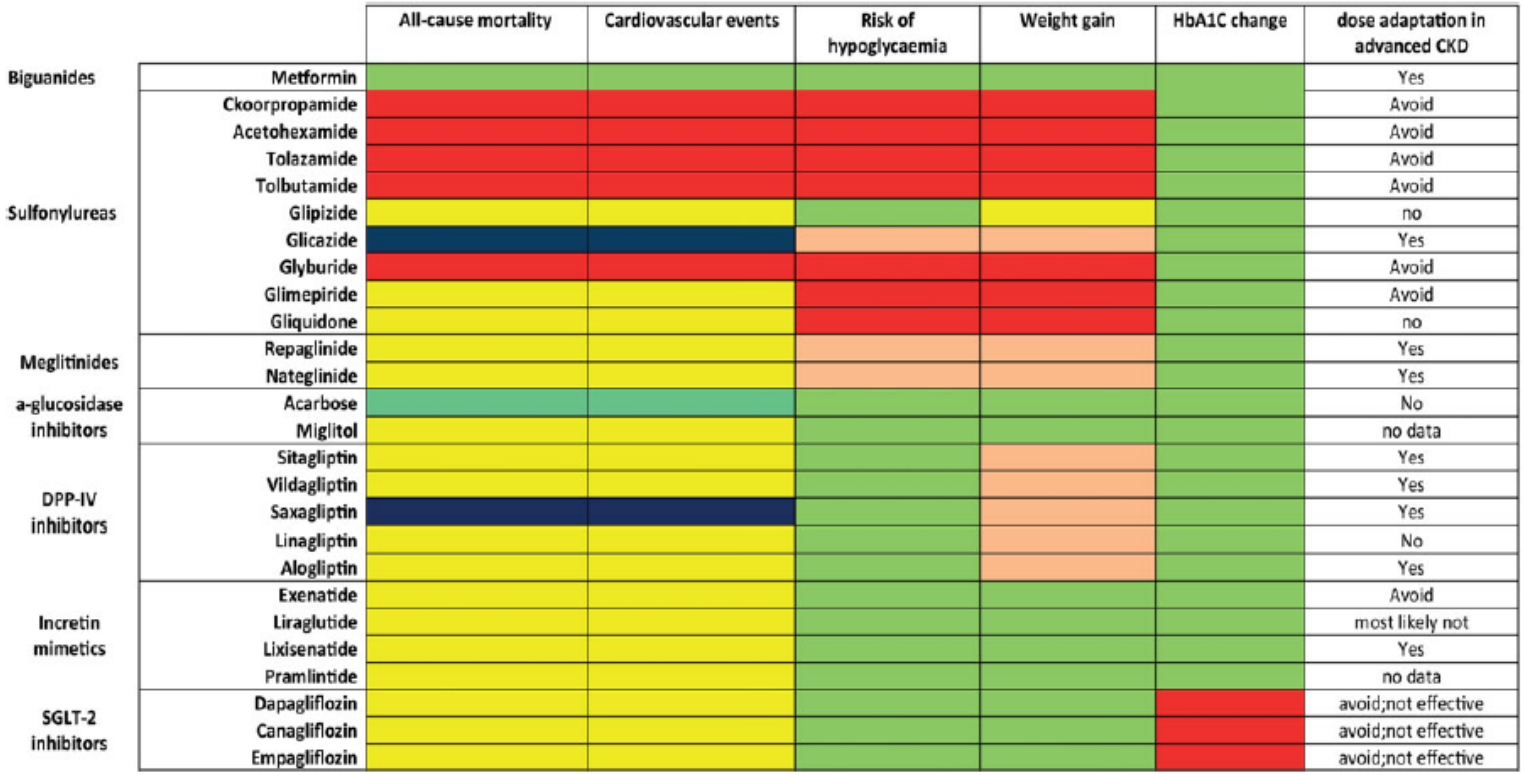
We recommend adding on a drug with a low risk for hypoglycaemia as additional agent when improvement of glycaemic control is deemed appropriate according to Figure 4 (1B).

We recommend instructing patients to temporarily withdraw metformin in conditions of pending dehydration, when undergoing contrast media investigations, or in situations with an increased risk for AKI (1C).

		CKD-1	CKD-2	CKD-3	CKD-4	CKD-5ND	CKD-5D
	Metformin	No adjustments		1,5g-850 mg/day*	500 mg/day**	Consider carefully/Awaiting further data	
Sulfonylureas	Chlorpropamide	No adjustments		100-125 mg/day	To be avoided		
	Acetohexamide	To be avoided					
	Tolazamide	To be avoided					
	Tolbutamide	250mg, 1-3 times/day				To be avoided	
	Glipizide	No adjustments					
	Glicazide	Start at low doses and dose titration every 1-4 weeks					
	Glyburide	To be avoided					
	Glimepiride	Recude dosage to 1 mg/day				To be avoided	
	Gliquidone	No adjustments					
α-gluc inhibitors	Repaglinide	No adjustments				Limited experience available	
	Nateglinide	No adjustments				Start at 60 mg/day	To be avoided
	Acarbose	No adjustments			use lowest dose and <50mg		
	Miglitol	Limited experience available					
	Pioglitazone	No adjustments					
DPP-IV inhibitors	Sitagliptin	No adjustments		Reduce to 50 mg/day	Reduce to 25 mg/day		
	Vildagliptin	No adjustments		Reduce to 50 mg/once daily			
	Saxagliptin	No adjustments		Reduce to 2,5 mg/once daily			
	Linagliptin	No adjustments					
	Alogliptin	No adjustments		Reduce to 12,5 mg/daily			
Incretin Mimetics	Exenatide	No adjustments	Reduce dose to 5 mcg/once to twice daily		To be avoided		
	Liraglutide	Limited experience available					
	Lixisenatide	No adjustments	Careful use if GFR 80-50 mL/min				No experience available
	Pramlintide	Limited experience available					
SGLT-2 inhibitors	Dapagliflozin	Limited experience available					
	Canagliflozin	Reduced efficacy		Careful monitoring		To be avoided	
	Empagliflozin	Limited experience available					

FIGURE 6: Dose recommendations in CKD.

Figure 25: dose recommendations of antidiabetic drugs in chronic kidney disease according to ERBP 2015



		All-cause mortality	Cardiovascular events	Risk of hypoglycaemia	Weight gain	HbA1C change	dose adaptation in advanced CKD
Biguanides	Metformin						Yes
Sulfonylureas	Ckoorpropamide						Avoid
	Acetohexamide						Avoid
	Tolazamide						Avoid
	Tolbutamide						Avoid
	Glipizide						no
	Glicazide						Yes
	Glyburide						Avoid
	Glimepiride						Avoid
	Gliquidone						no
Meglitinides	Repaglinide						Yes
	Nateglinide						Yes
a-glucosidase inhibitors	Acarbose						No
	Miglitol						no data
DPP-IV inhibitors	Sitagliptin						Yes
	Vildagliptin						Yes
	Saxagliptin						Yes
	Linagliptin						No
	Alogliptin						Yes
Incretin mimetics	Exenatide						Avoid
	Liraglutide						most likely not
	Lixisenatide						Yes
	Pramlintide						no data
SGLT-2 inhibitors	Dapagliflozin						avoid;not effective
	Canagliflozin						avoid;not effective
	Empagliflozin						avoid;not effective

FIGURE 7: Impact of different classes of glycaemia-lowering drugs on different outcomes. (For full data extraction: see Supplementary tables) and Arnouts *et al.* [110]. Dark green denotes evidence for beneficial effect; red indicates evidence for negative effect; yellow represents not investigated or insufficient data; salmon denotes evidence for weak negative effect; aquamarin represents evidence for neutral to weak positive effect; dark blue indicates evidence for lack of effect/neutral.

Figure 26: ERBP 2015 comparative table of antidiabetic drugs

4 Albiglutide – evidence tables and conclusions

4.1 Monotherapy

4.1.1 Albigutide versus placebo

4.1.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Nauck 2016 HARMONY-2(15) Design: RCT (DB) (PG) Duration of follow-up:52 weeks	n:309 Race/Ethnicity: 80% caucasian Mean age: +/- 53y Prior/current treatment: diet and exercise DMII duration: +/- 4y Baseline HbA1c:+/- 8.1% Mean BMI: +/- 33.5% Previous CV event (MI): 3% Renal impairment: NR <u>Inclusion</u> ≥18 years, with type 2 diabetes uncontrolled	Albiglutide 30 mg once weekly Vs Albiglutide 30 mg once weekly with uptitration to 50mg at week 12 vs placebo in addition to this background treatment: standard dietary, exercise and home glucose	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: <u>Study completers:</u> albi 30 mg: 85.3% albi 50 mg: 72.5% pla: 75.2% reason described: yes balanced across groups: no <u>Hyperglycaemic rescue</u> albi 30 mg:29.7% albi 50 mg:15.5% pla: 49.5%
			Change in HbA1c from baseline (PO) ANCOVA *adjusted for treatment group, region, history of prior myocardial infarction, age, baseline HbA1c*	Albi 30 mg : -0.70% Albi 50 mg : -0.89% pla : +0.15% Albi 30 mg vs pla: LSMD −0.84% [95% CI −1.11%, −0.58%] p<0.0001 Albi 50 mg vs pla: LSMD −1.04% [−1.31%, −0.77%] p<0.0001 **SS in favour of albiglutide**	
			Body weight change from baseline	Albi 30 mg vs pla: -0.39kg vs -0.66kg Albi 50 mg vs pla -0.86kg vs -0.66 kg NS reported by authors	
			Blood pressure change	mmHg (SD)	

	by diet and exercise (HbA1c ≥7.0% and ≤10.0%) and a BMI of 20–45 kg/m2. Creatinin Clearance >60ml/min Exclusion - history of type 1 diabetes - recent cardiovascular and/or cerebrovascular disease - BP > 160/100 detailed in/exclusion criteria in on-line data supplement	monitoring advice **Hyperglycaemia rescue protocol:** if persistent hyperglycaemia or HbA1c above a certain level (metformin or insulin preferred – last observation before rescue carried forward for analysis) details see below stratification by HbA1c, history of MI and age (> 65 vs <65)	**from baseline (SystBP/DiastBP)**	SBP Albi 30 mg: -2.8(12.14) Albi 50 mg:-1.3(13.37) Pla: 1.3(13.09) DBP Albi 30 mg: -0.8(8.21) Albi 50 mg:- 0.8(8.95) Pla: 0.1(9.17) NT, described as 'small trend for lower blood pressure'	Statistical method for drop out/missing data : LOCF Data handling for rescued patients: last value before rescue ITT: all patients with at least 1 dose of study drug and both baseline and post-baseline HbA1c assessments included in analysis SELECTIVE REPORTING: confusing reporting of hypoglycaemic events Other important methodological remarks "While the analysis of overall hypoglycaemic events was pre-specified, analysis of events that occurred pre-rescue was considered post hoc at the primary endpoint" post hoc MMRM sensitivity analysis Sponsor:glaxosmithkline
			Safety		
			Death	Albi 30 mg: 0 Albi 50 mg : 3 (considered unrelated to study drug) Pla: 0	
			Cardiovascular adverse events	Albi 30 mg: 16.8% Albi 50 mg: 8.1% Pla: 16.8% NT, described as 'lower' with albi 50 mg	
			Any adverse events	Albi 30 mg: 78.2% Albi 50 mg:81.8% Pla:76% NT, described as 'higher' with albi	
			Serious adverse events	Albi 30 mg: 10.9% Albi 50 mg:10.1% Pla: 7.9% NT, described as 'similar'	
			Adverse event leading to withdrawal	Albi 30 mg: 5.0% Albi 50 mg:13.1% Pla:2.0% NT, described as 'more' with albi	

			Any gastro-intestinal adverse event	Albi 30 mg: 31.7% Albi 50 mg:30.3% Pla:26.7% NT, described as 'similar'	
			Diarrhoea	Albi 30 mg: 9.9% Albi 50 mg:13.1% Pla:11.9% NT, described as 'similar'	
			Nausea	Albi 30 mg: 9.9% Albi 50 mg:9.1% Pla:7.9% NT, described as 'similar'	
			Vomiting	Albi 30 mg: 3% Albi 50 mg: 3% Pla:1% NT, described as 'higher' with albi	
			Severe hypoglycaemia (ADA criteria see below)	Albi 30 mg:0 Albi 50mg:0 Pla: 0	
			Documented symptomatic hypoglycaemic event (ADA criteria see below)	Albi 30 mg: 1% Albi 50 mg: 0% Pla:2% NT	
			Injection site reaction	Albi 30 mg: 17.8% Albi 50 mg:22.2% Pla:9.9% NT	

Table 38

Hyperglycaemia rescue: < week 4 FPG >280mg/dl; Week 4- week 12: FPG > 250mg/dl; Week 12- week 48 HbA1C >8.5%; Week 48- .. HbA1c >8.0%

Hypoglycaemia:

American Diabetes Association criteria: Severe—event requiring another person to administer a resuscitative action; Documented symptomatic—plasma glucose concentration ≤3.9 mmol/l (70 mg/dl) and presence of hypoglycaemic symptoms

4.1.1.2 *Summary and conclusions*

Albiglutide 30 mg or 50mg once weekly versus placebo			
Bibliography: Nauck 2016 HARMONY-2(15)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	309 (1) 52 weeks	Mean difference Albi 30 mg vs pla **−0.84% (95%CI −1.11%,−0.58%)** **p<0.0001** Albi 50 mg vs pla **−1.04% (95%CI −1.31%,−0.77%)** **p<0.0001** **SS in favour of albiglutide**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 large drop out (>20%) + large number of hyperglycaemic rescue (15-50%)with LOCF , but sensitivity analysis Consistency:NA Directness:ok Imprecision:ok
Body weight change from baseline	309 (1) 52 weeks	Albi 30 mg vs pla: -0.39kg vs -0.66kg Albi 50 mg vs pla -0.86kg vs -0.66 kg NS	⊕⊕⊖⊖ **LOW** Study quality: -2 large drop out (>20%), large number of hyperglycaemic rescue (15-50%), all these were LOCF Consistency:NA Directness:ok Imprecision: unable to assess
Adverse events leading to withdrawal	309 (1) 52 weeks	Albi 30 mg: 5.0% Albi 50 mg:13.1% Pla:2.0% NT, described as 'more' with albiglutide compared to placebo	Not applicable
Diarrhea	309 (1) 52 weeks	Albi 30 mg: 9.9% Albi 50 mg:13.1% Pla:11.9% NT, described as 'similar' to placebo	Not applicable
Nausea	309 (1) 52 weeks	Albi 30 mg: 9.9% Albi 50 mg:9.1% Pla:7.9% NT, described as 'similar'	Not applicable
Vomiting	309 (1) 52 weeks	Albi 30 mg: 3% Albi 50 mg: 3% Pla:1% NT, described as 'higher' with albiglutide	Not applicable
Severe hypoglycaemia	309 (1) 52 weeks	Albi 30 mg:0 Albi 50mg:0 Pla: 0	Not applicable

Table 39

In this double blind RCT, 309 patients with type 2 diabetes, inadequately controlled by diet and exercise, were randomized to once weekly albiglutide 30 mg, albiglutide 50 mg or placebo for 52 weeks. The mean age was 53y, mean duration of diabetes 4y, mean baseline HbA1c was 8.1% and mean BMI was 33.5 kg/m^2. Only 3% of participants had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

There was a large drop-out throughout the study (>20%) and a large proportion of patients received rescue therapy with other antidiabetic drugs because of hyperglycaemia (up to almost 50% in the placebo group). This limits our confidence in the estimate of the between-group differences.

At 52 weeks, the HbA1c change from baseline was lowered with both doses of albiglutide monotherapy compared to placebo (mean difference -0.84% with albiglutide 30 mg and -1.04% with albiglutide 50mg compared to placebo).
GRADE: MODERATE quality of evidence

At 52 weeks, there was no difference in weight loss from baseline between albiglutide (both doses) and placebo.
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported.

The authors stated that there were more adverse events leading to withdrawal with albiglutide 30 mg (5%) and albiglutide 50 mg (13%) compared to placebo (2%).
GRADE: not applicable

Rates of diarrhea and nausea were described as ‘similar’ between the groups.
Rates of vomiting were described as ‘higher’ with albiglutide (3% in both groups) compared to placebo (1%).
GRADE: not applicable

There were no events of severe hypoglycaemia.
GRADE: not applicable

4.2 Combination therapy with metformin

4.2.1 Albiglutide + metformin versus placebo + metformin

4.2.1.1 *Clinical evidence profile: albiglutide versus sitagliptin, glimepiride, placebo (all + metformin)*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Ahren 2014 HARMONY 3(16) Design: RCT (DB) (PG) superiority testing vs placebo, non-inferiority vs sitagliptin and glimepiride Duration of follow-up:104 w	n:1049 Mean age: 55y (84.3% were <65 years old) Prior/current treatment: metformin DMII duration: 6y Baseline HbA1c: 8.2% Mean BMI: 33 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> -Patients ≥18 y, -type 2 diabetes, -inadequate glycemic control while taking	Albiglutide 30-50 mg (mean 40.5) vs Sitagliptin 100 mg vs glimepiride 2-4 mg (mean 3.1) Vs placebo in addition to this background treatment: metformin ≥1500mg or maximum tolerated dose Uptitration of albiglutide and glimepiride (or placebo) based on predefined	Efficacy		RANDO: unclear ALLOCATION CONC: unclear, not described BLINDING : Participants: yes (double dummy) Personnel: probably yes Assessors: yes FOLLOW-UP: <u>Study completers</u>: overall: 67% sita 67.7% glime 68.8% albi 68.3% pla 59.6% reason described: yes <u>blinded uptitration of albi or glime or matching placebo</u> albi: 53% sita: 59% glime 54% pla: 69%
			Change in HbA1c from baseline at 104 weeks (PO) **ANCOVA** *adjusting for region, history of previous MI, age category, and baseline HbA1*	Albi: -0.63% Sita:-0.28% glime:-0.36% pla:+ 0.27% albi + MET vs pla + MET MD -0.9% (95%CI -1.2 to -0.7) p<0.0001 for superiority SS in favour of albi albi + met vs sita + met MD -0.4% (95%CI -0.5 to -0.2) p<0.0001 for superiority noninferiority only calculated for ITT population **SS in favour of albi** albi + met vs glime + met MD -0.3%; 95%CI -0.5 to -0.1) p= 0.0033 for superiority noninferiority only calculated for ITT population	

	background metformin (≥1,500 mg or maximum tolerated dose) ≥3 months before screening. –baseline HbA1c of 7.0% to 10.0% -BMI 20 to 45 kg/m2; -creatinine clearance >60 mL/min (Cockcroft-Gault formula); - normal TSH or clinically euthyroid <u>Exclusion</u> current ongoing symptomatic biliary disease or history of pancreatitis, recent clinically significant cardiovascular and/or cerebrovascular disease (<2 months before screening), treated gastroparesis, history of GI surgery thought to significantly affect upper GI function,	hyperglycemia criteria (final threshold from week 12 : HbA1c 7.5%) <u>Hyperglycaemia rescue protocol</u>**:** if persistent hyperglycaemia: dose titration and/or rescue, see below. They remained in the trial Eligible patients were stratified by HbA1c level (<8.0% vs. >8.0%)history of myocardial infarction (MI), and age (<65 vs. >65 years)		**SS in favour of albi** *"Subgroup analyses for age, race, ethnicity, sex, baseline BMI, and baseline HbA1c were all consistent with the primary end point"*	<u>Hyperglycaemic rescue</u>: albi: 25.8% sita 36.4% glime 32.7% pla 59.2% <u>Statistical method for drop out/missing data</u> : LOCF <u>Data handling for rescued patients</u>: last value before rescue <u>ITT</u>: all patients who did not receive any dose of study drug were excluded. <u>Some additional exclusions were made but reason is unclear.</u> SELECTIVE REPORTING: inadequate reporting of non-inferiority calculations. Other important methodological remarks - run-in/stabilisation period 4 w before randomization, unclear what this consisted of -non-inferiority margin: 0.3% (no
			Body weight change from baseline	albi:-1.21 kg sita:-0.86 kg glim:+1.17kg pla:-1.0kg **albi + met vs glime + met p<0.0001** **SS in favour of albiglutide**	
			Blood pressure change from baseline (SystBP/DiastBP)	mmHg difference (SD) SBP albi:-1.0(14.2) sita:0.2(14.7) glime:1.5(14.1) pla:2.2(14.0) DBP albi:- 0.7(9.3) sita: 0.2(10.4) glime: 1.0(10.3) pla: 0 reported as NS for all comparisons	
			Safety		
			Death (number of events)	albi:3 sita:1 glime:3	

	history of most cancers not in remission for at least 3 years, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, resting systolic blood pressure (SBP) >160 mmHg and/or diastolic blood pressure (DBP)>100 mmHg, lipase above the upper limit of normal (ULN), hemoglobinopathy that could affect HbA1c, alanine aminotransferase or aspartate aminotransferase more than two and a half times the ULN			pla:1 none of the events were considered to be related tot he study drug	details as to the caculcation method); no per protocol calculation for non-inferiority AEs were analyzed by incidence proportion and incidence density rate overall and before rescue (with additional type 2 diabetes medication); in this article, overall incidence/rate is used for all events except hypoglycemia. Sponsor: GlaxoSmithKline
			Cardiovascular adverse events	not reported	
			Any adverse events	albi:83.8% sita:79.1% glime:83.1% pla: 79.2% NT	
			Serious adverse events	albi:11.9% sita:8.9% glime:9.4% pla:12.9% NT	
			Adverse event leading to withdrawal	albi:6.6% sita:3.6% glime:4.6% pla:5% NT	
			Any gastro-intestinal adverse event	albi:36.4% sita:24.8% glime:27.7% pla:37.6% NT. Sita and glime described as ‘fewer’ than albi	
			Diarrhoea	albi:12.6% sita:8.6% glime:9.1% pla:10.9% NT	
			Nausea	albi:10.3% sita:6.6%	

				glime:6.2% pla:7.9% NT, described as 'comparable' between the groups	
			Vomiting	albi:5.6% sita:4.3% glime:6.2% pla:1.0% NT	
			Severe hypoglycaemia (prerescue incidence rate)	albi:0 sita:0 glime:0 pla:0	
			Documented symptomatic hypoglycaemia	albi:3.0% sita:1.7% glime:17.9% pla:4.0% *NT. Reported as 'low' compared to glimepiride*	
			Injection site reaction	albi:17.2% sita:6.3% glime:7.8% pla:5%	
			Pancreatitis	albi:2 events adjudicated as possibly related to study drug sita: glime: pla:	
			Thyroid cancer	albi:1 event, considered unrelated to study drug sita:2 events, considered unrelated to study drug glime:0	

				pla:0	

Table 40

ADA guidelines for categorization of hypoglycemic event : severe = required assistance of another person; documented symptomatic = typical symptoms accompanied by a plasma glucose concentration of ≤3.9 mmol/L; and asymptomatic = no symptoms but plasma glucose concentration ≤3.9 mmol/L.

Rescue thresholds early in the trial were based on FPG (≥280 mg/dL from week 2 to week 4, ≥250 mg/dL from week 4 to week 12), and, later, on HbA1c (≥8.5% and a ≤0.5% reduction from baseline from week 12 to week 24; ≥8.5% from week 24 to week 104).

4.2.1.2 *Summary and conclusions. Albiglutide + metformin versus placebo + metformin*

Albiglutide 30 to 50 mg + metformin versus placebo + metformin			
Bibliography: Ahren 2014 HARMONY 3(16)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	403 for this comparison (1) 104 w	Mean difference **-0.9% (95%CI -1.2 to -0.7) p<0.0001 SS in favour of albiglutide**	⊕⊕⊖⊖ **LOW** Study quality: -2 drop out 33% and high rate of hyperglycaemic rescue (26% albi and 59% pla), unclear randomization and allocation concealment Consistency:NA Directness: cfr hyperglycemic rescue Imprecision:ok
Body weight change from baseline	403 for this comparison (1) 104 w	Albi: -1.21 kg Pla: -1.0 kg NS	⊕⊕⊖⊖ **LOW** Study quality: -2 drop out 33% and high rate of hyperglycaemic rescue (26% albi and 59% pla), unclear randomization and allocation concealment Consistency:NA Directness: cfr hyperglycemic resuce Imprecision: unable to assess
Adverse events leading to withdrawal	403 for this comparison (1) 104 w	Albi: 6.6% Pla: 5% NT	Not applicable
Diarrhea	403 for this comparison (1) 104 w	albi:12.6% pla:10.9% NT	Not applicable
Nausea	403 for this comparison (1) 104 w	albi:10.3% pla:7.9% NT	Not applicable
Vomiting	403 for this comparison (1) 104 w	albi:5.6% pla:1.0% NT	Not applicable
Severe hypoglycaemia	403 for this comparison (1) 104 w	Albi: 0 Pla: 0	Not applicable

Table 41

This was a double blind, 4-arm RCT, comparing albiglutide versus sitagliptin versus glimepiride versus placebo. The other treatment arms will be reported elsewhere.
403 patients with type 2 diabetes, inadequately controlled by metformin (≥1500 mg or maximum tolerated dose), were randomized to albiglutide 30 mg or placebo for 104 weeks. Albiglutide 30 mg could be titrated to 50 mg if persistent hyperglycemia was present (which happened in 53% of patients).
The mean age was 55y, mean duration of diabetes 6y, mean baseline HbA1c was 8.2% and mean BMI was 33kg/m2. It is unclear how many participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

There was a large drop-out throughout the study (33%) and a large proportion of patients received rescue therapy with other antidiabetic drugs because of hyperglycaemia (26% in the albiglutide group and 59% in the placebo group). This limits our confidence in the estimate of the between-group differences.

At 104 weeks, the HbA1c change from baseline was lowered with albiglutide compared to placebo (mean difference -0.9%).
GRADE: LOW quality of evidence

At 104 weeks, there was no statistically significant difference in weight loss between albiglutide and placebo.
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported.

Withdrawal from the study due to adverse events was seen in 6.6% with albiglutide and 5% with placebo.
GRADE: not applicable

Rates of diarrhea were 13% with albiglutide and 11% with placebo.
Rates of nausea were 10 % with albiglutide and 7.9% with placebo and described as 'comparable'.
Rates of vomiting were 5.6% with albiglutide and 1.0% with placebo
GRADE: not applicable

There were no events of severe hypoglycaemia.
GRADE: not applicable

4.2.2 Albiglutide + metformin versus glimepiride + metformin

4.2.2.1 *Clinical evidence profile*

see 4.2.1.1

4.2.2.2 *Summary and conclusions*

Albiglutide 30 to 50 mg + metformin ≥1500mg versus glimepiride 2 to 4 mg + metformin ≥1500mg			
Bibliography: Ahren 2014 HARMONY 3(16)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	609 for this comparison (1) 104 w	Mean difference **MD -0.3% (95%CI -0.5 to -0.1)** **p= 0.0033 for superiority SS in favour of albiglutide**	⊕⊕⊖⊖ **LOW** Study quality: -2 drop out 33% and high rate of hyperglycemic rescue (26% albi and 33% glim), with LOCF, incomplete noninferiority testing, unclear allocation concealment and randomization Consistency: NA Directness: cfr hyperglycemic rescue Imprecision:ok
Body weight change from baseline	609 for this comparison (1) 104 w	Albi: -1.21 kg glim:+1.17kg **p<0.0001** **SS in favour of albiglutide**	⊕⊕⊖⊖ **LOW** Study quality: -2 drop out 33% and high rate of hyperglycaemic rescue (26% albi and 33% glim), with LOCF, incomplete noninferiority testing, unclear allocation concealment and randomization Consistency:NA Directness: cfr hyperglycemic resuce Imprecision: ok
Adverse events leading to withdrawal	609 for this comparison (1) 104 w	Albi: 6.6% Glim: 4.6% NT	Not applicable
Diarrhea	609 for this comparison (1) 104 w	albi: 12.6% Glim: 9.1% NT	Not applicable
Nausea	609 for this comparison (1) 104 w	albi:10.3% glim:6.2% NT	Not applicable
Vomiting	604 for this comparison (1) 104 w	Albi:5.6% Glim:6.2% NT	Not applicable
Severe hypoglycaemia	609 for this comparison (1) 104 w	Albi: 0 Glim: 0	Not applicable

Table 42

This was a double blind, 4-arm RCT, comparing albiglutide versus sitagliptin versus glimepiride versus placebo. The other treatment arms will be reported elsewhere.
609 patients with type 2 diabetes, inadequately controlled by metformin (≥1500 mg or maximum tolerated dose), were randomized to albiglutide 30 mg or glimepiride 2 mg for 104 weeks. Albiglutide 30 mg could be titrated to 50 mg if persistent hyperglycemia was present (mean dose at end of trial 40.5 mg). Glimepiride could be titrated to 4 mg in case of persistent hyperglycemia (mean dose at end of trial 3.1 mg).

The mean age was 55 years, mean duration of diabetes 6 years, mean baseline HbA1c was 8.2% and mean BMI was 33 kg/m^2. It is unclear how many participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

There was a large drop-out throughout the study (33%) and a large proportion of patients received rescue therapy with other antidiabetic drugs because of hyperglycaemia (26% in the albiglutide group and 33% in the glimepiride group). This limits our confidence in the estimate of the between-group differences.

In patients who were inadequately controlled on metformin, at 104 weeks, the HbA1c had decreased more with albiglutide than with glimepiride.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin, at 104 weeks, the addition of albiglutide resulted in a weight loss, which was significantly different from the addition of glimepiride (which resulted in weight gain).
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 6.6% with albiglutide and 4.6% with glimepiride.
GRADE: not applicable

Rates of diarrhea were 12.6% with albiglutide and 9.1% with glimepiride.
Rates of nausea were 10.3 % with albiglutide and 6.2% with glimepiride and described as 'comparable'.
Rates of vomiting were 5.6% with albiglutide and 6.2% with glimepiride.
GRADE: not applicable

There were no events of severe hypoglycaemia.
GRADE: not applicable

4.2.3 Albiglutide + metformin versus sitagliptin + metformin

4.2.3.1 *Clinical evidence profile*

See 4.2.1.1

4.2.3.2 *Summary and conclusions: Albiglutide + metformin versus sitagliptin + metformin*

Albiglutide 30 to 50 mg + metformin ≥1500mg versus sitagliptin 100 mg + metformin ≥1500mg			
Bibliography: Ahren 2014 HARMONY 3(16)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	604 for this comparison (1) 104 w	Mean difference **-0.4% (95%CI -0.5 to -0.2) p<0.0001 for superiority SS in favour of albiglutide**	⊕⊕⊖⊖ **LOW** Study quality: -2 drop out 33% and high rate of hyperglycemic rescue (26% albi and 36% sita), , incomplete noninferiority testing, unclear allocation concealment and randomization Consistency: NA Directness: cfr hyperglycemic rescue Imprecision:ok
Body weight change from baseline	604 for this comparison (1) 104 w	Albi: -1.21 kg Sita:-0.86 kg NS	⊕⊕⊖⊖ **LOW** Study quality: -2 drop out 33% and high rate of hyperglycaemic rescue (26% albi and 36% sita), incomplete noninferiority testing, unclear allocation concealment and randomization Consistency:NA Directness:cfr hyperglycemic resuce Imprecision: unable to assess
Adverse events leading to withdrawal	604 for this comparison (1) 104 w	Albi: 6.6% Sita: 3.6% NT	Not applicable
Diarrhea	604 for this comparison (1) 104 w	Albi: 12.6% Sita: 8.6% NT	Not applicable
Nausea	604 for this comparison (1) 104 w	albi: 10.3% sita: 6.6% NT	Not applicable
Vomiting	604 for this comparison (1) 104 w	albi: 5.6% sita: 4.3% NT	Not applicable
Severe hypoglycaemia	604 for this comparison (1) 104 w	Albi: 0 Sita: 0	Not applicable

Table 43

This was a double blind, 4-arm RCT, comparing albiglutide versus sitagliptin versus glimepiride versus placebo. The other treatment arms will be reported elsewhere.
604 patients with type 2 diabetes, inadequately controlled by metformin (≥1500 mg or maximum tolerated dose), were randomized to albiglutide 30 mg or sitagliptin 100 mg for 104 weeks. Albiglutide 30 mg could be titrated to 50 mg if persistent hyperglycemia was present (which happened in 53% of patients).
The mean age was 55 years, mean duration of diabetes 6 years, mean baseline HbA1c was 8.2% and mean BMI was 33 kg/m^2. It is unclear how many participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

There was a large drop-out throughout the study (33%) and a large proportion of patients received rescue therapy with other antidiabetic drugs because of hyperglycaemia (26% in the albiglutide group and 36% in the sitagliptin group). This limits our confidence in the estimate of the between-group differences.

In patients who were inadequately controlled on metformin, at 104 weeks, the HbA1c had decreased more with albiglutide than with sitagliptin.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin, at 104 weeks, there was no statistically significant difference in weight loss between albiglutide and sitagliptin.
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 6.6% with albiglutide and 3.6% with placebo.
GRADE: not applicable

Rates of diarrhea were 12.6% with albiglutide and 8.6% with sitagliptin.
Rates of nausea were 10.3 % with albiglutide and 6.6% with sitagliptin and described as 'comparable'.
Rates of vomiting were 5.6% with albiglutide and 4.3% with sitagliptin.
GRADE: not applicable

There were no events of severe hypoglycaemia.
GRADE: not applicable

4.3 Combination therapy with metformin and sulphonylurea

4.3.1 Albiglutide + metformin + glimepiride versus placebo + metformin + glimepiride

4.3.1.1 *Clinical evidence profile: albiglutide versus placebo or pioglitazone (all + metformin and glimepiride)*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Home 2015(17) HARMONY 5 Design: RCT (DB) (PG) superiority vs placebo, noninferiority vs pioglitazone Duration of follow-up: 52 weeks	n:685 Race/Ethnicity: 69.8% caucasian Mean age: 55.2 Prior/current treatment: metformin ≥ 1500mg/d or maximum tolerated dose + SU equivalent to ≥4mg/d DMII duration:8.9y (SD 6.2) Baseline HbA1c: mean 8.24(SD 0.91) Mean BMI: 32.2 (SD 5.5) Previous MI: 4.2% Renal impairment: NR	Albiglutide 30-50mg/w (mean 41.9) vs pioglitazone 30-45 mg/d (mean 37.1) vs placebo in addition to this background treatment: metformin (≥1500mg/d) + glimepiride (standardized to 4mg/d, decrease possible if hypoglycaemia) target of HbA1c <7.0% and FPG ≤100%	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: <u>Study completers</u>: 79.6%(assessed by Zaccardi 2015) reason described: yes <u>discontinued treatment</u>: pla n=30% pio n=19% albi n=18% <u>uptitration of study medication</u> albi 59.5% pio 47.3% <u>Hyperglycaemic rescue</u>:
			Change in HbA1c from baseline (PO) *analysis of covariance with treatment group, region, history of myocardial infarction and age (<65 vs. ≥65 years) as factors, and baseline HbA1c as a continuous covariate*	mean (standard error) albi: −0.55 (0.06) pio: −0.80 (0.06) pla: 0.33 (0.08) albi + met + glim vs pla + met + glim difference= **-0.87% [95%CI –1.07, –0.68)** **p<0.001** **SS in favour of albiglutide** albi + met + glim vs pio + met + glim difference= 0.25 (95% CI 0.10, 0.40) alib is not non-inferior to pio	
			Body weight change from baseline	mean (standard error) albi:-0.42(+/-0.2)kg pio:+4.4(+/-0.2)kg pla:-0.4(+/-0.4)kg albi + met + glim vs pio + met + glim **treatment difference -4.9 (95%CI -5.5 to -4.2)** **p<0.001**	

	Inclusion ≥18 y; historical diagnosis of T2DM; inadequate glycaemic control on current regimen of metformin and a sulfonylurea; (BMI) from≥20.0 to ≤45.0 kg/m2, (HbA1c) 7.0–10.0% , fasting C-peptide ≥0.26 nmol/l, creatinine clearance >60 ml/min Cockcroft–Gault) Exclusion history of cancer (except non-melanoma skin cancers) not in remission for 3 years, treated diabetic gastroparesis, current symptomatic biliary disease, a history of pancreatitis, previous significant gastrointestinal surgery, or recent clinically significant cardiovascular disease. defined more extreme abnormalities of liver	hyperglycaemia uptitration of albi, pio or matching placebo according to predefined protocol: see below Hyperglycaemia rescue protocol: see below **preferred rescue: insulin** Randomization was stratified by HbA1c (<8.0 vs. ≥8.0%), history of myocardial infarction and age (<65 vs. ≥65 years)		**SS in favour of albiglutide**	albi 21.6% pio 19.6% pla 55.8% Statistical method for drop out/missing data : LOCF Data handling for rescued patients: value at time of rescue carried forward rescued patients either had rescue medication added to their study medication or had study medication discontinued and replaced by rescue medication (in this case, only cardiovascular or other safety information was gathered) 'modified' ITT: all participants who received ≥1 dose of study medication and had a baseline and ≥1 further HbA1c measurement were analysed in the 'ITT' population SELECTIVE REPORTING: no Other important methodological remarks 6-8 week run-in/stabilization
			Blood pressure change from baseline (SystBP/DiastBP)	not reported	
			Safety		
			Death	albi:0 pio:3 pla:1	
			Cardiovascular adverse events (defined as myocardial infarction, stroke or death)	albi:11.1% pio:15.5% pla: 8.7%	
			Any adverse events (on-therapy)	albi:79.7% pio:76.6% pla:69.6%	
			Serious adverse events	albi:6.3% pio:9.0% pla:6.1% NT 'lower' than pio	
			Adverse event leading to withdrawal	albi:4.4% pio:6.9% pla: 5.2% NT, described as 'similar'	
			Any gastro-intestinal adverse event	albi:33.6% pio:26.0% pla:17.4%	
			Diarrhoea	albi:8.9% pio:5.4% pla:2.6% NT, described as 'more common with	

	function tests, circulating lipase and amylase and plasma triglycerides			albi'	period (stabilized on glimepiride 4 mg), after which randomization of eligible patients occurred non-inferiority testing on ITT population and not on per-protocol population noninferiority margin of 0.30%, no reason for this margin provided Except for hypoglycaemia, all summarized AEs were pre- and post-hyperglycaemic rescue. AE's were described as 'post hoc to the primary endpoint) Sponsor: GlaxoSmithKline
			Nausea	albi:9.6% pio:4.3% pla:3.5% NT, described as 'more common' with albi	
			Vomiting	albi:2.6% pio:1.8% pla:0.9%	
			Severe hypoglycaemia (pre-rescue) classified by the American Diabetes Association criteria	albi:0.4% pio:1.1% pla:0%	
			documented symptomatic hypoglycaemia (pre-rescue) classified by the American Diabetes Association criteria	albi:13.7% pio:25.3% pla:7%	
			Injection site reactions	albi:12.9% pio:3.2% pla:3.5%	
			thyroid cancer	albi:0% pio:0% pla:0.9%	
			pancreatitis	albi:0.4% pio:0% pla:0%	

Table 44

Conditions for dose titration and hyperglycaemia rescue
Based on FPG > 250mg/dl or 280 mg/dl in first 12 weeks, based on HbA1C >7.5 or > 8.5 afterward

4.3.1.2 *Summary and conclusions*

albiglutide 30 to 50 mg/week + metformin ≥1500mg/d + glimepiride 4mg/d versus placebo + metformin ≥1500mg/d + glimepiride 4mg/d			
Bibliography: Home 2015(17) HARMONY 5			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	397 for this comparison (1) 52 weeks	Mean difference **-0.87% (95%CI –1.07, –0.68) p<0.001 SS in favour of albiglutide**	⊕⊕⊖⊖ **LOW** Study quality:-2 (high drop out >20%, high rate of hyperglycemic rescue 22% albi vs 56% pla) with LOCF and no sensitivity analysis Consistency:NA Directness: cfr hyperglyc. rescue Imprecision: ok
Body weight change from baseline	397 for this comparison (1) 52 weeks	albi: -0.42kg pla: -0.4 kg NS	⊕⊕⊖⊖ **LOW** Study quality:-2 (high drop out >20%, high rate of hyperglycemic rescue 22% albi vs 56% pla)all with LOCF Consistency:NA Directness: cfr hyperglyc. rescue Imprecision: unable to assess
Adverse events leading to withdrawal	397 for this comparison (1) 52 weeks	albi:4.4% pla: 5.2% NT, described as 'similar'	Not applicable
Diarrhea	397 for this comparison (1) 52 weeks	albi:8.9% pla:2.6% NT, described as 'more common with albiglutide'	Not applicable
Nausea	397 for this comparison (1) 52 weeks	albi:9.6% pla:3.5% NT, described as 'more common' with albiglutide	Not applicable
Vomiting	397 for this comparison (1) 52 weeks	albi:2.6% pla:0.9% NT	Not applicable
Severe hypoglycaemia	397 for this comparison (1) 52 weeks	albi:0.4% pla:0% NT	Not applicable

Table 45

This was a double blind, 3-arm RCT, comparing albiglutide versus pioglitazone versus placebo. The other treatment arms will be reported elsewhere.

397 patients with type 2 diabetes, inadequately controlled by metformin ≥1500mg/d + glimepiride 4mg/d , were randomized to receive additional albiglutide or placebo for 52 weeks. The mean age

was 55 years, mean duration of diabetes 9 years, mean baseline HbA1c was 8.2% and mean BMI was 32 kg/m^2. Only 4.2% of participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

Albiglutide 30 mg could be titrated to 50 mg if persistent hyperglycemia was present (mean dose at end of trial 41.9 mg).

There was a large drop-out throughout the study (21%) and a large proportion of patients received rescue therapy with other antidiabetic drugs because of hyperglycaemia (22% in the albiglutide group and 56 % in the placebo group). This limits our confidence in the estimate of the between-group differences.

In patients who were inadequately controlled on metformin and glimepiride, the addition of albiglutide resulted in a HbA1c that was -0.87% lower compared to placebo after 52 weeks.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin and glimepiride, there was no difference in weight loss between albiglutide and placebo after 52 weeks.
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 4.4% with albigutide and 5.2% with placebo.
GRADE: not applicable

Rates of diarrhea were 8.9% with albiglutide and 2.6% with placebo.
Rates of nausea were 9.6% with albiglutide and 3.5% with placebo.
Rates of vomiting were 2.6% with albiglutide and 0.9 % with placebo.
GRADE: not applicable

Severe hypoglycemia occurred in 0.4% with albiglutide and 0% with placebo.
GRADE: not applicable

4.3.2 Albiglutide + metformin + glimepiride versus pioglitazone + metformin + glimepiride

4.3.2.1 *Clinical evidence profile*

See 4.3.1.1

4.3.2.2 *Summary and conclusions*

albiglutide 30 to 50 mg/week + metformin ≥1500mg/d + glimepiride 4mg/d versus pioglitazone 30-45 mg/d + metformin ≥1500mg/d + glimepiride 4mg/d			
Bibliography: Home 2015(17) HARMONY 5			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	569 for this comparison (1) 52 weeks	Mean difference 0.25 (95% CI 0.10, 0.40) **albiglutide is not non-inferior to pioglitazone**	⊕⊕⊖⊖ **LOW** Study quality:-2 (high drop out >20%, high rate of hyperglycemic rescue 22% albi vs 19% pio, all with LOCF). Incomplete non-inferiority testing Consistency:NA Directness: cfr hyperglyc. rescue Imprecision: ok
Body weight change from baseline	569 for this comparison (1) 52 weeks	Mean difference -4.9 kg(95%CI -5.5 to -4.2) **p<0.001** **SS in favour of albiglutide**	⊕⊕⊖⊖ **LOW** Study quality:-2 (high drop out >20%, high rate of hyperglycemic rescue 22% albi vs 19% pio, all with LOCF) Consistency:NA Directness: cfr hyperglyc. rescue Imprecision: ok
Adverse events leading to withdrawal	569 for this comparison (1) 52 weeks	albi:4.4% pio:6.9% NT, described as 'similar'	Not applicable
Diarrhea	569 for this comparison (1) 52 weeks	albi:8.9% pio:5.4% NT, described as 'more common with albiglutide'	Not applicable
Nausea	569 for this comparison (1) 52 weeks	albi:9.6% pio:4.3% NT, described as 'more common' with albiglutide	Not applicable
Vomiting	569 for this comparison (1) 52 weeks	albi:2.6% pio:1.8% NT	Not applicable
Severe hypoglycaemia	569 for this comparison (1) 52 weeks	albi:0.4% pio:1.1% NT	Not applicable

Table 46

This was a double blind, 3-arm RCT, comparing albiglutide versus pioglitazone versus placebo. The other treatment arm will be reported elsewhere.

569 patients with type 2 diabetes, inadequately controlled by metformin ≥1500mg/d + glimepiride 4mg/d , were randomized to receive additional albiglutide 30 mg/w or pioglitazone 30 mg/d for 52 weeks. The mean age was 55 years, mean duration of diabetes 9 years, mean baseline HbA1c was 8.2% and mean BMI was 32 kg/m^2. Only 4.2% of participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

Albiglutide 30 mg could be titrated to 50 mg if persistent hyperglycemia was present (mean dose at end of trial 41.9 mg). Pioglitazone could be titrated to 45 mg in case of persistent hyperglycemia (mean dose at end of trial 37.1 mg).

There was a large drop-out throughout the study (21%) and a large proportion of patients received rescue therapy with other antidiabetic drugs because of hyperglycemia (22% in the albiglutide group and 20 % in the pioglitazone group). This limits our confidence in the estimate of the between-group differences.

In patients who were inadequately controlled on metformin and glimepiride, the addition of albiglutide resulted in a decreased HbA1c that was however 0.25% higher compared to the HbA1c decrease with pioglitazone after 52 weeks. The non-inferiority of albiglutide compared to pioglitazone was not established.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin and glimepiride, the weight in the albiglutide group was decreased compared to the pioglitazone group (in which the weight had increased from baseline).
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 4.4% with albigutide and 6.9% with pioglitazone.
GRADE: not applicable

Rates of diarrhea were 8.9% with albiglutide and 5.4% with pioglitazone.
Rates of nausea were 9.6% with albiglutide and 4.3% with pioglitazone.
Rates of vomiting were 2.6% with albiglutide and 1.8 % with pioglitazone.
GRADE: not applicable

Severe hypoglycemia occurred in 0.4% with albiglutide and 1.1% with pioglitazone.
GRADE: not applicable

4.3.3 Albiglutide + metformin +/- sulphonylurea versus insulin glargine + metformin +/- sulphonylurea

4.3.3.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Weissman 2014(18) HARMONY 4 Design: RCT (OL) (PG) non-inferiority study Duration of follow-up:52 weeks (trial will last for 3 years)	n:779 Mean age: 55.5y (84%<65y) Prior/current treatment: metformin + SU 81.9%; metformin alone 18.1% DMII duration: mean 8.8y Baseline HbA1c:mean 8.31% Mean BMI: 33.1kg/m2 Previous MI: 5.0% Renal impairment: NR <u>Inclusion</u> ≥18 years with type 2 diabetes treated with metformin ≥1,500 mg or maximum tolerated dose ± sulfonylurea for at least 3 months with a baseline HbA1c 7.0–10.0%;	Albiglutide 30mg/w (uptitration to 50mg/w if necessary) (mean 43.4mg/w) vs insulin glargine (10U once a day) (dose adjustment if necessary)(mean 35.1 units) in addition to this background treatment: metformin metformin ≥1,500 mg +/- SU doses adjusted on the basis of glycaemic	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: unclear (yes for cardiovascular or pancreatitis) FOLLOW-UP: <u>Study completers</u>: albi 78.8% ins glar: 83.8% Reason dropout described: yes <u>Uptitration of study medication</u>: albi 67.1% ins glar: ? <u>Hyperglycaemic rescue</u>: albi 25.6% ins glar 23.8%
			Change in HbA1c from baseline (PO) *(model-adjusted)* ANCOVA	albi:-0.67% ins glar:-0.79% treatment difference: 0.11%(95%CI -0.04% to 0.27%) **albi is non-inferior to insulin glargine when added to MET+/- SU (p=0.0086)** **(based on modified ITT population)**	
			Body weight change from baseline *(model-adjusted)*	albi: - 1.06±3.80 kg ins glar:+ 1.57±3.81 kg treatment difference: -2.61 kg (95%CI -3.20 to -2.02) p<0.0001 **SS in favour of albiglutide**	
			Blood pressure change from baseline	SBP (SD) albi:-1.4(+/-14.4) ins glar:0.3(+/-13.7) DBP albi:- 0.8(+/-10.0) ins glar: 1.8(+/-8.8) NT	
			Safety (pre- and post rescue data, except for hypoglycaemia)		

	BMI 20-45 kg/m2, creatinine clearance >60ml/min Exclusion history of cancer, treated diabetic gastroparesis, current symptomatic biliary disease or history of pancreatitis, significant gastrointestinal surgery, or recent significant cardiovascular (within 2 months) or cerebrovascular (within 1 month) events and history or family history of medullary carcinoma or multiple endocrine neoplasia type 2. Elevated levels of total bilirubin, alanine aminotransferase, aspartate aminotransferase, amylase, lipase or fasting triacylglycerol	response Hba1c target: no target specified Hyperglycaemia uptitration protocol: for albi mostly based on HbA1c, for ins glargine based on FPG Hyperglycaemia rescue protocol**:** see below choice of rescue medication by investigator Stratification: stratified by HbA1c level (<8.0% vs ≥8.0% [<63.9 vs ≥63.9 mmol/mol]), age (<65 vs ≥65 years), history of myocardial infarction (yes vs	**Death**	albi:3 ins glar:3	Statistical method for drop out/missing data : LOCF Data handling for rescued patients: last prerescue value carried forward ITT population: all randomised patients who received ≥1 dose of study medication and had both a baseline and ≥1 post-baseline assessments of HbA1c albi: 96% ins glar: 91% safety population: all patients who received at least 1 dose of study medication. SELECTIVE REPORTING: no (but cardiovascular events not reported here) Other important methodological remarks placebo run-in 4 weeks (before randomization) prespecified non-inferiority margin 0.3% (no reason for this calculation given)
			Cardiovascular adverse events	"will be reported seperately as part of a meta-analysis"	
			Any adverse events	albi: 81.7% ins glar:75.1% NT, described ad 'higher' with albiglutide	
			Serious adverse events	albi:8.3% ins glar:8.3% NT 'similar'	
			Adverse event leading to withdrawal	albi:6.9% ins glar:2.5% NT, 'more' with albiglutide	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	albi:7.5% ins glar:4.1%	
			Nausea	albi:9.9% ins glar:3.7% NT, 'more' with albiglutide	
			Vomiting	albi:3.7% ins glar:3.8% NT, 'similar'	
			Severe hypoglycaemia (ADA criteria: Event requiring another person to administer a resuscitative action)	total safety population albi:0.4% ins glar:0.4% Metformin alone (n= 91+44) albi:0	

		no), and current glucose-lowering treatment (metformin alone vs metformin+SU) in the event of severe or recurrent hypoglycaemia, the dose of SU could be reduced or discontinued		ins glar:0 Metformin + SU (n=413+196) albi:0.5% ins glar:0.5%	Sponsor: GlaxoSmithKline
			Documented symptomatic hypoglycaemia (ADA criteria: Plasma glucose ≤3.9 mmol/l (70 mg/dl) and presence of hypoglycaemic symptoms**)**	albi:17.5% ins glar:27.4% metformin alone albi:1.1% ins glar:18.2% metformin + SU albi:21.1% ins glar:29.6% 'The model-adjusted incidence rate was higher in the insulin glargine group (108.8 events per 100 person-years) than in the albiglutide group (61.4 events per 100 personyears)' p=0.0377)	
			Injection site reactions (investigator-identified)	albi:13.9% ins glar:8.7% NT 'greater in the albiglutide group'	
			Thyroid cancer	albi:0 ins glar:0	

			Pancreatitis (blinded adjudication committee)	albi:0 ins glar:0	

Table 47

Protocol for titration or hyperglycemic rescue: until week 12 based on FPG > 250 or > 280; afterwards based on HbA1c > 7% or >8.5%

'The incidence rates of AEs occurring before receiving hyperglycaemic rescue therapy were similar to the overall rate up to week 52 (80.2% and 73.4%for albiglutide and insulin glargine, respectively)'

4.3.3.2 *Summary and conclusions*

Albiglutide 30 to 50 mg/w + metformin +/- sulfonylurea versus insulin glargine titrated + metformin +/- sulfonylurea			
Bibliography: Weissman 2014(18) HARMONY 4			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	779 (1) 52 weeks	albi: -0.67% ins glar: -0.79% treatment difference 0.11% (95%CI -0.04 to 0.27) **albiglutide is non-inferior to insulin glargine when added to MET+/- SU**	⊕⊕⊖⊖ **LOW** Study quality: -2 open label, 20% drop out, 25% hyperglycaemic rescue, all with LOCF, incomplete noninferiority testing Consistency: NA Directness: ok Imprecision: ok
Body weight change from baseline	779 (1) 52 weeks	albi: - 1.06kg ins glar:+ 1.57kg treatment difference: **-2.61kg (95%CI -3.20 to -2.02)** **p<0.0001** **SS in favour of albiglutide**	⊕⊕⊖⊖ **LOW** Study quality: -2 open label, 20% drop out, 25% hyperglycaemic rescue, all with LOCF Consistency: NA Directness: ok Imprecision: ok
Adverse events leading to withdrawal	779 (1) 52 weeks	albi:6.9% ins glar:2.5% NT, described as 'more' with albiglutide	Not applicable
Diarrhea	779 (1) 52 weeks	albi:7.5% ins glar:4.1% NT	Not applicable
Nausea	779 (1) 52 weeks	albi:9.9% ins glar:3.7% NT, described as 'more' with albiglutide	Not applicable
Vomiting	779 (1) 52 weeks	albi:3.7% ins glar:3.8% NT, described as 'similar'	Not applicable
Severe hypoglycaemia	779 (1) 52 weeks	albi:0.4% ins glar:0.4% (all in metformin + SU) NT	Not applicable

Table 48

In this open label non-inferiority RCT, 779 patients with type 2 diabetes, inadequately controlled by metformin ≥1,500 mg with or without a sulfonylurea, were randomized to albiglutide 30 mg/w or insulin glargine once daily for 52 weeks. Albiglutide could be titrated to 50 mg/w in case of persistent hyperglycaemia (mean dose at end of study 43.4 mg/w). Insulin glargine was titrated based on fasting plasma glucose (mean daily dose at end of study 35.1 units).
81% of participants were on a combination of metformin + a sulfonylurea.
The mean age was 55.5 years, mean duration of diabetes 8.8 years, mean baseline HbA1c was 8.3% and mean BMI was 33 kg/m^2. Only 5% of participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

There was a large drop-out throughout the study (20%) and a large proportion of patients received rescue therapy with other antidiabetic drugs because of hyperglycemia (25%). This, in combination with the open label design, limits our confidence in the estimate of the between-group differences.

In patients who were inadequately controlled on metformin with or without a sulfonylurea, the addition of albiglutide was non-inferior to the addition of daily insulin glargine for the HbA1c decrease after 52 weeks.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin with or without a sulfonylurea, the addition of albiglutide resulted in a weight decrease compared to insulin glargine (which caused weight gain from baseline).
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 6.2% with albiglutide and 2.5% with insulin glargine.
GRADE: not applicable

Rates of diarrhea were 7.5% with albiglutide and 4.1% with insulin glargine.
Rates of nausea were 9.9% with albiglutide and 3.7 % with insulin glargine.
Rates of vomiting were 3.7% with albiglutide and 3.8% with insulin glargine.
GRADE: not applicable

Severe hypoglycemia occurred in 0.4% with albiglutide and 0.4 % with insulin glargine. All these events occurred in patients who were taking metformin + a sulfonylurea.
GRADE: not applicable

4.4 Combination therapy with pioglitazone +/- metformin

4.4.1 Albiglutide + pioglitazone +/- metformin versus placebo + pioglitazone + metformin

4.4.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Reusch 2014(19) HARMONY 1 Design: RCT (DB) (PG) Duration of follow-up: 52 weeks (total duration of trial 3 y)	n:310 Mean age: 55.0y (84.1%<65y) Prior/current treatment:79.7% pioglitazone + metformin 20.3% pioglitazone only DMII duration: mean 8y Baseline HbA1c:mean 8.1% Mean BMI: 34.1% Previous MI: 4.3% Renal impairment: NR <u>Inclusion</u> ≥18 years old, with a	Albiglutide 30 mg once weekly (no uptitration) vs placebo in addition to this background treatment: pioglitazone +/- metformin <u>Hyperglycaemia rescue protocol</u>: on the basis of prespecified HbA1c and/or fasting plasma glucose (FPG) values, to	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: unclear (only for cardiovascular and pancreatitis was blinded adjudication specifically described) FOLLOW-UP: <u>Study completers</u>: albi: 85.8% pla: 74.2% Reason described: yes <u>Hyperglycaemic rescue</u>: albi:24.4% pla: 47.7%
			Change in HbA1c from baseline (PO) (model-adjusted least squares mean)	albi: −0.8% pla: −0.1% treatment difference total population −0.8%, (95% CI−1.0 to −0.6) p<0.0001 SS in favour of albiglutide pio + met −0.8% (95% CI −1.0, −0.53) SS in favour of albiglutide pio only −0.8% (95% CI −1.2, −0.3) SS in favour of albiglutide	
			Body weight change from baseline	albi: 0.28kg pla: 0.45kg treatment difference -0.2kg NS	
			Blood pressure change	NR	

	body mass index of 20–45 kg/m2, and were diagnosed with T2DM. HbA1c 7.0–10.0% on stable doses of pioglitazone (≥30mg pioglitazone daily or the patient's maximum tolerated dose) with or without a stable dose of metformin (≥1500mg or maximum tolerated dose) for at least 2months before randomization. Fasting C-peptide ≥0.8 ng/ml, creatinine clearance >60 ml/min (Cockcroft Gault formula), haemoglobin≥11 g/dl (110 g/L) for men and≥10 g/dl (100 g/L) for women, normal levels of thyroid-stimulating hormone or clinically euthyroid <u>Exclusion</u> a history of cancer (except squamous cell or basal cell carcinoma); a	undergo hyperglycaemia rescue, see below <u>Stratification:</u> Randomization was stratified according to current antidiabetic medicine (with vs. without metformin), history of myocardial infarction [(MI) yes vs. no], and age (<65 vs. ≥65 years)	**from baseline (SystBP/DiastBP)**		<u>Statistical method for drop out/missing data</u> : LOCF <u>Data handling for rescued patients</u>: last value before rescue <u>ITT</u>: all participants with both baseline and post-baseline HbA1c assessments (97%) SELECTIVE REPORTING: no 4 week run-in Sponsor: GlaxoSmithKline
			Safety		
			Death	albi:0 pla:3 (none considered to be related to study drug)	
			Cardiovascular adverse events blinded adjudication	'will be reported separately as part of a meta-analysis'	
			Any adverse events	albi:81.3% pla:84.1% NT, described as 'similar'	
			Serious adverse events	albi:3.3% pla:9.9% (different numbers cited in text: severe AE: severe AEs [10.0% (15 patients)with albiglutide and 17.2% (26 patients) with placebo) NT, described as 'similar'	
			Adverse event leading to withdrawal	albi:4.7% pla:6.6%	
			Any gastro-intestinal adverse event	albi:31.3% pla:29.8%	
			Diarrhoea	albi:11.3% pla:8.6% NT, reported as 'more frequently)	
			Nausea	albi:10.7%	

	history of treated diabetic gastroparesis; current ongoing symptomatic biliary disease or history of pancreatitis; significant GI surgery or surgeries thought to significantly affect upper GI function; recent (≤2months) clinically significant cardiovascular and/or cerebrovascular disease; a history of human immunodeficiency virus infection; a history or family history of medullary carcinoma or multiple endocrine neoplasia type 2; and acute symptomatic hepatitis B or C infection, additional criteria, including requirements for screening or baseline values for total bilirubin, alanine aminotransferase, aspartate aminotransferase, amylase, lipase or fasting triglycerides			pla:11.3%	
			Vomiting	albi:4.0% pla:4.0%	
			Severe hypoglycaemia *(ADA criteria)*	albi:3.3% pla:1.3%	
			Documented symptomatic hypoglycaemia *(ADA criteria)*	albi:1.3% pla:0	
			Injection site reactions	albi:11.3% pla:7.9%	
			Thyroid cancer	albi:0 pla:0	
			Pancreatitis *blinded adjudication*	albi:0 pla:0	

Table 49

Hyperglyceamia rescue before week 12 FPG > 250mg/dl, up to 48 weeks HbA1c > 8.5%; till end of trial HbA1C > 8%

4.4.1.2 *Summary and conclusions*

Albiglutide 30 mg once weekly + pioglitazone +/- metformin versus placebo + pioglitazone +/- metformin			
Bibliography: Reusch 2014(19) HARMONY 1			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	310 (1) 52 weeks	albi: −0.8% pla: −0.1% treatment difference total population **−0.8%, (95% CI−1.0 to −0.6)** **p<0.0001** **SS in favour of albiglutide** (similar results in treatment subgroups pio + met; pio only)	⊕⊕⊖⊖ **LOW** Study quality:- 2 drop out +/- 20% and hyperglycaemic rescue 24% albi, 48% pla) all + LOCF, no sensitivity analysis Consistency:NA Directness:ok Imprecision:ok
Body weight change from baseline	310 (1) 52 weeks	albi: +0.28kg pla: +0.45kg treatment difference -0.2kg NS	⊕⊕⊖⊖ **LOW** Study quality:- 2 drop out +/- 20% and hyperglycaemic rescue 24% albi, 48% pla) all + LOCF Consistency:NA Directness:ok Imprecision: unable to assess
Adverse events leading to withdrawal	310 (1) 52 weeks	albi:4.7% pla:6.6%	Not applicable
Diarrhea	310 (1) 52 weeks	albi:11.3% pla:8.6% NT, reported as 'more frequently)	Not applicable
Nausea	310 (1) 52 weeks	albi:10.7% pla:11.3%	Not applicable
Vomiting	310 (1) 52 weeks	albi:4.0% pla:4.0%	Not applicable
Severe hypoglycaemia	310 (1) 52 weeks	albi:3.3% pla:1.3%	Not applicable

Table 50

In this double blind RCT, 310 patients with type 2 diabetes, inadequately controlled by pioglitazone ≥ 30 mg with or without metformin ≥1500 mg, were randomized to albiglutide 30 mg or placebo for 52 weeks. 80% of patients were taking pioglitazone + metformin.

The mean age was 55 years, mean duration of diabetes 8y, mean baseline HbA1c was 8.1% and mean BMI was 34.1 kg/m^2. Only 4.3% of participants had had a previous myocardial infarction. Patients

with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

There was a large drop-out throughout the study (+/- 20 %) and a large proportion of patients received rescue therapy with other antidiabetic drugs because of hyperglycemia (24% with albiglutide and 47% with placebo). This limits our confidence in the estimate of the between-group differences.

In patients who were inadequately controlled on pioglitazone with or without metformin, at 52 weeks, the addition of albiglutide resulted in a larger decrease of HbA1c compared to placebo.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on pioglitazone with or without metformin, weight change at 52 weeks did not differ significantly between albiglutide and placebo.
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 4.7% with albiglutide and 6.6% with placebo.
GRADE: not applicable

Rates of diarrhea were 11.3 % with albiglutide and 8.6% with placebo.
Rates of nausea were 10.7% with albiglutide and 11.3% with placebo.
Rates of vomiting were 4.0% with albiglutide and 4.0% with placebo.
GRADE: not applicable

There were no events of severe hypoglycemia.
Severe hypoglycemia occurred in 3.3% with albiglutide and 1.3% with placebo.
GRADE: not applicable

4.5 Combination therapy with one or more oral antidiabetic drugs

4.5.1 Albiglutide + 1 or more OAD versus liraglutide + 1 or more OAD

4.5.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Pratley 2014(20) HARMONY 7 Design: RCT (OL) (PG) non-inferiority study Duration of follow-up:32 weeks	n:841 Mean age: 55y Prior/current treatment: (35% MET, 44% MET + SU, 9% MET + SU + TZD, 5% MET + TZD…) DMII duration:8.4y Baseline HbA1c: 8.1% Mean BMI: 32.8 Previous CV event: 4% Renal impairment: NR <u>Inclusion</u> <u>at</u> least 18 years old, with type 2 diabetes uncontrolled (HbA1c ≥7·0% and ≤10·0%) on metformin, thiazolidinediones,	albiglutide 30 mg/w titrated to 50 mg/w at week 6 Vs liraglutide 0.6mg/d titrated to 1.2mg/d at week 1 and 1.8 mg at week 2 in addition to this background treatment: 1 or more OAD <u>Hyperglycaemia rescue protocol</u>**:** predefined criteria, see	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: no FOLLOW-UP: <u>Discontinued treatment</u>: albi: 13.7% lira: 16.2% <u>Hyperglycaemic rescue</u>: albi: 15% lira: 8% <u>Statistical method for drop out/missing data</u> : LOCF <u>Data handling for rescued patients</u>:last observation before rescue
			Change in HbA1c from baseline at week 32 (PO) *ANCOVA model, with main effects for treatment group, region, history of myocardial infarction, and age, with baseline HbA1c as a continuous covariate.*	albi:-0.79% (-0.78 adjusted) lira: -0.98 (-0.98 adjusted) treatment difference: 0.21 (95%CI 0.08 to 0.34) p for non-inferiority 0.0846 non-inferiority criterion not met a per protocol analysis that excluded patients with major protocol violations was consistent with the primary analysis 'Subgroup analyses on the primary efficacy endpoint (baseline HbA1c, sex, race, ethnicity, age, diabetes duration, and background oral antidiabetic drugs) were consistent with the primary endpoint for the overall population' results presented in forest plot but no sensitivity analysis reported
			Body weight change from baseline	albi:-0.64kg,(95%CI -1.00 to -0.28) lira: -2.19kg, (95%CI -2.55 to -1.83)	

	sulfonylureas, or any combination of these drugs, and a BMI of at least 20 kg/m² but no higher than 45 kg/m², Creatinine clearance >60 mL/min (calculated using the Cockcroft-Gault formula) <u>Exclusion</u> History of cancer, , that has not been in full remission for at least 3 years before screening. 2. History of treated diabetic gastroparesis. Current ongoing symptomatic biliary disease or history of pancreatitis. History of significant GI surgery. Recent clinically significant cardiovascular and/or cerebrovascular disease: Previous history of stroke or transient ischemic attack within 1 month	below <u>Stratification:</u> by HbA1c value at week –1 (<8·0% vs ≥8·0%), previous history of myocardial infarction (yes or no), and age (<65 years vs ≥65 years)		**treatment difference -1.55 kg (95%CI -1.05 to -2.06)** **SS more weight loss with lira**	'<u>modified' ITT</u>: all randomly assigned patients who received at least one dose of study drug and had a baseline assessment and at least one post-baseline HbA1c assessment 402/422 albi 403/419 lira safety population : all patients who received at least 1 dose of study drug: 96% albi 97% lira SELECTIVE REPORTING: no Other important methodological remarks 4 week run-in and stabilization before treatment 95% CI non-inferiority upper margin of 0·3% for the change in HbA1c. Sponsor: GlaxoSmithKline
			Blood pressure change from baseline (SystBP/DiastBP)	NR	
			Safety		
			Death	NR	
			Cardiovascular adverse events investigator-assessed (also included hypertension)	albi:8.2% lira: 10.5% risk difference –2.4% (95% CI –6.4% to 1.6%)	
			Any adverse events	albi:75.5% lira: 77.7% risk difference –2·2% (–8·0% to 3·6%) NS	
			Serious adverse events	NR	
			Adverse event leading to withdrawal	albi:7.7% lira: 10.0% (calculated by literature group)	
			Any gastro-intestinal adverse event	albi:35.9% lira: 49.0% risk difference –13.1% [95% CI –19.9 to –6.4%] p = 0.0001	
			Diarrhoea	albi:14.9% lira: 13.5% risk difference 1·4% (–3·4% to 6·2%)	
			Nausea	albi:9.9%	

	before screening. Acute coronary syndrome, documented MI within the 2 months before screening and during the period up until receiving the first dose of study medication; Any cardiac surgery within the 2 months before screening and during the period up until receiving the first dose of study medication; Unstable angina the 2 months before screening and during the period up until receiving the first dose of study medication; Unstable cardiac rhythm; For patients taking a TZD (e.g., pioglitazone or rosiglitazone), current or history of heart failure (New York Heart Association class I to IV); for patients not taking a TZD, current or history of heart failure (New York			lira: 29.2% risk difference 19·3% (–24·6% to –14·0%) SS in favour of albi (less nausea with albi)	
			Vomiting	albi: 5% lira: 9% risk difference –4·4% (–7·9% to –0·8%) SS (more vomiting with lira)	
			Severe hypoglycaemia defined according to the criteria of the American Diabetes Association Workgroup on Hypoglycaemia (pre rescue)	albi:0 lira: 0	
			Documented symptomatic hypoglycaemia defined according to the criteria of the American Diabetes Association Workgroup on Hypoglycaemia (pre rescue)	albi:10.4% lira: 13.0% risk difference: –2.4%; 95% CI –7.0 to 1.8%; p=0.25) 'Most hypoglycaemia events in the albiglutide (>90%) and liraglutide (>85%) groups occurred in patients taking concomitant sulfonylurea therapy'	
			Injection site reactions (and related terms)	albi:12.9% lira: 5.4% 7·5% [95% CI 3·6–11·4]; p=0·0002 ss in favour of lira	
			Thyroid cancer	albi:0 lira: 0	

	Heart Association class II to IV); Resting systolic pressure is >160 mm Hg and/or diastolic pressure >100 mm Hg.				
			Pancreatitis (adjudication committee) number of patients	definite or probable pancreatitis albi:1 lira: 2	

Table 51

Hyperglycaemia rescue before week 12 FPG >250mg/dl, after week 12 HbA1C > 8.5%

4.5.1.2 *Summary and conclusions*

Albiglutide 50 mg/w + oral antidiabetic drugs versus liragltutide 1.8mg/d + oral antidiabetic drugs			
Bibliography: Pratley 2014(20) HARMONY 7			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	841 (1) 32 weeks	albi:-0.79% lira: -0.98 treatment difference: 0.21 (95%CI 0.08 to 0.34) **non-inferiority of albiglutide not established**	⨁⨁⨀⨀ **LOW** Study quality: -1 15% drop out and 12 % hyperglycaemic rescue with LOCF. Open label. Consistency:NA Directness: -1 no distinctions as to concomitant treatment Imprecision:ok
Body weight change from baseline	841 (1) 32 weeks	albi:-0.64kg lira: -2.19k **treatment difference** **-1.55 kg (95%CI -1.05 to -2.06)** **SS more weight loss with liraglutide**	⨁⨁⨀⨀ **LOW** Study quality: -1 15% drop out and 12 % hyperglycaemic rescue. Open label. Consistency:NA Directness: -1 no distinctions as to concomitant treatment Imprecision:ok
Adverse events leading to withdrawal	841 (1) 32 weeks	albi:7.7% lira: 10.0% (calculated by literature group)	Not applicable
Diarrhea	841 (1) 32 weeks	albi:14.9% lira: 13.5% risk difference 1·4% (–3·4% to 6·2%) NS	⨁⨁⨀⨀ **LOW** Study quality: - 1 15% drop out; open label Consistency: NA Directness: -1 no distinctions as to concomitant treatment Imprecision: ok
Nausea	841 (1) 32 weeks	albi:9.9% lira: 29.2% risk difference **19·3% (–24·6% to –14·0%)** **SS** **(less nausea with albiglutide)**	⨁⨁⨀⨀ **LOW** Study quality: - 1 15% drop out and open label Consistency: NA Directness: -1 no distinctions as to concomitant treatment Imprecision: ok
Vomiting	841 (1) 32 weeks	albi:5% lira: 9% risk difference **–4·4% (–7·9% to –0·8%)** **SS** **(more vomiting with liraglutide)**	⨁⨁⨀⨀ **LOW** Study quality: - 1 15% drop out and open label Consistency: NA Directness: -1 no distinctions as to concomitant treatment Imprecision: ok
Severe hypoglycaemia	841 (1) 32 weeks	albi:0 lira: 0	Not applicable

Table 52

In this open label, non-inferiority RCT, 841 patients with type 2 diabetes, inadequately controlled by 1 or more oral antidiabetic drugs, were randomized to albiglutide 50 mg/w (titrated from 30 mg the first 6 weeks) or liraglutide 1.8mg/d (titrated from 0.6 mg to 1.2mg, both for 1 week) for 32 weeks. The mean age was 55 years, mean duration of diabetes 8.4 years, mean baseline HbA1c was 8.1% and mean BMI was 32.8 kg/m^2. Only 4% of participants had had a previous cardiovascular event. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

The methodological limitations of this study were the open label design, a drop out of 15% and a hyperglycaemic rescue in 15% of albiglutide users and 8% of liraglutide users. This limits our confidence in the estimate of the between-group differences.
The interpretation of these results is further limited because of the inclusion of patients with any concomitant oral antidiabetic therapy. Based on these results, it is difficult to make statements about the combination of a glp-1 receptor agonist with a specific oral antidiabetic agent.

In patients who were inadequately controlled on 1 or more oral antidiabetic drugs, the addition of albiglutide **cannot be considered non-inferior** to the addition of liraglutide for HbA1c decrease at 32 weeks.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on 1 or more oral antidiabetic drugs, at 32 week, there was less weight loss with albiglutide than with liraglutide (mean difference -1.55kg)
GRADE: LOW quality of evidence

Withdrawal from the study due to adverse events was seen in 7.7% with albiglutide and 10.0% with liraglutide.
GRADE: not applicable

Rates of diarrhea were 14.9% with albiglutide and 13.5% with liraglutide. The difference was **not** statistically significant.
GRADE: LOW quality of evidence

Rates of nausea were 9.9% with albiglutide and 29.2% with liraglutide. . The difference was statistically significant.
GRADE: LOW quality of evidence

Rates of vomiting were 5 % with albiglutide and 9% with liraglutide. . The difference was statistically significant.
GRADE: LOW quality of evidence

There were no events of severe hypoglycemia.
GRADE: not applicable

4.5.2 Albiglutide +/- OAD versus sitagliptin +/- OAD in patients with renal impairment

4.5.2.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Leiter 2014(21) HARMONY 8 Design: RCT (DB) (PG) non-inferiority study Duration of follow-up: 52 w	n:507 Race/Ethnicity: 45.8% Caucasian Mean age: 63.3y Prior/current treatment:OAD, no further specification DMII duration:11.2Y Baseline HbA1c: 8.2% (more patients with HbA1C below 8% with albi) Mean BMI: 30.4kg/m2 Previous MI: 8.7% Renal impairment: mild (≥60 ≤89): 52% moderate(≥30 ≤59)41% severe (≥15 ≤29):7% mL/min/1.73 m2, respectively) (MDRD formula) <u>Inclusion</u> >18 years of age with type 2	albiglutide 30 mg once weekly (with treatment-masked uptitration, if needed, to 50 mg weekly) Vs sitagliptin 100 mg, 50 mg and 25 mg for mild, moderate or severe renal impairment respectively in addition to this background treatment: All patients continued to receive their prescribed oral antihyperglycemic medication regimen (metformin, thiazolidinedione, sulfonylurea, or any combination of these oral antihyperglycemic medications) for the duration of the	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: unclear FOLLOW-UP: <u>Discontinued treatment by 52 weeks</u>: albi 20% sita 25% Reason dropout described: yes <u>Uptitration of study medication</u>: albi: 57% (35% by week 26) <u>Hyperglycaemic rescue</u>: albi (week 26 and 52) 6.1% and 17.9% sita (week 26 and 52): 12.1% and 28.3% (metformin most commonly used)
			Change in HbA1c from baseline at week 26(PO) *model-adjusted LS mean*	ITT population albi: -0.83% sita:-0.52% *"with similar results across all three baseline eGFR groups (data not shown)."* treatment difference: -0.32% (95%CI -0.49 to -0.15) albiglutide noninferior to sitagliptin albiglutide superior to sitagliptin (P = 0.0003). mild RI -0.13(95%CI-0.37 to 0.11) moderate RI -0.53(95% -0.80 to -0.26) severe RI -0.47 (95%CI-1.12 to 0.18)	
			Change in HbA1c from baseline at week 52 (SO)	per protocol (only patients with data at this time point) represented in a figure, no statistical test given	
			Body weight change from baseline	26 weeks ITT (with LOCF) albi:-0.79kg sita:-0.19 kg	

	diabetes; baseline HbA1c between 7.0 and 10.0%; BMI between 20 and 45 kg/m2, fasting C-peptide level of >0.8 ng/mL GFR of >15 to <90 mL/min/1.73 m2, hemoglobin of >10 g/dL for male patients and >9 g/dL for female patients, and normal levels of thyroid-stimulating hormone or clinically euthyroid. <u>Exclusion</u> Patients with malignant disease (except squamous cell or basal cell carcinoma); a history of diabetic gastroparesis, current ongoing symptomatic biliary disease or history of pancreatitis, significant gastrointestinal	study with the exception of patients with GFR <60 mL/min/1.73 m2, who were washed off their background metformin. Instructions for downtitration of sulfonylureas were also provided <u>Hyperglycaemia uptitration of albiglutide or matching placebo protocol:</u> see below <u>Hyperglycaemia rescue protocol</u>**:** yes, see below <u>Stratification:</u> stratified according to severity of renal impairment (mild, moderate, or severe), prior history of myocardial infarction (yes or no), and age		p<0.05 52 weeks per protocol (observed cases, excluding hyperglycaemic rescue) albi:-0.82kg sita:0.32kg p<0.05	<u>Statistical method for drop out/missing data</u> : LOCF <u>Data handling for rescued patients</u>: last observation before rescue carried forward values carried forward at 26 weeks albi 16% sita 24% <u>ITT</u>:all patients having pre- and postbaseline data 96% SELECTIVE REPORTING: yes unclear reporting of secondary endpoints at 52 weeks - 4 week run-in - noninferiority margin of 0.4 (no explanation for this choice given) - noninferiority testing done on ITT population only, not on per protocol population Sponsor: GlaxoSmithKline
			Blood pressure change from baseline (SystBP/DiastBP)	NR	
			Safety: "on therapy" defined as events that occurred within 56 days of treatment regardless of rescue		
			Death	albi:4 sita:4	
			Cardiovascular adverse events (blinded adjudication)	albi: sita:	
			Any adverse events	albi:83.5% sita:83.3%	
			Serious adverse events	albi:13.7% sita:14.6%	
			Adverse event leading to withdrawal	albi:10.4% sita:10.6%	
			Any gastro-intestinal adverse event	albi:31.7% sita:25.2%	
			Diarrhoea	albi:10.0% sita:6.5% NT	

	(GI) surgery or surgeries thought to significantly affect upper GI function, recent (within predefined time scales) clinically significant cardiovascular and/or cerebrovascular disease, a history of human immunodeficiency virus infection, and acute symptomatic hepatitis B or C infection. Requirements for levels of total bilirubin, alanine aminotransferase, aspartate aminotransferase, amylase, lipase, or fasting triglycerides	(<65 or >65 years of age).	**Nausea**	albi:4.8% sita:3.3% NT, described as 'no marked difference'	
			Vomiting	albi:1.6% sita:1.2% NT, described as 'no marked difference'	
			Severe hypoglycaemia *no definition given, not clear if prerescue or total population*	albi:0.4% sita:1.6%	
			Documented symptomatic hypoglycaemia *no definition given, not clear if prerescue or total population*	albi:11.6% sita:6.1% NT, described as 'a higher proportion' with albiglutide	
			Injection site reactions	albi:8% sita:3.7% NT, described as 'a higher proportion' with albiglutide	
			Thyroid cancer	albi:0 sita:0	
			Pancreatitis (blinded adjudication)	albi:0.4% sita:0	

Table 53

The mean albiglutide dose was 40.2 mg at week 26 and 42.4 mg at week 52

Hyperglycaemia titration or rescue (simplified): before week 12 FPG > 250mg/dl or > 280 mg/dl; from week 12 HbA1c> 7% or > 8.5%

4.5.2.2 *Summary and conclusions*

Albiglutide 30 to 50mg once weekly +/- OAD versus sitagliptin 25 to 100 mg +/- OAD in patients with renal impairment			
Bibliography: Leiter 2014(21) HARMONY 8			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	507 (1) 26 weeks	26 weeks albi: -0.83% sita:-0.52% treatment difference: **-0.32% (95%CI -0.49 to -0.15)** **SS** **albiglutide superior to sitagliptin**	⊕⊕⊖⊖ **LOW** Study quality:-1 values carried forward albi 16% and sita 24%. No per protocol analysis for non-inferiority Consistency: NA Directness:-1 no information on concomitant medication insufficient Imprecision: ok
Body weight change from baseline	507 (1) 26 weeks 52 weeks	26 weeks (modified ITT) albi:-0.79kg sita:-0.19 kg p<0.05 52 weeks (per protocol, excluding rescued patients) albi:-0.82kg sita:0.32kg p<0.05	⊕⊕⊖⊖ **LOW** Study quality:-1 values carried forward albi 16% and sita 24%. Consistency: NA Directness:-1 information on concomitant medication insufficient Imprecision: unable to assess ⊕⊖⊖⊖ **VERY LOW** Study quality:-2 per protocol population is 1/3 to ½ of total population Consistency: NA Directness:-1 no information on concomitant medication Imprecision: see drop out: small sample size
Adverse events leading to withdrawal	507 (1) 52 weeks	albi:10.4% sita:10.6% NT	Not applicable
Diarrhea	507 (1) 52 weeks	albi:10.0% sita:6.5% NT	Not applicable
Nausea	507 (1) 52 weeks	albi:4.8% sita:3.3% NT, described as 'no marked difference'	Not applicable
Vomiting	507 (1) 52 weeks	albi:1.6% sita:1.2% NT, described as 'no marked difference'	Not applicable
Severe hypoglycaemia	507 (1) 52 weeks	albi:0.4% sita:1.6% NT	Not applicable

Table 54

This double blind, noninferiority RCT included 507 patients with type 2 diabetes and mild to severe renal impairment, who were inadequately controlled by diet/exercise or 1 or more OAD. They were randomized to albiglutide 30 mg once weekly or sitagliptin once daily for 52 weeks. Albiglutide could be uptitrated to 50 mg/w in case of persistent hyperglycaemia, sitagliptin was dosed according to eGFR (100 mg for mild renal impairment, 50 mg for moderate and 25 mg for severe renal impairment).
The mean age was 63 years, mean duration of diabetes 11.2 years, mean baseline HbA1c was 8.2% and mean BMI was 30.4 kg/m^2. 8.7% of participants had had a previous myocardial infarction.
The primary endpoint was measured at 26 weeks.

There was a large drop-out throughout the study (23% by 52 weeks) and a large proportion of patients received rescue therapy with other antidiabetic drugs because of hyperglycemia (18% with albiglutide and 29% with sitagliptin at 52 weeks).
The authors did not report the concomitant antidiabetic treatment of the participants. It is unclear what OADs were being used and whether this was similar in both arms of the study.

In type 2 diabetic patients with renal impairment who were inadequately controlled on diet and exercise +/- oral antidiabetic drugs, the addition of albiglutide resulted in a larger decrease of HbA1c **at 26 weeks** compared to the addition of sitagliptin.
GRADE: LOW quality of evidence
In the different subgroups of patients with mild, moderate or severe renal impairment, the results were consistent: albiglutide was non-inferior to sitagliptin in mild and severe renal impairment. In moderate renal impairment, albiglutide was superior, but drop out and hyperglycaemic rescue in this subgroup was higher than average.
GRADE for subgroups: VERY LOW quality of evidence

In type 2 diabetic patients with renal impairment who were inadequately controlled on diet and exercise +/- oral antidiabetic drugs, there was more weight loss with albiglutide than with sitagliptin, **at 26 weeks and at 52 weeks**.
GRADE at 26 weeks: LOW quality of evidence
GRADE at 52 weeks: VERY LOW quality of evidence

Adverse events were reported at 52 weeks, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 10.4% with albiglutide and 10.6% with sitagliptin.
GRADE: not applicable

Rates of diarrhea were 10% with albiglutide and 6.5 % with sitagliptin.
Rates of nausea were 4.8% with albiglutide and 3.3 % with sitagliptin.
Rates of vomiting were 1.6% with albiglutide and 1.2 % with sitagliptin.
GRADE: not applicable

Severe hypoglycemia occurred in 0.4% with albiglutide and 1.6% with sitagliptin.
GRADE: not applicable

4.6 Combination therapy with basal insulin

4.6.1 Albiglutide + basal insulin + OAD versus prandial insulin + basal insulin + OAD

4.6.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Rosenstock 2014(22) HARMONY 6 Design: RCT (OL) (PG) non-inferiority study Duration of follow-up:52 weeks (26 week follow-up reported here)	n:586 Mean age: 54.8 to 56.3y Prior/current treatment:any basal insulin +/- oral agents (69% MET,2% TZD, 23 % neither) Mean DMII duration:11y Mean baseline HbA1c:8.4 to 8.5 Mean BMI: NR weight: 91.6 to 92.5kg Previous MI: 7.7% to 9.6% Renal impairment: NR <u>Inclusion</u>	albiglutide 30 (uptitrated to 50 mg/w if necessary) Vs prandial insulin lispro 3x/d (titrated) in addition to this background treatment: insulin glargine 1x/d (titrated according to FPG) + MET and or PIO and/or alpha-glucosidase (SU, glinides, DPP4 discontinued)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: unclear FOLLOW-UP: <u>Study completers</u>: >90% in each group reached 26 weeks Reason described: yes <u>Uptitration of study medication</u>: albi:51% ins lispro:average 15.5IU to 30.6IU <u>Hyperglycaemic rescue</u>:
			Change in HbA1c from baseline (PO) model-adjusted leastsquares mean	albi:-0.82 +/- 0.06% ins lispro:-0.66 +/- 0.06% treatment difference, -0.16% (95% CI -0.32 to 0.00) P < 0.0001 albiglutide is noninferior to insulin lispro when added to insulin glargine statistical superiority not reached (borderline significance) p=0.0533 *no difference between treatment arms in HbA1c change from baseline at 26 weeks when postrescue values were included in the analysis (least-squares mean difference, -0.06%; (95% CI -0.22 to 0.11)*	
			Body weight change from baseline	albi:-0.73(SE+/-0.2) kg ins lispro:+0.81 (SE+/-0.2)kg treatment difference -1.5 kg (95% CI-2.1 to -1.0) p<0.0001 SS in favour of albiglutide	
			Blood pressure change	NR	

	18–75 years; type 2 diabetes inadequately controlled on glargine, detemir, or NPH insulin, with or without oral antidiabetes drugs, for >6 months and <5 years; HbA1c ≥7.0% and ≤10.5%; BMI ≥20 kg/m2 and ≤45 kg/m2 HbA1c between 7.0% and 10.5%, inclusive, at visit 5 (week −1). Creatinine clearance >60 mL/min; TSH normal or clinically euthyroid <u>Exclusion</u> ongoing symptomatic biliary disease or history of pancreatitis, lipase level above upper limit of normal (ULN), recent clinically significant cardiovascular or cerebrovascular disease, and history or family history of medullary carcinoma	<u>Hyperglycaemia uptitration protocol:</u> albi according to hba1c, glargine according to FPG, lispro according to preprandial /postprandial glucose level <u>Hyperglycaemia rescue protocol</u>**:** not meeting prespecified HbA1c goals (weeks 4–12: 9.0% and <0.5% change from baseline; weeks 12–16: 8.5%; weeks 16–26: 8.0%) and had not received a recent titration.	**from baseline (SystBP/DiastBP)**		criteria fulfilled: albi:28% ins lispro:38% actual rescue received albi: 21% ins lispro: 21% <u>Statistical method for drop out/missing data</u> : LOCF <u>Data handling for rescued patients</u>:last value before rescue <u>ITT</u>:received at least 1 dose of study medication and had both baseline and postbaseline HbA1c assessments. albi: 97% ins lispro: 96% SELECTIVE REPORTING: no information on cardiovascular outcomes Other important methodological remarks run-in: glargine stabilization period 4-8w (other basal insulin was switched to insulin glargine) non-inferiority margin: 0.4%, no reason for this margin given
			Safety (pre and postrescue, except hypoglycaemia, which is prerescue only)		
			Death	NR	
			Cardiovascular adverse events *adjudicated by masked committee*	NR	
			Any adverse events	albi:73.3% ins lispro:70.8% NT 'The proportion of patients who had events in the prerescue period was similar to that of the overall population.'	
			Serious adverse events	albi:7.4% ins lispro: 6.8% NT	
			Adverse event leading to withdrawal	albi:5.3% ins lispro:0.4% NT	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	albi:13.0% ins lispro:4.3% NT 'more frequently with albiglutide'	
			Nausea	albi:11.2%	

	or multiple endocrine neoplasia type 2	<u>Stratification:</u> stratified by HbA1c (≤8.5% or >8.5%, history of myocardial infarction (yes or no), and current oral therapy (MET without PIO, PIO without MET, both, or neither)		ins lispro:1.4% NT 'more frequently with albiglutide'	A multiple comparisons adjustment strategy was implemented for the multiple inferential tests among the secondary objectives to preserve the study's nominal criterion significance level of 0.05. Of note, 30 patients (15 per arm) continued sulfonylurea treatment at study entry and during the study. A sensitivity analysis that used observed HbA1c values with no missing data imputation showed findings consistent with the intent-to-treat population. Sponsor: GlaxoSmithKline
			Vomiting	albi:6.7% ins lispro:1.4% NT 'more frequently with albiglutide'	
			Severe hypoglycaemia according to American Diabetes Association criteria; prerescue events	albi:0% ins lispro:0.7%	
			Documented symptomatic hypoglycaemia according to American Diabetes Association criteria	albi:15.8% ins lispro:29.9%	
			Injection site reactions	albi:9.5% ins lispro:5.3% NT 'more frequently with albiglutide'	
			Thyroid cancer	albi:1 ins lispro:0	
			Pancreatitis *adjudicated by masked committee*	albi: 0 ins lispro:0	

Table 55

The mean glargine dose increased from 47 to 53 IU (albiglutide) and from 44 to 51 IU (lispro).

Definitions according to Workgroup on Hypoglycemia, American Diabetes Association (ADA), 2005.
severe, requires assistance;
documented symptomatic, symptoms, glucose of <3.9 mmol/L;
asymptomatic, no symptoms, glucose <3.9 mmol/L;
probable symptomatic, symptoms,glucose not measured;

4.6.1.2 *Summary and conclusions*

Albiglutide + insulin glargine +/- oral antidiabetic drugs versus prandial insulin lispro + insulin glargine +/- oral antidiabetic drugs			
Bibliography: Rosenstock 2014(22) HARMONY 6			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	586 (1) 26 weeks	albi:-0.82 ins lispro:-0.66 treatment difference **-0.16% (95% CI -0.32 to 0.00)** **P < 0.0001** **albiglutide is non-inferior to insulin lispro**	⊕⊕⊖⊖ **LOW** Study quality:- 1 open label, <10% drop out but 20% rescue, Consistency: NA Directness: -1 glargine stabilization, inadequate titration of insulin, no distinction as to concomitant OAD Imprecision: ok
Body weight change from baseline	586 (1) 26 weeks	albi: -0.73kg ins lispro: +0.81kg treatment difference **-1.5 kg (95% CI-2.1 to -1.0)** **p<0.0001** **SS in favour of albiglutide**	⊕⊕⊖⊖ **LOW** Study quality:- 1 open label, <10% drop out but 20% rescue, Consistency: NA Directness: -1 glargine stabilization, inadequate titration of insulin, no distinction as to concomitant OAD Imprecision: ok
Adverse events leading to withdrawal	586 (1) 26 weeks	albi:5.3% ins lispro:0.4% NT	Not applicable
Diarrhea	586 (1) 26 weeks	albi:13.0% ins lispro:4.3% NT, described as 'more frequently with albiglutide'	Not applicable
Nausea	586 (1) 26 weeks	albi:11.2% ins lispro:1.4% NT, described as 'more frequently with albiglutide'	Not applicable
Vomiting	586 (1) 26 weeks	albi:6.7% ins lispro:1.4% NT, described as 'more frequently with albiglutide'	Not applicable
Severe hypoglycaemia	586 (1) 26 weeks	albi:0% ins lispro:0.7% NT	Not applicable

Table 56

In this open label, non-inferiority RCT, 586 patients with type 2 diabetes, inadequately controlled by basal insulin with or without oral antidiabetic agents, were switched to insulin glargine + existing oral antidiabetic agents (but stopping sulfonylurea, glinides and DPP-4 inhibitors).

After stabilization, the participants were randomized to albiglutide 30 mg once weekly or prandial insulin lispro for 52 weeks. Albiglutide could be titrated to 50 mg in case of persistent elevated

HbA1c, insulin glargine was titrated according to FPG, insulin lispro was titrated according to pre-/post prandial glucose level.
The 26-week results (with primary endpoint) are reported here.
The mean age was 55y, mean duration of diabetes 11 years, mean baseline HbA1c was 8.5% and mean weight was 92 kg. About 8% of participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

The applicability of the results of this study to a population with inadequate control on basal insulin is somewhat impaired by all the switches that took place before randomisation. Also, the authors state that the titration of insulin glargine and insulin lispro throughout the study was not optimal. This limits our confidence in the results.

In patients who were inadequately controlled on insulin glargine +/- OAD, the addition of albiglutide was non-inferior to the addition of prandial insulin lispro for the HbA1c decrease at 26 weeks.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on insulin glargine +/- OAD, at 26 weeks, the weight in the albiglutide group was decreased compared to the insulin lispro group (in which the weight had increased from baseline).
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 5.3% with albiglutide and 0.4% with insulin lispro.
GRADE: not applicable

Rates of diarrhea were 13.0 % with albiglutide and 4.3 % with insulin lispro.
Rates of nausea were 11.2 % with albiglutide and 1.4 % with insulin lispro.
Rates of vomiting were 6.7% with albiglutide and 1.4% with insulin lispro.
GRADE: not applicable

Severe hypoglycemia occurred in 0% with albiglutide and 0.7% with insulin lispro.
GRADE: not applicable

4.7 Albiglutide: other endpoints from the RCTs

4.7.1 Blood pressure

Blood pressure change from baseline was reported in 3 of the 8 trials that were eligible for this review.
Only 1 trial performed statistical tests for this outcome (Ahren 2014(16)). It found no statistically significant difference in the blood pressure change at 104 weeks between albiglutide, sitagliptin, glimepiride and placebo, when added to exisiting metformin therapy.
Karagiannis 2015(23) performed a meta-analysis of 4 trials that compared albiglutide versus placebo (in the presence of any concomitant OAD) and found no statistically significant difference in the blood pressure change between albiglutide and placebo.
The level of evidence is LOW to VERY LOW because of inconsistent reporting and the large drop-out in the included trials.

4.7.2 Injection site reactions

Injection site reactions (ISR) were reported in all the trials that were eligible for this review.
Only 1 trial performed statistical tests for this outcome: Pratley 2014(20) compared albiglutide to liraglutide, added to exisiting OAD, and found less ISR with liraglutide (5.4%) than with albiglutide (12.9%), p=0.0002.
Injection site reactions were reported in 8% to 22.2% of patients on albiglutide compared to 3.5% to 9.9% of patients in the placebo group.
The definition of what was considered to be an injection site reaction was usually not specified.

4.7.3 Cardiovascular adverse events (including heart failure)

To date, there are no results from trials that are designed to evaluate the cardiovascular safety of albiglutide.
Cardiovascular adverse events were reported in most of the trials that were eligible for this review. There was no independent adjudication for cardiovascular events in these trials. Statistical tests were not performed and would be of little value due to the relatively short duration of the trials and the low event rate.

A prespecified meta-analysis of all the HARMONY trials by Fisher 2015(24) reported on cardiovascular safety. 5107 patients were included. The primary endpoint was a composite of first occurrence of **major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) or hospital admission for unstable angina**.
No statistically significant difference could be found between albiglutide and all comparators (HR 1.00; 95% CI 0.68-1.49). The overall event rate was 1.1 events per 100 person-years with albiglutide and 1.2 events with all comparators.
When a separate analysis was done for albiglutide versus placebo (added to existing OAD) or albiglutide versus active treatment, again, no differences were found.
No statistically significant difference was found between albiglutide and all comparators for hospital admission due to **heart failure**.

The quality of this evidence is VERY LOW, because these trials were not designed to evaluate cardiovascular safety, studies with different comparators and concomitant treatment were pooled, event rates were low and the confidence interval does not exclude clinically significant benefit or harm.

4.7.4 Pancreatitis and thyroid cancer

Because of the low event rate of pancreatitis and thyroid cancer, these outcomes will be discussed in the chapter 'rare safety outcomes'.

5 Dulaglutide – evidence tables and conclusions

5.1 Monotherapy

5.1.1 Dulaglutide versus metformin

5.1.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref	n:807	Dulaglutide	Efficacy		RANDO:
Umpierrez 2014 AWARD-3(25)	Race/Ethnicity:74% caucasian Mean age: 56	1.5mg 1x/w vs dulaglutide 0.75	**Change in HbA1c from baseline at 26 weeks (PO)**	dula 1.5: -0.78% (SE+/- 0.06%) dula 0.75: -0.71% (SE+/- 0.06%) met: -0.56% (SE+/-0.06%) treatment difference:	Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes
Design: RCT (DB) (PG) noninferiority trial	Prior/current treatment: no previous OAD or low dose OAD monotherapy (70%, mostly metformin) DMII duration:3 Baseline HbA1c:7.6 Mean BMI: 34 Previous CV event: NR	mg 1x/w Vs metformin (up to 1500-2000mg/d) Standard		dula 1.5 vs met -0.22% [95%CI -0.36 to -0.08] **SS p=0.002** **dulaglutide noninferior to metformin** **'dulaglutide superior to metformin'** dula 0.75 vs met -0.15% (no CI reported) P = 0.020	Personnel: yes Assessors: unclear Remarks on blinding method: double-blind, double-dummy (both injectable and oral placebo) FOLLOW-UP:
Duration of follow-up:52 weeks + 4 weeks safety follow up	Renal impairment: NR <u>Inclusion</u>	dietary and physical activity counseling was provided.		'dulaglutide noninferior to metformin' '*Treatment differences between dulaglutide arms and metformin were*	<u>Discontinued treatment</u>: up to 26 weeks dula 1.5: 13.4% dula 0.75: 10.4% met: 15.7%

	Patients ≥18 years of age were eligible to participate if they had type 2 diabetes for a duration of ≥3 months and ≤5 years, glycosylated hemoglobin A1c (HbA1c) ≥6.5% and ≤9.5%, were on diet and exercise alone, or on one oral antihyperglycemic medication (OAM) for ≥3 months prior to screening. Individuals who were receiving an OAM were only eligible if they were taking ≤50% of the approved maximum daily dose per respective labels in participating countries. Exclusion thiazolidinediones or GLP-1 receptor agonists during the 3 months prior to screening or had ever received chronic insulin therapy.	Hyperglycaemia rescue protocol: patients who met prespecified criteria for severe, persistent hyperglycemia could be rescued, thresholds and method not provided. (they remained in the study) Stratification: stratified by country and prior OAM use		*consistent within the two subgroups (treatment by- OAM status interaction P = 0.80)'.* No subgroup analyses reported	up to 52 weeks dula 1.5: 18.2% dula 0.75: 19.3% met: 20.5% Reason described: yes Hyperglycaemic rescue : 26 weeks (rescue for severe, persistent hyperglycaemia: dula 1.5: 2.2% dula 0.75: 2.2% met: 2.6% 52 weeks (rescue for severe, persistent hyperglycaemia: dula 1.5: 4.5% dula 0.75: 3.0% met: 5.2% Statistical method for drop out/missing data : LOCF Data handling for rescued patients:last value before rescue ITT: all randomized patients who received at least one dose of study treatment. SELECTIVE REPORTING: unclear
			Change in HbA1c from baseline at 52 weeks	dula 1.5: -0.70 %(SE+/- 0.07%) dula 0.75: -0.55 %(SE+/- 0.07%) met: -0.51% (SE+/- 0.07%) Compared with metformin, the HbA1c reduction was greater with dulaglutide 1.5 mg (adjusted P = 0.02) and similar with dulaglutide 0.75 mg in ANCOVA with LOCF. dula 1.5 and 0.75mg/w were noninferior to metformin in MMRM analysis	
			Body weight change from baseline	at 26 weeks: dula 1.5:-2.29 (+/-0.24kg) dula 0.75:-1.36(+/-0.24kg) met: -2.22(+/-0.24kg) at 52 weeks: NR 'maintained across treatment groups' 'Compared with metformin, decrease in body weight was similar with dulaglutide 1.5 mg and smaller with dulaglutide 0.75 mg at 26 (P = 0.003) and 52 weeks (P = 0.001).'	
			Blood pressure change from baseline	26 weeks dula 1.5:-1.9/0.05	

			(SystBP/DiastBP)	dula 0.75:-2.6/-1.0 met:-0.9/-0.64 52 weeks dula 1.5:-0.1/0.3 dula 0.75:-2.7/-1.4 met:-1.0/-0.4 described as 'comparable'	reporting for some outcomes Other important methodological remarks 2 weeks lead-in period in which OAD were discontinued uptitration of metformin in the first 4 weeks to 2000mg/day or 1500mg depending on tolerability The study was designed with 90% power to detect noninferiority of dulaglutide 1.5 mg versus metformin on HbA1c change from baseline at the 26-week primary end point with a margin of 0.4%, a SD of 1.3%, and a one-sided a of 0.025, assuming no true difference between treatments non-inferiority testing based on ITT inadequate information on rescue protocol (stated as 'provided in supplement', but no such data in supplement) 'A mixed-effects, repeated-measures (MMRM)
			Safety		
			Death	dula 1.5:0 dula 0.75:0 met:0	
			Cardiovascular adverse events	NR	
			Any adverse events	26 weeks dula 1.5:60.6% dula 0.75:55.6% met:56.3% 52 weeks dula 1.5:66.5% dula 0.75:65.6% met:63.4%	
			Serious adverse events	52 weeks dula 1.5: 5.6% dula 0.75: 7.4% met:6.0%	
			Adverse event leading to withdrawal	26 weeks dula 1.5:4.8% dula 0.75:2.2%	

				met:3.7% 52 weeks dula 1.5:5.2% dula 0.75:3.0% met:4.5% NT	analysis with additional factors for visit and treatment-by-visit interaction and patient as a random effect was used for assessment of other continuous secondary end points, as well as for sensitivity analyses of HbA1c and weight over time' note: however, this was reported in a graph, p value was usally reported but CI was not Sponsor: Eli Lily
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	26 weeks dula 1.5:10.0% dula 0.75:5.2% met:13.8% (SS less diarrhea with dulaglutide 0.75mg/week compared to metformin, p<0.001) 52 weeks dula 1.5:11.2% dula 0.75:7.8% met:13.8%	
			Nausea	26 weeks dula 1.5:19.0% dula 0.75:10.7% met:14.6% 52 weeks dula 1.5:19.7% dula 0.75:11.5% met:16.0%	

			Vomiting	26 weeks dula 1.5:8.6% dula 0.75:5.9% met:4.1% 52 weeks dula 1.5:9.7% dula 0.75:7.4% met:4.9%	
			Constipation	26 weeks dula 1.5:6.3% dula 0.75:3.3% met:0.7% 52weeks dula 1.5:6.7% dula 0.75:4.8% met:1.1% SS less constipation with metformin compared to dulaglutide 0.75 and 1.5mg/w ($p<0.05$)	
			Severe hypoglycaemia	dula 1.5:0 dula 0.75:0 met:0	
			Documented symptomatic hypoglycaemia	NR	
			Total hypoglycaemia	dula 1.5:12.3% dula 0.75:11.1% met:12.7%	

			Injection site reactions (n patients)	dula 1.5:10 dula 0.75:6 met:4	
			Thyroid cancer	NR	
			Pancreatitis independent adjudication group	dula 1.5:0 dula 0.75:0 met:0	

Table 57

Hypoglycaemic events: Workgroup on Hypoglycemia, American Diabetes Association
Total hypoglycemia was defined as plasma glucose <70 mg/dL (<3.9 mmol/L) and/or symptoms and/or signs attributable to hypoglycemia (16). Severe hypoglycemia was any episode requiring the assistance of another person to actively administer therapy
For the assessment of efficacy and hypoglycemia, only data obtained prior to rescue medication were used.

5.1.1.2 *Summary and conclusions*

Dulaglutide 0.75 mg or 1.5mg 1x/w versus metformin 1500-2000mg/d			
Bibliography: Umpierrez 2014 AWARD-3(25)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
HbA1c change from baseline (PO)	807 (1) 26 weeks	dula 1.5: -0.78% dula 0.75: -0.71% met: -0.56% dula 1.5 vs met treatment difference: -0.22% [95%CI -0.36 to -0.08] p=0.002 'dulaglutide 1.5 non-inferior to metformin' 'dulaglutide 1.5 superior to metformin' dula 0.75 vs met treatment difference: -0.15% (no CI reported) 'dulaglutide 0.75 noninferior to metformin'	⊕⊕⊕⊖ MODERATE Study quality: -1 inappropriate method of dealing with missing values (only 10% missing) and sensitivity analysis partially unreported+ see directness. Consistency: NA Directness: some patients had previous use of MET Imprecision: ok ⊕⊕⊖⊖ LOW Study quality: -1 inappropriate method of dealing with missing values (only 10% missing) and sensitivity analysis partially unreported+ see directness. Consistency: NA Directness: some patients had previous use of MET Imprecision: -1 unable to assess
	52 weeks	dula 1.5: -0.70 % dula 0.75: -0.55 % met: -0.51% dula 1.5 vs met treatment difference: p=0.02 SS (in ANCOVA analysis) dula 0.75 vs met treatment difference: NS but dula 1.5 and 0.75mg/w noninferior to metformin (in MMRM analysis)	⊕⊕⊖⊖ LOW Study quality: -1 inappropriate method of dealing with missing values (>20% missing), sensitivity analysis partially reported Consistency: NA Directness: some patients had previous use of MET Imprecision: -1 unable to assess
Body weight change from baseline	807 (1) 26 weeks	at 26 weeks: dula 1.5:-2.29 kg dula 0.75:-1.36 kg	⊕⊕⊕⊖ MODERATE Study quality: -1 inappropriate method of dealing with missing

		met: -2.22 kg NS for dula 1.5 vs met less weight loss with dulaglutide 0.75 compared to metformin p=0.003 at 52 weeks: 'maintained across treatment groups' less weight loss with dula 0.75 vs met p=0.001	values (only 10% missing) + see directness Consistency: NA Directness: some patients had previous use of MET Imprecision: unable to assess ⊕⊕⊖⊖ LOW Study quality: -1 >20% of attrition, LOCF and incomplete reporting of sensitivity analysis Consistency: NA Directness: ok Imprecision: -1 unable to assess
Adverse events leading to withdrawal	807 (1) 52 weeks	26 weeks dula 1.5:4.8% dula 0.75:2.2% met:3.7% 52 weeks dula 1.5:5.2% dula 0.75:3.0% met:4.5% NT	Not applicable
Diarrhea	807 (1) 52 weeks	26 weeks dula 1.5:10.0% dula 0.75:5.2% met:13.8% (SS less diarrhea with dulaglutide 0.75mg/week compared to metformin, p<0.001) 52 weeks dula 1.5:11.2% dula 0.75:7.8% met:13.8%	Not applicable
Nausea	807 (1) 52 weeks	26 weeks dula 1.5:19.0% dula 0.75:10.7% met:14.6% 52 weeks dula 1.5:19.7% dula 0.75:11.5% met:16.0%	Not applicable

Vomiting	807 (1) 52 weeks	26 weeks dula 1.5:8.6% dula 0.75:5.9% met:4.1% 52 weeks dula 1.5:9.7% dula 0.75:7.4% met:4.9%	Not applicable
Severe hypoglycaemia	807 (1) 52 weeks	dula 1.5:0 dula 0.75:0 met:0	Not applicable

Table 58

In this double blind, noninferiority RCT, 807 patients with type 2 diabetes, inadequately controlled by diet and exercise alone, or taking one oral antihyperglycaemic agent, were randomized to dulaglutide 1.5 mg once weekly, dulaglutide 0.75 mg once weekly or metformin titrated to 1500-2000mg for 52 weeks. About 70% of the included patients were already on one (low dose) oral antidiabetic agent (mostly metformin), for whom a 2 week washout period was required. The primary outcome was HbA1c change at 26 weeks.
The mean age was 56 years, mean duration of diabetes 3 years, mean baseline HbA1c was 7.6% and mean BMI was 34 kg/m^2.

Our confidence in the estimate of the between-group differences is limited by some questions regarding drop out and dealing with missing values. The authors performed a sensitivity analysis of their main outcomes (HbA1c and weight), however, these latter analyses were incompletely reported, raising doubts about the superiority claims for HbA1c with dulaglutide 1.5 mg and the non-inferiority claim for dulaglutide 0.75 mg (mainly at 26 weeks)..

In patients who were inadequately controlled on diet and exercise or 1 OAD, at 26 weeks, the monotherapy of **dulaglutide 1.5 mg** once weekly was **non-inferior** and also **superior** for the decrease of HbA1c compared to the monotherapy of metformin (treatment difference -0.22% [95%CI -0.36 to -0.08]). It is unclear whether the superiority was also established in the more conservative sensitivity analysis (not reported). The clinical relevance of the difference is uncertain.
GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on diet and exercise or 1 OAD, at 26 weeks **dulaglutide 0.75 mg** once weekly was **non-inferior** for decreasing HbA1c compared to metformin.
GRADE: LOW quality of evidence

At 52 weeks, **dulaglutide 1.5 mg and 0.75 mg were non-inferior** to metformin for the decreasing HbA1c.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on diet and exercise or 1 OAD, at 26 weeks, there was a statistically significant difference in weight change with dulaglutide 0.75 mg compared to **metformin**. There was more weight loss with metformin than with dulaglutide 0.75 mg.
There was **no** statistically significant difference in weight change with **dulaglutide 1.5 mg** compared to metformin.
GRADE: MODERATE quality of evidence

At 52 weeks, these difference in weight loss between the three groups were maintained.
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 4.8% with dulaglutide 1.5 mg, 2.2% with dulaglutide 0.75 mg and 3.7% with metformin at 26 weeks.
GRADE: not applicable

Rates of diarrhea were 10% with dulaglutide 1.5 mg, 5.2% with dulaglutide 0.75 mg and 13.8% with metformin at 26 weeks. The difference between dulaglutide 0.75 and metformin was statistically significant.
Rates of nausea were 19% with dulaglutide 1.5 mg, 10.7% with dulaglutide 0.75 mg and 14.6% with metformin at 26 weeks.
Rates of vomiting were 8.6% with dulaglutide 1.5 mg, 5.9% with dulaglutide 0.75 mg and 4.1% with metformin at 26 weeks.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

5.2 Combination therapy with metformin

5.2.1 Dulaglutide + metformin versus placebo + metformin

5.2.1.1 *Clinical evidence profile: dulaglutide + metformin versus placebo or sitagliptin + metformin*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Nauck 2014(26) AWARD-5 and Weinstock 2015(27) (104 weeks) Design: RCT (DB) (PG) non-inferiority and superiority trial	n:1098 dula 1.5 n=304 dula 0.75 n=302 sita n= 315 pla n= 177 Mean age: 54y Prior/current treatment:94% on OAM (+/-67% on 1 medication class) DMII duration: mean 7y Baseline HbA1c:mean 8.1% Mean BMI: 31kg/m2 Previous CV event:NR Renal impairment: NR	dulaglutide 1.5mg/w vs dulaglutide 0.75mg/w vs sitagliptin 100mg vs placebo* (* pla only until 26 weeks) in addition to this background treatment: metformin	Efficacy		RANDO: adequate ALLOCATION CONC: adequate BLINDING : Participants: unclear, high risk of bias Personnel: unclear, high risk of bias Assessors: unclear, high risk of bias described as 'blinded', but no further information given 'Limited sponsor staff were unblinded at 52weeks to assess the primary objective' 'Participants and physicians were unblInded at 104 weeks'.
			Change in HbA1c from baseline at 52 weeks(PO) ANCOVA WITH locf confirmed with MMRM	dula 1.5:-1.10 (+/-0.06)% dula 0.75:-0.87 (+/-0.06)% sita:-0.39 (+/-0.06) % p<0.001 for superiority treatment difference dula 1.5 vs sita - 0.71%, (95% CI: -0.87, -0.55%) **dula 0.75 vs sita** **-0.47% (95% CI -0.63 to -0.31%)** **both dulaglutide doses superior to sitagliptin** non-inferiority testing NR 'MMRM supports results'	

Duration of follow-up:104 weeks	<u>Inclusion</u> 18–75 years old, had type 2 diabetes (≥6 months) with an HbA1c value of >8% and ≤9.5% on diet and exercise alone or ≥7% and ≤9.5% on oral antihyperglycemic medication (OAM) monotherapy or combination therapy (metformin plus another OAM), a BMI between 25 and 40 kg/m2, and a stable weight during the 3-month period before entering the study. <u>Exclusion</u> taking GLP-1 receptor agonists during the 6	≥1500mg/d lead-in period up to 11 weeks (minimum six weeks), in which metformin was titrated up to ≥1,500 mg/day) and all other OAMs were washed out <u>Hyperglycaemia rescue protocol</u>**:** Patients who developed persistent or worsening hyperglycemia based on prespecified thresholds <u>were</u>	**Change in HbA1c from baseline at 26weeks(SO)**	dula 1.5:-1.22% (+/-0.05) dula 0.75:-1.01% (+/-0.06) sita:-0.61 % (+/-0.05) pla: 0.03% (+/-0.07) dula 1.5 vs pla LS mean difference: -1.26% p<0.001 dula 0.75 vs pla LS mean difference: -1.05% p<0.001 dula 1.5 vs sita LS mean difference:NR p<0.001 dula 0.75 vs sita LS mean difference NR p<0.001	FOLLOW-UP: <u>Study completers 26 weeks</u>: dula 1.5: 85.9% dula 0.75: 88.7% sita: 85.7% pla: 70.1% <u>study completers 52 weeks</u> dula 1.5: 78.3% dula 0.75: 80.5% sita: 75.6% <u>study completers 104 weeks</u> total 59.8% dula 1.5:63% dula 0.75:61% sita: 59% Reason described: yes <u>discontinuation due to hyperglycaemia</u>: time period ? dula 1.5 : 1.3% dula 0.75:0.3% sita:1.9% pla: 9.6% 104 weeks
			Change in HbA1c from baseline at 104 weeks(SO)	dula 1.5:-0.99% (+/-0.06) dula 0.75:-0.71%(+/-0.07) sita:-0.32%(+/-0.06) LS mean difference dula 1.5 vs sita **-0.67 (95%CI -0.84 to -0.50)** LS mean difference dula 0.75 vs sita **-0.39% (95%CI -0.56 to -0.22)** **(p<0.001,both dulaglutide doses vs sitagliptin)** **SS in favour of dula**	

	months prior to screening or were on chronic insulin therapy	discontinued from the study and an adverse event of hyperglycemia was reported in the database Stratification: NR	**Body weight change from baseline at 52 weeks** ANCOVA with LOCF	dula 1.5:-3.03 +/-0.22kg dula 0.75: -2.6+/-0.23kg sita: -1.53+/-0.22kg p<0.001 more weight loss with both dulaglutide doses compared to sitagliptin results confirmed by MMRM mean difference dula 1.5 vs sita -1.50 kg p< 0.001 dula 0.75 vs sita -1.07 kg p<0.001 note: Both dulaglutide doses were associated with significantly greater (P < 0.001) reductions in body weight compared with placebo and sitagliptin **at 26 weeks** (presented in figure - MMRM)	dula 1.5:10% dula 0.75:13% sita:16% Statistical method for drop out/missing data : LOCF ITT: defined as all randomized patients. Of 1,098 patients included in the ITT population, 13 did not contribute to the primary analysis due to missing baseline or postbaseline HbA1c measurements SELECTIVE REPORTING: no OTHER IMPORTANT METHODOLOGICAL REMARKS before randomization: lead-in period up to 11 weeks (minimum six weeks), in which metformin was titrated up to ≥1,500 mg/day) and all other OAMs were washed out. This was before randomization! there was also a dose finding
			Body weight change from baseline at 104weeks	dula 1.5: -2.88kg (+/-0.25) dula 0.75: -2.39kg (+/-0.26) sita: -1.75kg (+/-0.25) LS mean difference dula 1.5 vs sita -1.14 kg p<0.001 **SS : more weight loss with dula 1.5** dula 0.75 vs sita NS	

				(supported by MMRM but p<0.05 with dula 1.5)	portion of this trial (adaptive randomization), followed by a fixed randomization after dose selection A total of 230 patients were adaptively randomized during the dosefinding portion. non-inferiority margin 0.25% All continuous measures, including sensitivity analyses of HbA1c and weight over time, were also analyzed using a mixed effects, repeated-measures (MMRM) analysis with additional factors for visit and treatment-by-visit interaction The analyses for the primary (noninferiority of dulaglutide 1.5 mg to sitagliptin at 52 weeks) and key secondary efficacy objectives (HbA1c change from baseline at 26 weeks vs. placebo and at 52 weeks vs. sitagliptin) used a treegatekeeping strategy to control the family-wise type 1 error rate with adjusted P values.
			Blood pressure change from baseline (SystBP/DiastBP)	26 weeks dula 1.5:-1.7/-0.4 (SE 0.7/0.4) dula 0.75:-1.4/-0.2 (SE 0.7/0.4) sita:-1.9/-1.1 (SE 0.7/0.4) pla: +1.1/0.7 (SE 0.9/0.6) dula 1.5 and dula 0.75 vs pla p<0.05 for SBP change at 26 weeks dula vs sita: NS 52 weeks dula 1.5:-0.8/0.3 (SE 0.7/0.3) dula 0.75:-0.5/0.2 (SE 0.7/0.5) sita: -0.5/-0.2 (SE 0.7/0.5) 'no differences' 104 weeks 'no differences' (except DBP dula 0.75 ss higher vs sita)	
			Safety		
			Death (number of patients)	26 weeks dula 1.5:1 dula 0.75:0 sita:0 pla: 0 52 weeks	

				dula 1.5:1 dula 0.75:0 sita:2 104 weeks dula 1.5:1 dula 0.75:0 sita:2	Superiority or noninferiority (noninferiority margin of 0.25%) of a dulaglutide dose to a comparator treatment was concluded if the (onesided) adjusted P value was <0.02. at 104 weeks: Sensitivity analyses showed similar results (data not shown). In the delta stress test in the ITT population, analysed with MMRM, an HbA1c delta of 1.8% was required to be added to the imputed data in the dulaglutide 1.5mg arm (no delta was added to the sitagliptin arm) for the difference between the dulagutide 1.5mg arm and the sitagliptin arm to become non-significant. Sponsor: Eli Lilly and company
			Cardiovascular adverse events (The following cardiovascular events were adjudicated by an independent Duke Clinical Research Institute committee: all deaths and non-fatal adverse events of myocardial infarction; hospitalization for unstable angina; hospitalization for heart failure; coronary revascularization procedures; and cerebrovascular events.)	NR 104 weeks total dula 1.5:5.6% dula 0.75:6.0% sita:4.4% adjudicated: 104 weeks dula 1.5:2.0% dula 0.75:1.3% sita:1.6%	
			Any adverse events	26 weeks dula 1.5:68% dula 0.75:68% sita:59% pla: 63%	

				dula 1.5 and dula 0.75 vs sita P< 0.05 more AE with dulaglutide both doses compared to sita 52 weeks dula 1.5:77% dula 0.75:77% sita:70% NT 'similar' 104 weeks dula 1.5: dula 0.75: sita:	
			Serious adverse events	26 weeks dula 1.5:6% dula 0.75:3% sita:4% pla: 3% 52 weeks dula 1.5:9% dula 0.75:5% sita:5% 104 weeks dula 1.5:12% dula 0.75:8% sita:10%	
			Adverse event leading	26 weeks	

			to withdrawal	dula 1.5:7% dula 0.75:4% sita:4% pla: 14% 52 weeks dula 1.5:11% dula 0.75:8% sita:10% the most common adverse events causing study discontinuation were hyperglycemia and nausea. 104 weeks dula 1.5:21% dula 0.75:21% sita:21%	
			Any gastro-intestinal adverse event	26 weeks dula 1.5:38% dula 0.75:32% sita:18% pla: 23% **SS more GI AE with dula 1.5 and dula 0.75 compared to sita and pla** ($p < 0.05$) 52 weeks dula 1.5:41% dula 0.75:37% sita:23%	

				SS more GI AE with dula 1.5 and dula 0.75 compared to sita (p<0.001) 104 weeks dula 1.5: dula 0.75: sita:	
			Diarrhoea	26 weeks dula 1.5:13% dula 0.75:9% sita:3% pla: 6% **SS more diarrhea with dula 1.5 vs sita (p<0.001) and vs pla (p<0.05)** **SS more diarrhea with dula 0.75 vs sita (p<0.001)** 52 weeks dula 1.5:15% dula 0.75:10% sita:3% **SS more diarrhea with dula 1.5 and dula 0.75 vs sita (p<0.001)** 104 weeks dula 1.5:16% dula 0.75:12% sita:6% **SS more diarrhea with dula 1.5 and 0.75 vs sita** p<0.05	
			Nausea	26 weeks	

				dula 1.5:17% dula 0.75:13% sita:4% pla: 4% **SS more nausea with dula 1.5 and dula 0.75 vs sita and pla** **(p <0.001 or <0.05)** 52 weeks dula 1.5:17% dula 0.75:14% sita:5% **SS more nausea with dula 1.5 and dula 0.75 vs sita** **(p<0.001)** 104 weeks dula 1.5:17% dula 0.75:15% sita:7%	
			Vomiting	26 weeks dula 1.5:12% dula 0.75:7% sita:2% pla: 1% **SS more vomiting with dula 1.5 and dula 0.75 vs sita and pla** (p<0.001 or <0.05) 52 weeks dula 1.5:13% dula 0.75:8%	

				sita:2% **SS more vomiting with dula 1.5 (p<0.001)and dula 0.75 (p<0.05)vs sita** 104 weeks dula 1.5:14% dula 0.75:8% sita:4% **SS more vomiting with dula 1.5 and dula 0.75 vs sita and pla** **p<0.05**	
			Severe hypoglycaemia	0 104 weeks 0	
			Total hypoglycaemia	52 weeks dula 1.5:10.2% dula 0.75:5.3% sita:4.8% NT 104 weeks dula 1.5:12.8% dula 0.75:8.6% sita:8.6%	
			Injection site reactions	NR at 26 and 52 weeks 104 weeks dula 1.5:1.3% dula 0.75:1.0% sita:1.0%	

			Thyroid cancer **number of patients**	0 104 weeks dula 1.5:1 dula 0.75: sita:	
			Pancreatitis (independent adjudication committee) **number of patients**	52 weeks= 104 weeks dula 1.5:0 dula 0.75:0 sita:2 (+1 in extended placebo period in which participants received sitagliptin)	

Table 59

Hypoglycemia was defined as plasma glucose ≤70 mg/dL and/or symptoms and/or signs attributable to hypoglycemia (20). Severe hypoglycemia was defined as an episode requiring the assistance of another person to actively administer therapy (ADA workgroup on hypoglycaemia)

5.2.1.2 *Summary and conclusions: Dulaglutide + metformin versus placebo + metformin*

dulaglutide 1.5 mg once weekly or dulaglutide 0.75 mg once weekly + metformin ≥ 1500 mg versus placebo + metformin ≥ 1500 mg			
Bibliography: Nauck 2014(26) AWARD-5			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	783 for this comparison (1) 26 weeks	dula 1.5:-1.22% dula 0.75:-1.01% pla: +0.03% LS mean difference: dula 1.5 vs pla -1.26% , p<0.001 dula 0.75 vs pla -1.05% , p<0.001 SS in favour of dulaglutide	⊕⊕⊖⊖ **LOW** Study quality:-1 > 20% drop out, unbalanced, but sensitivity analysis seems to confirm. High risk of bias for blinding Consistency: NA Directness: ok Imprecision: -1 unable to assess
Body weight change from baseline	783 for this comparison (1) 26 weeks	**SS more weight loss with both doses of dulaglutide compared to placebo (p<0.001)** results in graph no details given	not assessed
Adverse events leading to withdrawal	783 for this comparison (1) 26 weeks	dula 1.5: 7% dula 0.75: 4% pla: 14% NT	Not applicable
Diarrhea	783 for this comparison (1) 26 weeks	dula 1.5: 13% dula 0.75: 9% pla: 6% **SS more diarrhea with dulaglutide 1.5 vs placebo (p<0.05)** dulaglutide 0.75 NS	⊕⊕⊖⊖ **LOW** Study quality:-1 > 20% drop out, unbalanced, but sensitivity analysis seems to confirm. High risk of bias for blinding Consistency: NA Directness: ok Imprecision: -1 unable to assess
Nausea	783 for this comparison (1)	dula 1.5:17% dula 0.75:13% pla: 4%	⊕⊕⊕⊖ **MODERATE** Study quality:-1 for unclear blinding and attrition

	26 weeks	**SS more nausea with both doses of dulaglutide vs placebo (p <0.05)**	Consistency: NA Directness: ok Imprecision: unable to assess, but ok
Vomiting	783 for this comparison (1) 26 weeks	dula 1.5:12% dula 0.75:7% pla: 1% **SS more vomiting with both doses of dulaglutide vs placebo** (p <0.05)	⊕⊕⊕⊖ **MODERATE** Study quality:-1 for unclear blinding and attrition and previous OAD use Consistency:NA Directness:ok Imprecision: unable to assess, but ok
Severe hypoglycaemia	783 for this comparison (1) 26 weeks	0	Not applicable

Table 60

This was a double blind, 4-arm RCT, comparing dulaglutide 1.5 mg versus dulaglutide 0.75 mg versus sitagliptin versus placebo. The comparison versus sitagliptin will be reported elsewhere.
783 patients with type 2 diabetes, inadequately controlled by 1 or 2 oral antihyperglycemic drugs entered a lead-in period in which all OAD were washed out and metformin was titrated up to ≥1500mg/d. After that, they were randomized to dulaglutide 1.5 mg once weekly versus dulaglutide 0.75 mg once weekly versus placebo for 26 weeks. The mean age was 54 years, mean duration of diabetes 7 years, mean baseline HbA1c was 8.1% and mean BMI was 31 kg/m^2.

Our confidence in the estimate of the between-group differences is limited by the fact that this population was previously on a different OAD treatment, by some concerns about blinding of outcome assessment, by drop-out and by the incomplete reporting of the outcomes.

In patients who were inadequately controlled on metformin, at 26 weeks, the addition of dulaglutide 0.75 or 1.5 mg resulted in a **statistically significant decrease of HbA1c** compared to the addition of placebo (which was increased from baseline).
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin, at 26 weeks, there was a statistically significant **difference in weight change** with the addition of both doses of dulaglutide compared to the addition of placebo. There was more weight loss with dulaglutide than with placebo.
GRADE: not assessed

Withdrawal from the study due to adverse events was seen in 7% with dulaglutide 1.5 mg , 4% with dulaglutide 0.75 mg and 14 % with placebo.
GRADE: not applicable

Rates of diarrhea were 13% with dulaglutide 1.5 mg, 9% with dulaglutide 0.75 mg and 6% with placebo. The difference between dulaglutide 1.5 mg and placebo was statistically significant.
GRADE: LOW quality of evidence

Rates of nausea were 17% with dulaglutide 1.5 mg, 13% with dulaglutide 0.75 mg and 4% with placebo. The difference between both doses of dulaglutide and placebo was statistically significant.
GRADE: MODERATE quality of evidence

Rates of vomiting were 12% with dulaglutide 1.5 mg , 7% with dulaglutide 0.75 mg and 1% with placebo. The difference between both doses of dulaglutide and placebo was statistically significant.
GRADE: MODERATE quality of evidence

There were no events of severe hypoglycemia.
GRADE: not applicable

5.2.2 Dulaglutide + metformin versus sitagliptin + metformin

5.2.2.1 *Clinical evidence profile*

See 5.2.1.1

5.2.2.2 *Summary and conclusions: dulaglutide + metformin versus sitagliptin + metformin*

dulaglutide 1.5 mg once weekly or dulaglutide 0.75 mg once weekly + metformin ≥ 1500 mg versus sitagliptin 100 mg/d + metformin ≥ 1500 mg			
Bibliography: Nauck 2014(26) AWARD-5 and Weinstock 2015(27) (104 weeks)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	921 for this comparison (1) 52 weeks	dula 1.5: -1.10% dula 0.75: -0.87% sita: -0.39 % treatment difference dula 1.5 vs sita **- 0.71% (95% CI: -0.87, -0.55%)** dula 0.75 vs sita **-0.47% (95% CI -0.63 to -0.31%)** **p<0.001** **Both dulaglutide doses superior to sitagliptin**	⊕⊕⊕⊖ **MODERATE** Study quality: - 1 high risk of bias for blinding, 20% drop out, but sensitivity analysis Consistency: NA Directness: see quality Imprecision: ok
	104 weeks	dula 1.5:-0.99% dula 0.75:-0.71% sita:-0.32% LS mean difference dula 1.5 vs sita **-0.67% (95%CI -0.84 to -0.50)** dula 0.75 vs sita **-0.39% (95%CI -0.56 to -0.22)** **p<0.001 for both comparisons** **SS in favour of both dulaglutide doses vs sitagliptin**	⊕⊕⊖⊖ **LOW** Study quality: - 2 for questions about blinding of outcome assessment, 40% drop out Consistency: NA Directness: see quality Imprecision: ok
Body weight change from baseline	921 for this comparison (1) 52 weeks	dula 1.5:-3.03 kg dula 0.75: -2.6 kg sita: -1.53kg **p<0.001** **SS more weight loss with both dulaglutide doses compared to sitagliptin**	⊕⊕⊕⊖ **MODERATE** Study quality: - 1 for questions about blinding, drop out Consistency: NA Directness: see quality Imprecision: -1 unable to assess

	104 weeks	dula 1.5 vs sita **p<0.05** dula 0.75 vs sita: NS	⊕⊕⊖⊖ **LOW** Study quality: -2 for questions about blinding, attrition Consistency: NA Directness: see quality Imprecision: unable to assess, combined with higher attrition at 104 weeks
Adverse events leading to withdrawal	921 for this comparison (1) 52 weeks 104 weeks	dula 1.5: 11% dula 0.75: 8% sita: 10% dula 1.5: 21% dula 0.75: 21% sita: 21%	Not applicable
Diarrhea	921 for this comparison (1) 52 weeks 104 weeks	52 weeks dula 1.5:15% dula 0.75:10% sita:3% **SS more diarrhea with dula 1.5 and dula 0.75 vs sita (p<0.001)** 104 weeks dula 1.5:16% dula 0.75:12% sita:6% **SS more diarrhea with dula 1.5 and 0.75 vs sita** p<0.05	⊕⊕⊕⊖ **MODERATE** Study quality: - 1 for questions about blinding, attrition Consistency: NA Directness: see quality Imprecision: unable to assess ⊕⊕⊖⊖ **LOW** Study quality: - 2 for questions about blinding, attrition Consistency: NA Directness: see quality Imprecision: unable to assess
Nausea	921 for this comparison (1) 52 weeks 104 weeks	52 weeks dula 1.5: 17% dula 0.75: 14% sita: 5% **SS more nausea with dula 1.5 and dula 0.75 vs sita (p<0.001)** 104 weeks dula 1.5:17%	⊕⊕⊕⊖ **MODERATE** Study quality: - 1 for questions about blinding, attrition and previous OAD use. Consistency: NA Directness: see quality Imprecision: unable to assess ⊕⊕⊖⊖ **LOW** Study quality: - 2 for

		dula 0.75:15% sita:7%	questions about blinding, attrition and previous OAD use. Consistency: NA Directness: see quality Imprecision: unable to assess
Vomiting	921 for this comparison (1) 52 weeks 104 weeks	52 weeks dula 1.5: 13% dula 0.75: 8% sita: 2% **SS more vomiting with dula 1.5 (p<0.001)and dula 0.75 (p<0.05)vs sita** 104 weeks dula 1.5:14% dula 0.75:8% sita:4% **SS more vomiting with dula 1.5 and dula 0.75 vs sita and pla p<0.05**	⊕⊕⊕⊖ **MODERATE** Study quality: - 1 for questions about blinding, attrition and previous OAD use. Consistency: NA Directness: see quality Imprecision: unable to assess ⊕⊕⊖⊖ **LOW** Study quality: - 2 for questions about blinding, attrition and previous OAD use. Consistency: NA Directness: see quality Imprecision: unable to assess
Severe hypoglycaemia		0	Not applicable

Table 61

This was a double blind, 4-arm RCT, comparing dulaglutide 1.5 mg versus dulaglutide 0.75 mg versus sitagliptin versus placebo. The comparison versus placebo is reported elsewhere.

In this non-inferiority RCT, 921 patients with type 2 diabetes, inadequately controlled by 1 or 2 oral antihyperglycemic drugs entered a lead-in period in which all OAD were washed out and metformin was titrated up to ≥1500mg/d. After that, they were randomized to dulaglutide 1.5 mg once weekly versus dulaglutide 0.75 mg once weekly versus sitagliptin 100 mg once daily for 104 weeks. The primary endpoint was HbA1c change at 52 weeks.
The mean age was 54 years, mean duration of diabetes 7 years, mean baseline HbA1c was 8.1% and mean BMI was 31 kg/m^2.

Our confidence in the estimate of the between-group differences is limited by the fact that this population was previously on a different OAD treatment, by some concerns about blinding and attrition and by the incomplete reporting of the outcomes.

In patients who were inadequately controlled on metformin, at 52 weeks and at 104 weeks, the addition of dulaglutide 0.75 or 1.5 mg resulted in a **statistically significant decrease of HbA1c** compared to the addition of sitagliptin 100 mg.
GRADE: MODERATE quality of evidence AT 52 WEEKS
GRADE: LOW quality of evidence AT 104 WEEKS

In patients who were inadequately controlled on metformin, at **52 weeks**, there was a statistically **significant difference in weight** change with the addition of both doses of dulaglutide compared to the addition of sitagliptin. There was more weight loss with dulaglutide than with sitagliptin.
GRADE: MODERATE quality of evidence

At 104 weeks, the **difference in weight** loss remained statistically significant for dulaglutide 1.5 mg compared to sitagliptin. The difference between dulaglutide 0.75 and sitagliptin was no longer statistically significant.
GRADE: LOW quality of evidence

At 104 weeks, withdrawal from the study due to adverse events was seen in 21% with dulaglutide 1.5 mg , 21% with dulaglutide 0.75 mg and 21 % with sitagliptin at 104 weeks.
GRADE: not applicable

At **52 weeks**, rates of **diarrhea** were 15% with dulaglutide 1.5 mg, 10% with dulaglutide 0.75 mg and 3% with sitagliptin. The difference between both doses of dulaglutide and sitagliptin was statistically significant. At 104 weeks, there was still a statistically significant difference between dulaglutide and sitagliptin.
At **52 weeks**, rates of **nausea** were 17% with dulaglutide 1.5 mg, 14% with dulaglutide 0.75 mg and 5% with sitagliptin. The difference between both doses of dulaglutide and sitagliptin was statistically significant. At 104 weeks, there was still a statistically significant difference between dulaglutide and sitagliptin.
At **52 weeks**, rates of **vomiting** were 13% with dulaglutide 1.5 mg , 8% with dulaglutide 0.75 mg and 2% with sitagliptin. The difference between both doses of dulaglutide and sitagliptin was statistically significant. At 104 weeks, there was still a statistically significant difference between dulaglutide and sitagliptin.
GRADE: at 52 weeks MODERATE quality of evidence
GRADE: at 104 weeks LOW quality of evidence

There were no events of **severe hypoglycemia**.
GRADE: not applicable

5.2.3 Dulaglutide + metformin versus liraglutide + metformin

5.2.3.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Dungan 2014(28) AWARD-6 Design: RCT (OL) (PG) non-inferiority Duration of follow-up:26 weeks+ 4 weeks safety follow up	n:599 Race/Ethnicity:86% caucasian Mean age: 56.5y 17-20% ≥65y Prior/current treatment:metformin +/-2045mg/d) DMII duration:7.2y Baseline HbA1c:8.1% Mean BMI: 33.5 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> type 2 diabetes (HbA1c ≥7·0% and ≤10·0%), 18 years or older, BMI 45 kg/m² or less, and were receiving a stable dose of metformin	dulaglutide 1.5mg/w vs liraglutide 1.8mg/d (uptitrated from 0.6mg/d week 1 and 1.2mg/d week 2) in addition to this background treatment: metformin ≥1500mg/d <u>Hyperglycaemia rescue protocol</u>**:** according to prespecified criteria, yes. Patients remain in the study	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: yes FOLLOW-UP: <u>Discontinued treatment</u>: dula:10% lira: 10% Reason described: yes <u>Hyperglycaemic rescue or other reason for initiation of alternative OAD</u>: dula:2% lira: 4% <u>Statistical method for drop out/missing data</u> :MMRM/ LOCF
			Change in HbA1c from baseline (PO) mixed model for repeated measures (MMRM) with treatment, country, visit, and treatment-by-visit interaction as fixed effects; baseline as covariate; and patient as random effect. sensitivity analysis for the primary endpoint was ANCOVA with country and treatment as fixed eff ects and baseline as a covariate with the last (postbaseline HbA1c)	dula:-1.42%(SE 0.05) lira: -1.36% (SE 0.05) MD: –0·06% (95% CI –0·19 to 0·07, p for non-inferiority<0·0001), **dulaglutide is non-inferior to liraglutide when added to metformin** 'We noted similar results with the ANCOVA (LOCF) sensitivity analysis'	
			Body weight change from baseline (LSMD)	dula: –2·90 kg (SE 0·22) lira: –3·61 kg (0·22) MD : 0.71 (95%CI 0.17 to 1.26) p 0.011 **SS less weight loss with dulaglutide**	

	(≥1500 mg/day) for 3 months or longer <u>Exclusion</u> type I diabetes, use of other antihyperglycaemic drugs, serum calcitonin concentration of 5·79 pmol/L or higher, serum creatinine concentration of 132·6 µmol/L or higher (men) or 123·8 µmol/L or higher (women), creatinine clearance of less than 60 mL/min, or history of pancreatitis or recent cardiovascular event	<u>Stratification:</u> by country and baseline HbA1c (≤8·5% and >8·5%			<u>Data handling for rescued patients</u>:last observation before rescue <u>ITT</u>: defined as all randomly assigned patients who took one or more doses of study drug (= total number randimised in this study) SELECTIVE REPORTING: no Other important methodological remarks margin of non-inferiority 0·4% for dulaglutide compared with liraglutide for change in HbA1c (least-squares mean change from baseline) Sponsor: Eli Lilly and Company
			Blood pressure change from baseline (SystBP/DiastBP) LSMchange	dula:-3.36/-0.22(SE 0.7/0.4) lira: -2.82/-0.31(SE0.7/0.4) NS	
			Safety		
			Death independent external committee adjudication	dula:0 lira: 0	
			Cardiovascular adverse events independent external committee adjudication	dula:0 lira: 1 (MI)	
			Any adverse events	dula:62% lira: 63% NS	
			Serious adverse events	dula:2% lira: 4% NS	
			Adverse event leading to withdrawal	dula:6% lira: 6%	
			Any gastro-intestinal adverse event	dula:36% lira: 36% NS	
			Diarrhoea	dula:12% lira: 12% NS	
			Nausea	dula:20% lira: 18% NS	

			Vomiting	dula:7% lira: 8% NS	
			Severe hypoglycaemia (ADA hypoglycaemia working group criteria) prerescue data	dula:0 lira: 0	
			Total hypoglycaemia (ADA hypoglycaemia working group criteria) prerescue data	dula:8.7%% lira: 5.7%% NT	
			Documented symptomatic hypoglycaemia (ADA hypoglycaemia working group criteria) prerescue data	dula:2.7% lira: 2.7% NT	
			Injection site reactions (number of patients)	dula:1 lira: 2	
			Thyroid cancer number of patients	dula:0 lira: 1	
			Pancreatitis independent external committee adjudication	dula:0 lira: 0	

Table 62

Total hypoglycaemia was defined as plasma glucose concentrationof 3.9 mmol/L or less, or signs or symptoms attributable to hypoglycaemia. Severe hypoglycaemia was an event needing assistance of another person to actively give therapy as determined by the investigator.

5.2.3.2 *Summary and conclusions*

Dulaglutide 1.5 mg once weekly + metformin +/-2000mg/d versus liraglutide 1.8 mg once daily + metformin+/- 2000mg/d			
Bibliography: Dungan 2014(28) AWARD-6			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	599 (1) 26 weeks	dula:-1.42% lira: -1.36% treatment difference: **–0.06% (95% CI –0.19 to 0.07)** **p for non-inferiority <0·0001** **dulaglutide is non-inferior to liraglutide when added to metformin**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 for open label and directness Consistency: NA Directness:ok, however: short duration of study Imprecision:ok
Body weight change from baseline	599 (1) 26 weeks	dula: –2·90 kg lira: –3·61 kg MD : 0.71kg (95%CI 0.17 to 1.26) p 0.011 **SS less weight loss with dulaglutide**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 for open label and directness Consistency: NA Directness: ok Imprecision: ok
Adverse events leading to withdrawal	599 (1) 26 weeks	dula:6% lira: 6% NT	Not applicable
Diarrhea	599 (1) 26 weeks	dula:12% lira: 12% NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 for open label Consistency: NA Directness: ok Imprecision: ok
Nausea	599 (1) 26 weeks	dula:20% lira: 18% NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 for open label Consistency: NA Directness: ok Imprecision: ok
Vomiting	599 (1) 26 weeks	dula:7% lira: 8% NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 for open label Consistency: NA Directness: ok Imprecision: ok
Severe hypoglycaemia	599 (1) 26 weeks	dula:0 lira: 0	Not applicable

Table 63

In this non-inferiority, open label RCT, 599 patients with type 2 diabetes, inadequately controlled by metformin (≥1500 mg/day, were randomized to dulaglutide 1.5 mg once weekly or liraglutide 1.8 mg once daily for 26 weeks. The mean dose of metformin was +/-2000 mg/ day. The mean age was 56.5 years, mean duration of diabetes 7.2 years, mean baseline HbA1c was .8.1% and mean BMI was 33.5 kg/m^2. The number of participants with a previous myocardial infarction was not reported. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

Our confidence in the estimate of the between-group differences is limited by the open-label design, but the most important limitation is the short study duration. It is for example unclear whether the small benefit in weight loss that is seen with liraglutide at 26 weeks, will persist in the longer term.

In patients who were inadequately controlled on metformin, at 26 weeks, the addition of dulaglutide was **non-inferior** to the addition of liraglutide for the **decrease of HbA1c**.
MODERATE quality of evidence

In patients who were inadequately controlled on metformin, at 26 weeks, there was a statistically significant difference in weight change with the addition of dulaglutide compared to the addition of liraglutide.
There was **more weight loss with liraglutide** than with dulaglutide. The difference was 0.71 kg (95%CI 0.17 to 1.26). The lower boundry of the confidence interval includes no clinically relevant effect.
MODERATE quality of evidence

Withdrawal from the study due to adverse events was seen in 6% with dulaglutide and 6% with liraglutide.
GRADE: not applicable

Rates of diarrhea were 12% with dulaglutide and 12% with liraglutide. The difference was **not** statistically significant.
Rates of nausea were 20% with dulaglutide and 18% with liraglutide. The difference was **not** statistically significant.
Rates of vomiting were 7% with dulaglutide and 8% with liraglutide. The difference was **not** statistically significant.
GRADE: MODERATE quality of evidence

There were no events of severe hypoglycemia.
GRADE: not applicable

5.3 Combination therapy with metformin + sulphonylurea

5.3.1 Dulaglutide + metformin + glimepiride versus insulin glargine + metformin +glimepiride

5.3.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Giorgino 2015(29) AWARD-2 Design: RCT (OL) (PG) (DB to dulaglutide dose) non-inferiority study Duration of follow-up: total 82 weeks, of which 78weeks of treatment	n:810 Mean age: 57y Prior/current treatment (16% 1 OAM, 66% 2 OAM, rest >2OAM) DMII duration:9y Baseline HbA1c:8.1% Mean BMI: 32kg/m2 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> adults with an HbA_{1c} of ≥7.0% and ≤11.0%, BMI ≥23 and ≤45 kg/m^2, and stable weight for ≥3 months, who were not optimally controlled	dulaglutide 1.5mg/w vs dulaglutide 0.75mg/w vs insulin glargine (10 units +standard titration algorithm) in addition to this background treatment (at baseline): metformin mean 2400mg/d + glimepiride mean 6.3mg/d <u>Hyperglycaemia rescue protocol</u>**:**	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: unclear FOLLOW-UP: <u>Study completers</u>: 91.4% 52 weeks 89.3% 78 weeks Reason described: yes <u>Uptitration of study medication</u>: At 52 weeks, the mean ± SD dose of glimepiride was 5.4 ± 2.3, 5.6 ± 2.2, and 5.4 ± 2.3 mg/day for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine, respectively; 85% of patients
			Change in HbA1c from baseline at 52 weeks (PO) ANCOVA with factors for treatment, country, and the baseline value as a covariate. (MMRM in graph)	dula 1.5: −1.08 ± 0.06% dula 0.75: −0.76 ± 0.06% ins glar: −0.63 ± 0.06% dula 1.5 vs ins glar **LSMD -0.45% (95%CI -0.60 to -0.29)** **p for superiority<0.001** **SS dula 1.5 superior to ins glar** dula 0.75 vs ins glar **LSMD -0.13% (95%CI -0.29 to 0.02)** **p for noninferiority <0.001** **dula 0.75 noninferior to ins glar**	
			Change in HbA1c from baseline at 78 weeks (SO)	dula 1.5: −0.90 ± 0.07% dula 0.75: −0.62 ± 0.07% ins glar: −0.59 ± 0.07% **dula 1.5 vs ins glar** **LSMD −0.31% (95%CI −0.50 to −0.13)** **p for superiority<0.001** **SS dula 1.5 superior to ins glar** dula 0.75 vs ins glar	

	with one, two, or three OAMs (of which one had to be metformin or a sulfonylurea) for at least 3 months Patients' OAM doses were then stabilized for ∼6–8 weeks before randomization, at which time a qualifying HbA_{1c} >6.5% (>48 mmol/mol) was required for ongoing eligibility. <u>Exclusion</u> chronic insulin therapy at any time in the past or had taken GLP-1 receptor agonists within 3 months of screening.	see below <u>Stratification:</u> by country and baseline HbA_{1c} ≤8.5%, >8.5%		**LSMD −0.03% (−0.21 to 0.15)** **p for noninferiority <0.001** **dula 0.75 noninferior to ins glar**	overall were taking at least 4 mg/day. At 52 weeks, the mean ± SD daily metformin dose was 2,332 ± 553, 2,397 ± 471, and 2,390 ± 497 mg/day, respectively, for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine At 52 weeks, ∼30% of patients had decreased or discontinued their dose of glimepiride, and ∼7% had decreased or discontinued their dose of metformin At 52 weeks, the daily dose of glargine (mean ± SD) was (LOCF) 29 ± 26 units (0.33 ± 0.24 units/kg). In the glargine group, 24% of patients achieved the FPG target of <100 mg/dL (<5.6 mmol/L), and 58% of glargine-treated patients had an FPG of <120 mg/dL (<6.7 mmol/L). <u>Hyperglycaemic rescue</u>: at 52 weeks dula 1.5:4% dula 0.75:7% ins glar: 3% at 78 weeks
			Body weight change from baseline at 52 weeks ANCOVA (MMRM in graph)	dula 1.5: −1.87 ± 0.24 dula 0.75: −1.33 ± 0.24 ins glar: 1.44 ± 0.24 kg **SS weight loss with dula 1.5 and dula 0.75 vs ins glar** **(p<0.001 for both comparisons)** 'at 78 weeks, the LS mean changes were maintained'	
			Blood pressure change from baseline (SystBP/DiastBP)	52 weeks dula 1.5: +0.17/-0.26 (SE 0.81/0.48) dula 0.75: +0.09/-0.19 (SE 0.8/0.47) ins glar: +0.51/-0.93 (SE0.83/0.49) 78 weeks dula 1.5 :-0.70/-0.44 (SE 0.9-85/0.52) dula 0.75: -0.59/-0.36 (SE 0.85/0.52) ins glar : 0.51/-1.04 (SE0.87/0.53) 'no significant differences'	
			Safety		
			Death (number of patients)	52 weeks dula 1.5:0 dula 0.75:0 ins glar:2	

				78 weeks dula 1.5:0 dula 0.75:1 ins glar:2	dula 1.5: 8.8% dula 0.75: 12.5% ins glar: 6.1% rescued patients remained in the study <u>Statistical method for drop out/missing data</u> : LOCF <u>Data handling for rescued patients</u>: last value before rescue <u>ITT</u>: "all randomized patients who received at least one dose of study treatment" SELECTIVE REPORTING: no Other important methodological remarks screening and lead-in period in which current OAD was changed to max tolerated doses of met + glim. Patients' OAM doses were then stabilized for ∼6–8 weeks before randomization, at which time a qualifying HbA_{1c} >6.5% (>48 mmol/mol) was required for ongoing eligibility. For the assessment of efficacy, weight, and hypoglycemia events,
			Cardiovascular adverse events Deaths and nonfatal cardiovascular AEs (e.g., myocardial infarction, coronary interventions, cerebrovascular events, hospitalization for unstable angina, and hospitalization for heart failure) were also adjudicated by a committee	NR	
			Any adverse events	dula 1.5:69.2% dula 0.75:64.3% ins glar:66.8% 78 weeks dula 1.5:73.6% dula 0.75:69.1% ins glar:73.3% 'similar'	
			Serious adverse events	52 weeks dula 1.5:8.8% dula 0.75:8.5% ins glar:10.7% 78 weeks	

				dula 1.5: 11.7% dula 0.75:10.3% ins glar: 12.2%	only data obtained before initiation of rescue therapy were used.
			Adverse event leading to withdrawal	52 weeks dula 1.5:2.9% dula 0.75:2.6% ins glar:1.5% 78 weeks dula 1.5:3.3% dula 0.75:2.9% ins glar:1.9% 'similar'	The study was designed with 90% power to show noninferiority of dulaglutide 1.5 mg versus glargine for change from baseline in HbA_{1c} at the 52-week primary end point with a margin of 0.4%, a SD of 1.3%, and a one-sided α of 0.025 Sponsor: Eli Lilly and Company
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	52 weeks dula 1.5:10.6%* dula 0.75:8.5%* ins glar:3.8% *** p<0.05 vs ins glar** 78 weeks dula 1.5:10.6% dula 0.75:9.2% ins glar:5.7% NS	
			Nausea	52 weeks dula 1.5:14.3% dula 0.75:6.6% ins glar:1.5%	

				SS more nausea with dula 1.5 and dula 0.75 vs ins glar (p resp. <0.001 and <0.05) 78 weeks dula 1.5:15.4% dula 0.75:7.7% ins glar:1.5% **SS more nausea with dula 1.5 and dula 0.75 vs ins glar (p. <0.001 for both comparisons)**	
			Vomiting	52 weeks dula 1.5: 6.2% dula 0.75: 3.3% ins glar: 2.3% **SS more vomiting with dula 1.5 vs ins glar (p<0.05)** 78 weeks dula 1.5: 7.0% dula 0.75: 3.3% ins glar: 2.3% **SS more vomiting with dula 1.5 vs ins glar (p<0.05)**	
			Severe hypoglycaemia prerescue	78 weeks dula 1.5:2 dula 0.75:0 ins glar:2	
			Documented symptomatic hypoglycaemia prerescue	52 weeks dula 1.5: 37.7% dula 0.75: 37.5% ins glar: 46.9%	

				p<0.05 vs glargine: more patients experiencing documented hypoglycaemia with ins glar compared to dula 1.5 and dula 0.75 78 weeks dula 1.5:40.3% dula 0.75:39.0% ins glar:51.1% **p<0.05 vs glargine: more patients experiencing documented hypoglycaemia with ins glar compared to dula 1.5 and dula 0.75**	
			Injection site reactions (number of patients) *discussed in context of hypersensitivity	78 weeks dula 1.5:2 dula 0.75:2 ins glar:0	
			Thyroid cancer	NR	
			Pancreatitis (adjudication by independent committee) number of patients	78 weeks dula 1.5:2 dula 0.75:1 ins glar:0	

Table 64

Glargine titration with a target fasting plasma glucose (FPG) of <100 mg/dL (<5.6 mmol/L) and a recommended dose adjustment of 0 to 2 units for FPG of 100 to 119 mg/dL (5.6–6.7 mmol/L) (21). Glargine dose adjustments occurred every 3 to 4 days for the first 4 weeks of treatment, followed by once weekly through week 8. After week 8, patients were to continue to adjust glargine per the titration algorithm; the glargine dose was also reviewed and revised, as needed, at subsequent office visits. There was no central oversight of insulin titration.

In all treatment groups, doses of glimepiride, followed by metformin, could be decreased or discontinued if the patient experienced recurrent hypoglycemia

5.3.1.2 *Summary and conclusions*

Dulaglutide 1.5 mg or dulaglutide 0.75 mg + metformin + glimepiride versus insulin glargine + metformin + glimepiride			
Bibliography: Giorgino 2015(29) AWARD-2			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	810 (1) 52 weeks	dula 1.5: −1.08% dula 0.75: −0.76% ins glar: −0.63% treatment difference dula 1.5 vs ins glar **-0.45% (95%CI -0.60 to -0.29)** **p for superiority<0.001** **dula 1.5 mg superior to insulin glargine** dula 0.75 vs ins glar **-0.13% (95%CI -0.29 to 0.02)** **p for noninferiority <0.001** **dula 0.75 noninferior to ins glar** (similar findings at 78 weeks)	⨁⨁⨀⨀ **LOW** Study quality:-1 open label Consistency: NA Directness:-1 non-optimal glargine titration, previously on different background therapy Imprecision: ok
Body weight change from baseline	810 (1) 52 weeks	dula 1.5: −1.87 kg dula 0.75: −1.33 kg ins glar: 1.44 kg **SS more weight loss with dulaglutide 1.5 and dulaglutide 0.75 vs insulin glargine** **p<0.001 for both comparisons** (similar findings at 78 weeks)	⨁⨁⨀⨀ **LOW** Study quality:-1 open label Consistency: NA Directness:-1 non-optimal glargine titration, previously on different background therapy Imprecision: ok
Adverse events leading to withdrawal	810 (1) 78 weeks	dula 1.5:3.3% dula 0.75:2.9% ins glar:1.9% reported as ‘similar’	Not applicable
Diarrhea	810 (1) 52 weeks 78 weeks	52 weeks dula 1.5:10.6%* dula 0.75:8.5%* ins glar:3.8% *** p<0.05 vs ins glar** dula 1.5:10.6%	⨁⨁⨁⨀ **MODERATE** Study quality:-1 open label Consistency: NA Directness: ok Imprecision: unable to assess

		dula 0.75:9.2% ins glar:5.7% NS	
Nausea	810 (1) 52 weeks 78 weeks	52 weeks dula 1.5:14.3% dula 0.75:6.6% ins glar:1.5% **SS more nausea with dula 1.5 and dula 0.75 vs ins glar (p resp. <0.001 and <0.05)** dula 1.5:15.4% dula 0.75:7.7% ins glar:1.5% **SS more nausea with dula 1.5 and dula 0.75 vs ins glar (p. <0.001 for both comparisons)**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 open label Consistency: NA Directness: ok Imprecision: unable to assess
Vomiting	810 (1) 52 weeks 78 weeks	52 weeks dula 1.5: 6.2% dula 0.75: 3.3% ins glar: 2.3% **SS more vomiting with dula 1.5 vs ins glar (p<0.05)** dula 1.5: 7.0% dula 0.75: 3.3% ins glar: 2.3% **SS more vomiting with dula 1.5 vs ins glar (p<0.05)**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 open label Consistency: NA Directness: ok Imprecision: unable to assess
Severe hypoglycaemia	810 (1) 78 weeks	number of patients dula 1.5:2 dula 0.75:0 ins glar:2	Not applicable

Table 65

In this open label, non-inferiority RCT, 810 patients with type 2 diabetes, inadequately controlled by 1 or more OAD (consisting of at least metformin or a sulfonylurea), underwent a run-in stabilization period in which they were switched to metformin ≥1,500 mg/day + glimepiride ≥4mg/d.
After stabilization, they were randomized to dulaglutide 1.5 mg once weekly, dulaglutide 0.75 mg once weekly or titrated insulin glargine for 78 weeks. The primary outcome was measured at 52 weeks. The mean age was 57 years, mean duration of diabetes 9 years, mean baseline HbA1c was 8.1% and mean BMI was 32kg/m^2. After 52 weeks the mean glargine dose was 29 units, the mean glimepiride dose was 5.4mg/d and the mean metformin dose was 2300mg/d.

Our confidence in the estimate of the between-group differences is mainly limited by the open label design and the titration of insulin glargine that was not externally supervised.

The participants were previously on a different background treatment than the metformin + glimepiride they received in the study. This raises some questions whether the population that was included in this study is adequately comparable to a general type 2 diabetic population that is inadequately controlled on metformin + glimepiride.

In patients who were inadequately controlled on metformin + glimepiride, at 52 weeks, the addition of **dulaglutide 1.5 mg** once weekly resulted in a statistically significant **decrease of HbA1c** compared to the addition of insulin glargine.
In patients who were inadequately controlled on metformin + glimepiride, at 52 weeks, the addition of **dulaglutide 0.75 mg** once weekly was **non-inferior** to the addition of insulin glargine for HbA1c decrease at 52 weeks.
These results were maintained at 78 weeks.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin + glimepiride, at 52 weeks, there was a statistically significant difference in weight change with the addition of dulaglutide 1.5 mg once weekly and 0.75mg once weekly compared to the addition of insulin glargine.
There was **more weight loss with both doses of dulaglutide** than with insulin glargine.
These results were maintained at 78 weeks.
GRADE: LOW quality of evidence

Withdrawal from the study due to adverse events was seen in 3.3% with dulaglutide 1.5 mg, 2.9% with dulaglutide 0.75% and 1.9% with insulin glargine.
GRADE: not applicable

At 52 weeks, rates of **diarrhea** were 10.6% with dulaglutide 1.5 mg, 8.5% with dulaglutide 0.75% and 3.8% with insulin glargine. The difference was statistically significant. At 78 weeks, the difference was **not** statistically significant.
At 52 weeks, rates of **nausea** were 14.3% with dulaglutide 1.5 mg, 6.6% with dulaglutide 0.75 mg and 1.5% with insulin glargine. The difference was statistically significant. At 78 weeks, the difference was still statistically significant.
At 52 weeks, rates of **vomiting** were 6.2% with dulaglutide 1.5mg, 3.3% with dulaglutide 0.75 mg and 2.3 % with insulin glargine. The difference between **dulaglutide 1.5 mg** and insulin glargine was statistically significant. These results were maintained at 78 weeks.
GRADE: MODERATE quality of evidence

At 78 weeks, **severe hypoglycemia** had occurred in 2 patients with dulaglutide 1.5 mg and 2 patients with insulin glargine.
GRADE: not applicable

5.4 Combination therapy with metformin + pioglitazone

5.4.1 Dulaglutide + metformin + pioglitazone versus placebo + metformin + pioglitazone

5.4.1.1 *Clinical evidence profile: Dulaglutide + metformin + pioglitazone versus placebo or exenatide + metformin + pioglitazone*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Wysham 2014(30) AWARD-1 Design: RCT (DB vs pla) (PG) non-inferiority vs exe superiority vs pla Duration of follow-up: 52 weeks	n:978 Mean age: 56y Prior/current treatment: 25% 1 OAM, 51% 2 OAM, 24% >2 OAM DMII duration:9y Baseline HbA1c:8.1% Mean BMI: 33kg/m2 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> ≥18 years of age with a BMI between 23 and 45 kg/m2 HbA1c between 7.0% and 11.0% OAM monotherapy or between 7.0% and	dulaglutide 1.5mg/w vs dulaglutide 0.75mg/w vs exenatide 10µg 2x/d vs placebo 1x/w (for 26 weeks only) Vs in addition to this background treatment: metformin (1,500–3,000 mg) and pioglitazone (30–45 mg)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: unclear Personnel: unclear Assessors: unclear FOLLOW-UP: <u>Discontinued treatment</u>: at 26 weeks dula 1.5: 6.8% dula 0.75: 6.1% exe:8.7% pla: 12.1% at 52 weeks dula 1.5: 12.2% dula 0.75: 9.3% exe: 14.9% Reason described: yes
			Change in HbA1c from baseline at 26 weeks (PO) ANCOVA, with factors for treatment, country, and baseline value as covariates.	dula 1.5: -1.51 +/- 0.06% dula 0.75: -1.30+/-0.06% exe: -0.99 +/- 0.06% pla: -0.46 +/- 0.08% dula 1.5 vs pla LSMD -1.05% (95%CI -1.22 to -0.88%) dula 0.75 vs pla LSMD -0.84% (95%CI -1.01 to -0.67) **dula 1.5 and dula 0.75 superior to pla** dula 1.5 vs exe LSMD -0.52% (95%CI -0.66 to -0.39%) dula 0.75 vs exe LSMD -0.31% (95%CI -0.44 to -0.18%) **dula 1.5 and dula 0.75 superior to exe** (confirmed in MMRM graph)
			Change in HbA1c from baseline at 52 weeks (SO)	dula 1.5: -1.36 +/-0.08% dula 0.75: -1.07 +/- 0.08% exe: -0.80 +/- 0.08% dula 1.5 vs exe LSMD -0.56%	

	10.0% (53–86 mmol/mol) on combination OAM therapy <u>Exclusion</u> taking GLP-1 receptor agonists during the 3 months before screening or were on long-term insulin therapy.	<u>Hyperglycaemia rescue protocol</u>: yes, see below <u>Stratification:</u> by country		dula 0.75 vs exe LSMD -0.27% adjusted P , 0.001, both comparisons **dula 1.5 and dula 0.75 superior to exe**	<u>Hyperglycaemic rescue</u>: at 26 weeks dula 1.5: 1.4% dula 0.75: 4.3% exe:4.0% pla: 15.6% at 52 weeks dula 1.5: 3.2% dula 0.75: 8.9% exe: 8.7% <u>Statistical method for drop out/missing data</u> : LOCF <u>Data handling for rescued patients</u>: last observation before rescue <u>ITT</u>: all randomized patients who received at least one dose of study treatment. (n=976) SELECTIVE REPORTING: no Other important methodological remarks before randomization: lead-in period up to 12 weeks to discontinue OAM and titrate t max tolerated MET (1500-
			Body weight change from baseline ANCOVA LOCf LS mean	dula 1.5: -1.30 +/- 0.29 kg dula 0.75: 0.20 +/- 0.29 kg exe: -1.07 +/- 0.29 kg pla: 1.24 +/- 0.37 kg **dula 1.5, dula 0.75 and exe vs pla** **change in weight with dulaglutide 1.5mg, dulaglutide 0.75 mg, and exenatide was significantly different (P < 0.001, P = 0.010, and P <0.001, respectively)** **dula 1.5 vs exe** LSMD -0.24 kg [P = 0.474] **dula 0.75 vs exe** **LSMD +**1.27 kg [P , 0.001] **change in weight SS: (more) weight loss with exe** **'the observed differences in weight were maintained at 52 weeks'**	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP dula 1.5: 0.11 +/-0.83 dula 0.75: -0.36+/-0.82 exe:0.06+/-0.83 pla: 3.4+/-1.13 **dula 1.5 and dula 0.75 SS different from pla**	

				DBP dula 1.5: 0.76+/-0.55 dula 0.75: 0.56+/-0.54 exe:-0.11+/-0.55 pla: 1.25+/-0.75 52 weeks NS for all comparisons	3000mg/d) plus pioglitazone (30-45mg/d) Patients were then stabilized for +/-8 weeks before randomization, at which time a qualifying HbA1c > 6.5% was required for ongoing eligibility. non-inferiority versus exenatide on the change from baseline in HbA1c at the 26-week primary end point with an SD of 1.3%, a one-sided a of 0.025, and a noninferiority margin of 0.40%. non-inferiority calculation not reported For the assessment of efficacy and hypoglycemia events, only data collected before the initiation of rescue medication were used. Secondary analysis methods for HbA1c and weight and methods for other continuous secondary end points over time included a mixed-effects, repeated-measures (MMRM) analysis, with additional factors for visit and treatment-by-visit interaction and the patient as a random effect (data not
			Safety		
			Death number of patients	52 weeks dula 1.5: 1 dula 0.75: 1 exe:0 pla: 0	
			Cardiovascular adverse events (not in protocol)	NR	
			Any adverse events	26 weeks dula 1.5: 77% dula 0.75: 71% exe:72% pla: 74% 52 weeks dula 1.5: 81% dula 0.75: 79% exe:80%	
			Serious adverse events	26 weeks dula 1.5: 4% dula 0.75: 5% exe:5%	

				pla: 9% 52 weeks dula 1.5: 7% dula 0.75: 8% exe:10%	reported) At randomization, 86% of patients were receiving ≥2,500 mg/day of metformin and 45 mg/day of pioglitazone, and the mean doses were similar across arms Sponsor: Eli Lilly and Company
			Adverse event leading to withdrawal	26 weeks dula 1.5: 3% dula 0.75: 1% exe:3% pla: 2% 52 weeks dula 1.5: 3% dula 0.75: 1% exe:4%	
			Any gastro-intestinal adverse event	<u>26 weeks</u> dula 1.5: 47% dula 0.75: 30% exe:42% pla: 18% **dula 1.5 and dula 0.75 vs pla**: **SS les GI adverse events with pla** ($p<0.001$ and $p<0.05$ resp) dula 1.5 vs exe NS **dula 0.75 vs exe** **SS less GI AE with dula 0.75 ($p<0.05$)**	

				52 weeks dula 1.5: 51% dula 0.75: 34% exe:46% dula 1.5 vs exe NS **dula 0.75 vs exe** **SS less GI AE with dula 0.75**	
			Diarrhoea	26 weeks dula 1.5: 11% dula 0.75: 8% exe: 6% pla: 6% NS 52 weeks dula 1.5: 13% dula 0.75: 9% exe:8% NS	
			Nausea	26 weeks dula 1.5: 28% dula 0.75: 16% exe:26% pla: 6% **dula 1.5 vs pla: SS more nausea p<0.001** **dula 0.75 vs pla: SS more nausea p<0.05** dula 1.5 vs exe: NS **dula 0.75 vs exe: SS less nausea p<0.05** 52 weeks dula 1.5: 29% dula 0.75: 17%	

				exe:28% dula 1.5 vs exe NS **dula 0.75 vs exe: SS less nausea p<0.05**	
			Vomiting	<u>26 weeks</u> dula 1.5: 17% dula 0.75: 6% exe:11% pla: 1% **dula 1.5 and 0.75 vs pla : SS more vomiting p<0.001 and p<0.05** **dula 1.5 vs exe: SS more vomiting p<0.05** **dula 0.75 vs exe: SS less vomiting p<0.05** <u>52 weeks</u> dula 1.5: 17% dula 0.75: 6% exe:12% dula 1.5 vs exe NS **dula 0.75 vs exe : SS less vomiting p<0.05**	
			Severe hypoglycaemia (ADA workgroup 2005 criteria) number of patients	52 weeks dula 1.5: 0 dula 0.75: 0 exe:2	
			Total hypoglycaemia (ADA workgroup 2005 criteria)	26 weeks dula 1.5: 10.4% dula 0.75: 10.7% exe:15.9% pla: 3.5%	

				dula 1.5 vs exe: SS less hypoglycaemia p<0.0007 52 weeks 'The incidences and rates of total hypoglycemia remained lower for dulaglutide 1.5 mg than for exenatide at 52 weeks'	
			Injection site reactions	NR	
			Thyroid cancer	NR	
			Pancreatitis (independent adjudication group) number of patients	52 weeks dula 1.5: 1 dula 0.75: 0 exe:0 pla: 0	

Table 66

5.4.1.2 *Summary and conclusions: Dulaglutide + metformin + pioglitazone versus placebo + metformin + pioglitazone*

Dulaglutide 1.5 mg once weekly or 0.75mg once weekly + metformin + pioglitazone versus placebo + metformin + pioglitazone			
Bibliography: Wysham 2014(30) AWARD-1			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	700 for this comparison (1) 26 weeks	dula 1.5: -1.51% dula 0.75: -1.30% pla: -0.46% treatment difference dula 1.5 vs pla -1.05% (95%CI -1.22, - 0.88%) dula 0.75 vs pla -0.84% (95%CI -1.01 to -0.67) **SS in favour of dulaglutide 1.5 and 0.75 versus placebo**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unequal drop out and rescue (more with pla), unclear blinding Consistency: NA Directness: previous background treatment was different, but ok Imprecision: ok
Body weight change from baseline	700 for this comparison (1) 26 weeks	dula 1.5: -1.30 kg dula 0.75: +0.20 kg pla: +1.24 kg treatment difference dula 1.5 vs pla **p<0.001** **SS more weight loss with dulaglutide 1.5 mg** dula 0.75 vs pla **p=0.01** **SS less weight gain with dula 0.75 mg**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unequal drop out and rescue (more with pla), unclear blinding Consistency: NA Directness: ok Imprecision: unable to assess
Adverse events leading to withdrawal	700 for this comparison (1) 26 weeks	dula 1.5: 3% dula 0.75: 1% pla: 2%	
Diarrhea	700 for this comparison (1) 26 weeks	dula 1.5: 11% dula 0.75: 8% pla: 6%	⊕⊕⊕⊖ **MODERATE** Study quality: -unclear blinding Consistency: NA Directness: see higher, but ok Imprecision: not assessable

Nausea	700 for this comparison (1) 26 weeks	dula 1.5: 28% dula 0.75: 16% pla: 6% **dula 1.5 vs pla:** **SS more nausea p<0.001** **dula 0.75 vs pla:** **SS more nausea p<0.05**	⊕⊕⊕⊖ **MODERATE** Study quality: -unclear blinding Consistency: NA Directness: see higher, but ok Imprecision: not assessable
Vomiting	700 for this comparison (1) 26 weeks	dula 1.5: 17% dula 0.75: 6% pla: 1% **dula 1.5 vs pla:** **SS more vomiting p<0.001** **dula 0.75 vs pla:** **SS more vomiting p<0.05**	⊕⊕⊕⊖ **MODERATE** Study quality: -unclear blinding Consistency: NA Directness: see higher, but ok Imprecision: not assessable
Severe hypoglycaemia	700 for this comparison (1) 26 weeks	NR	Not applicable

Table 67

This was a 4 –arm RCT, comparing dulaglutide 1.5 mg once weekly versus dulaglutide 0.75 mg once weekly versus exenatide 10µg twice daily versus placebo. The other treatment arms will be reported elsewhere.
The patients in this trial were inadequately controlled on 1 or more OAD. They entered a lead-in stabilization period in which they were switched to maximum tolerated doses of metformin + pioglitazone. At randomization, the mean dose of metformin was ≥ 2500mg/d and the dose of pioglitazone was 45 mg/d.
700 patients were randomized to dulaglutide 1.5 mg, dulaglutide 0.75 mg or placebo for 26 weeks. The mean age was 56 years, mean duration of diabetes 9 years, mean baseline HbA1c was 8.1% and mean BMI was 33kg/m^2.

Our confidence in the estimate of the between-group differences is limited by a larger drop-out and hyperglycaemia rescue in the placebo group and by an unclear blinding procedure.
The participants were previously on a different background treatment than the metformin + pioglitazone they received in the study. This raises some questions whether the population that was included in this study is adequately comparable to a general type 2 diabetic population that is inadequately controlled on metformin + pioglitazone.

In patients who were inadequately controlled on metformin + pioglitazone, at 26 weeks, the addition of dulaglutide 1.5 mg or dulaglutide 0.75 mg resulted in a statistically significant **decrease of HbA1c** compared to the addition of placebo.
GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on metformin + pioglitazone, at 26 weeks, there was a statistically significant difference in **weight change** with the addition of dulaglutide 1.5 mg compared to the addition of placebo.
The weight in the **dulaglutide 1.5 mg group was decreased** compared to the placebo group (in which the weight had increased from baseline).
There was **less weight gain with dulaglutide 0.75mg** than with placebo.
GRADE: MODERATE quality of evidence

Withdrawal from the study due to adverse events was seen in 3% with dulaglutide 1.5 mg, 1% with dulaglutide 0.75 mg and 2% with placebo.
GRADE: not applicable

Rates of **diarrhea** were 11% with dulaglutide 1.5 mg, 8% with dulaglutide 0.75 mg and 6% with placebo. The difference was **not** statistically significant.
Rates of **nausea** were 28% with dulaglutide 1.5 mg, 16% with dulaglutide 0.75 mg and 6% with placebo. The difference between both dulaglutide doses and placebo was statistically significant.
Rates of **vomiting** were 17% with dulaglutide 1.5 mg, 6% with dulaglutide 0.75mg and 1% with placebo. The difference between both dulaglutide doses and placebo was statistically significant.
GRADE: MODERATE quality of evidence

At 26 weeks severe hypoglycemia was not reported.
GRADE: not applicable

5.4.2 Dulaglutide + metformin + pioglitazone versus exenatide + metformin + pioglitazone

5.4.2.1 *Clinical evidence profile:*

See 5.4.1.1

5.4.2.2 *Summary and conclusions: Dulaglutide + metformin + pioglitazone versus exenatide + metformin + pioglitazone*

Dulaglutide 1.5 mg once weekly or 0.75mg once weekly + metformin + pioglitazone versus exenatide 10µg twice daily + metformin + pioglitazone			
Bibliography: Wysham 2014(30) AWARD-1			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	835 for this comparison (1) 26 weeks	dula 1.5: -1.51% dula 0.75: -1.30% exe: -0.99% treatment difference dula 1.5 vs exe -0.52% (95%CI -0.66, -0.39%) dula 0.75 vs exe -0.31% (95%CI -0.44, -0.18%) **dula 1.5 and dula 0.75 superior to exe**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 no blinding for this comparison Consistency: NA Directness: previous background treatment was different, but ok Imprecision: ok
	52 weeks	results were maintained at 52 weeks	⊕⊕⊖⊖ **LOW** Study quality:-1 no blinding for this comparison, unequal drop out and incomplete reporting of sensitivity analysis Consistency: NA Directness: previous background treatment was different, but ok Imprecision: -1 unable to assess
Body weight change from baseline	835 for this comparison (1) 26 weeks	dula 1.5: -1.30 kg dula 0.75: +0.20 kg exe: -1.07 kg treatment difference dula 1.5 vs exe -0.24 kg [P = 0.474] NS	⊕⊕⊖⊖ **LOW** Study quality:-1 for inadequate dealing with missing values and undescribed blinding Consistency: NA Directness: previous background treatment was different , but ok

		dula 0.75 vs exe +1.27 kg [P , 0.001] **SS more weight loss with exe**	Imprecision: -1 unable to assess
	52 weeks	'the observed differences in weight were maintained at 52 weeks'	⊕⊕⊖⊖ **LOW** Study quality:-1 no blinding for this comparison, unequal drop out and incomplete reporting of sensitivity analysis Consistency: NA Directness: previous background treatment was different, but ok Imprecision: -1 unable to assess
Adverse events leading to withdrawal	835 for this comparison (1) 26 weeks	dula 1.5: 3% dula 0.75: 1% exe:3%	
Diarrhea	835 for this comparison (1) 26 weeks	dula 1.5: 11% dula 0.75: 8% exe: 6% NS similar results at 52 weeks	⊕⊕⊖⊖ **LOW** Study quality: -1 unclear blinding Consistency: NA Directness: see higher, but ok Imprecision: -1 not assessable
Nausea	835 for this comparison (1) 26 weeks	dula 1.5: 28% dula 0.75: 16% exe: 26% dula 1.5 vs exe: NS dula 0.75 vs exe: **SS less nausea p<0.05** similar results at 52 weeks	⊕⊕⊖⊖ **LOW** Study quality: -1unclear blinding Consistency: NA Directness: see higher, but ok Imprecision: not assessable
Vomiting	835 for this comparison (1) 26 weeks 52 weeks	dula 1.5: 17% dula 0.75: 6% exe:11% dula 1.5 vs exe: **SS more vomiting with dula 0.75 p<0.05** dula 0.75 vs exe: **SS less vomiting with dula 0.75 p<0.05** dula 1.5 vs exe: NS	⊕⊕⊖⊖ **LOW** Study quality: -1 unclear blinding Consistency:-1inconsistent throughout time for dula 1.5 Directness: see higher, but ok Imprecision: not assessable

		dula 0.75 vs exe: SS less vomiting with dula 0.75	
Severe hypoglycaemia	835 for this comparison (1) 52 weeks	dula 1.5: 0 dula 0.75: 0 exe:2	Not applicable

Table 68

This was a 4 –arm RCT, comparing dulaglutide 1.5 mg once weekly versus dulaglutide 0.75 mg once weekly versus exenatide 10µg twice daily versus placebo. The comparison versus placebo is reported elsewhere.
The comparison versus exenatide was designed as a non-inferiority trial.
The patients in this trial were inadequately controlled on 1 or more OAD. They entered a lead-in stabilization period in which they were switched to maximum tolerated doses of metformin + pioglitazone. At randomization, the mean dose of metformin was ≥ 2500mg/d and the dose of pioglitazone was 45 mg/d.
835 patients were randomized to dulaglutide 1.5 mg, dulaglutide 0.75 mg or placebo for 26 weeks.
The mean age was 56 years, mean duration of diabetes 9 years, mean baseline HbA1c was 8.1% and mean BMI was 33kg/m^2.

Our confidence in the estimate of the between-group differences is limited by the fact that it was not blinded for this comparison and by some issues with the handling of missing values.
The participants were previously on a different background treatment than the metformin + pioglitazone they received in the study. This raises some questions whether the population that was included in this study is adequately comparable to a general type 2 diabetic population that is inadequately controlled on metformin + pioglitazone.

In patients who were inadequately controlled on metformin + pioglitazone, at 26 weeks, the addition of dulaglutide 1.5 mg or dulaglutide 0.75 mg was **superior** to the addition of exenatide for **decreasing HbA1c**. The difference was maintained at 52 weeks.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin + pioglitazone, at 26 weeks, there was a **no** statistically significant difference in **weight change** with the addition of dulaglutide 1.5 mg compared to the addition of exenatide.
There was however **more weight loss with the addition of exenatide** compared to the addition of dulagltudide 0.75mg.
These differences were maintained at 52 weeks.
GRADE: LOW quality of evidence

Withdrawal from the study due to adverse events was seen in 3% with dulaglutide 1.5 mg, 1% with dulaglutide 0.75 mg and 3% with exenatide at 26 weeks.
GRADE: not applicable

At 26 weeks, rates of **diarrhea** were 11% with dulaglutide 1.5 mg, 8% with dulaglutide 0.75 mg and 6% with exenatide. The difference was **not** statistically significant.
These differences were maintained at 52 weeks.
At 26 weeks Rates of **nausea** were 28% with dulaglutide 1.5 mg, 16% with dulaglutide 0.75 mg and 26% with exenatide. The difference between **dulaglutide 1.5 mg** and exenatide was **not** statistically significant. The difference between **dulaglutide 0.75 mg** and exenatide was statistically significant.
These differences were maintained at 52 weeks.
At 26 weeks Rates of **vomiting** were 17% with dulaglutide 1.5 mg, 6% with dulaglutide 0.75mg and 11% with exenatide. There was more vomiting with dulaglutide 1.5 mg compared to exenatide and less vomiting with dulaglutide 0.75 compared to exenatide. At 52 weeks, results for dulaglutide 1.5 were **not** statistically significant. For dulaglutide 0.75 mg, the differences were maintained.
GRADE: LOW quality of evidence

At 52 weeks, severe hypoglycemia occurred in 2 patients with exenatide and 0 patients with dulaglutide.
GRADE: not applicable

5.5 Combination therapy with sulphonylurea

5.5.1 Dulaglutide + glimepiride versus placebo + glimepiride

5.5.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Dungan 2016(31) AWARD-8 Design: RCT (DB) (PG) Duration of follow-up:24 w	n:300 Race/Ethnicity: 83% caucasian Mean age: 58y Prior/current treatment: sulphonylurea (≥half-maximal dose, stable ≥3months) DMII duration:7.6y Baseline HbA1c:8.4% baseline weight: 84.5kg dula vs 89.5kg pla (p=0.038) Mean BMI: 30.9 to 32.4 Previous CV event: NR Renal impairment: NR <u>Inclusion</u>	dulaglutide 1.5mg/w vs placebo in addition to this background treatment: glimepiride mean 4.8mg/d at baseline and at 24 weeks (the dose could be reduced, followed by discontinuation, in the case of hypoglycaemia or for an AE) <u>Hyperglycaemia</u>	Efficacy		RANDO: unclear NR ALLOCATION CONC: NR BLINDING : Participants: unclear Personnel: unclear Assessors: unclear Remarks on blinding method: described as double blind but no further info FOLLOW-UP: <u>Discontinued treatment</u>: dula:10.4% pla: 6.7% Reason described: yes <u>Titration of study medication</u>: A total of 22 participants [dulaglutide, n=16 (6.7%); placebo, n=6 (10.0%)]
			Change in HbA1c from baseline (PO) (MMRM), with treatment, country, visit and treatment-by-visit as fixed effects, baseline as a covariate, and patient as a random effect.	dula:-1.4% pla:-0.1% LSMD-**1.3% (95% CI −1.6 to−1.0)** **p<0.001** **SS greater change from baseline with dula**	
			Body weight change from baseline MMRM and ancova	dula: −0.91 (+/-0.21) kg pla:-0.24(+/-0.40)kg LSMD (SE) −0.68 (95% CI −1.53, 0.18) NS	
			Blood pressure change from baseline LS mean change from baseline	SBP dula:-0.52(+/-0.96) pla:0.0(+/-1.54) NS DBP dula:-0.03(0.61) pla:-0.76(+/-0.98) NS	
			Safety		

	≥18 years, body mass index (BMI) ≤45 kg/m2] with T2D not optimally controlled [HbA1c ≥7.5 and ≤9.5% (≥58 and ≤80mmol/mol)] with diet and exercise on a stable dose of SU that was at least 50% of the maximum dose per country-specific label for at least 3months before screening. Exclusion Patients treated with any other antihyperglycaemic medication (including insulin) <3months before screening were excluded from the study, as were patients with a history of pancreatitis, signs or symptoms of liver disease, impaired renal function (estimated glomerular filtration rate <30 ml/min/1.73m2),	uptitration protocol: Hyperglycaemia rescue protocol: Patients with severe, persistent hyperglycaemia based on mean fasting self-monitored plasma glucose (SMPG) measurements and prespecified criteria (Table S1, Supporting Information) could either increase the glimepiride dose or initiate additional glycaemic rescue therapy. Stratification:	**Death** number of patients	dula:1 pla:0	decreased or stopped glimepiride therapy (p=0.407) Hyperglycaemic rescue: dula:2.1% pla: 11.7% Statistical method for drop out/missing data: MMRM (LOCF as alternative but not reported) Data handling for rescued patients:last value before rescue ITT: defined as all randomized patients who took ≥1 dose of study medication SELECTIVE REPORTING: no Other important methodological remarks - 2 week lead-in period in which participants either continued their prestudy dose of glimepiride or replaced their previous SU with an approximately equivalent dose of glimepiride. -Efficacy (e.g. HbA1c, FSG, weight) and
			Cardiovascular adverse events (adjudicated)	dula:2 pla:0	
			Any adverse events	dula:46.4% pla:38.3% NS	
			Serious adverse events	dula:3.8% pla:0% NS	
			Adverse event leading to withdrawal	dula:4.2% pla:0.0% NT	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	dula:8.4% pla:0 **SS more diarrhea with dula**	
			Nausea	dula:10.5% pla:0 **SS more nausea with dula**	
			Vomiting	dula:4.2% pla:NR	
			Severe hypoglycaemia (pre rescue)	dula:0 pla:0	
			Documented symptomatic hypoglycaemia (pre rescue)	dula:11.3% pla:1.7% **p<0.05** **SS more with dula**	

	elevated serum calcitonin concentration (20 ng/L), or recent history of severe hypoglycaemia.	by country and baseline HbA1c.	**Injection site reactions**	dula:0 pla:0	hypoglycaemia measurements were censored after therapeutic intervention for persistent hyperglycaemia (post-rescue). The secondary analysis for the primary endpoint was analysis of covariance (ancova) for change in HbA1c from baseline to endpoint, with country and treatment as fixed effects and baseline as a covariate (does not seem to be reported) Sponsor: Eli Lilly and Company
			Thyroid cancer	dula:0 pla:0	
			Pancreatitis (adjudicated)	dula:0 pla:0	

Table 69

Hypoglycaemia was defined as plasma glucose ≤3.9mmol/l (≤70mg/dl) and/or signs and/or symptoms associated with hypoglycaemia [13]. Hypoglycaemia was also analysed at the <3.0mmol/l (<54mg/dl) threshold. Severe hypoglycaemia was defined as an episode requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions

5.5.1.2 *Summary and conclusions*

Dulaglutide 1.5 mg once weekly + glimepiride (mean 4.8 mg/d) versus placebo + glimepiride			
Bibliography: Dungan 2016(31) AWARD-8			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	300 (1) 24 weeks	dula:-1.4% pla:-0.1% treatment difference **-1.3% (95% CI −1.6 to−1.0)** **p<0.001** **SS in favour of dulaglutide**	⊕⊕⊖⊖ **LOW** Study quality:-1 unclear rando, allocation concealment, blinding; 15% attrition Consistency:NA Directness: -1 dose of glimepiride not fixed and no HbA1c stabilisation Imprecision:ok
Body weight change from baseline	300 (1) 24 weeks	dula: −0.91 kg pla:-0.24 kg treatment difference −0.68kg (95% CI −1.53, 0.18) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 unclear rando, allocation concealment, blinding; 15% attrition Consistency:NA Directness: -1 dose of glimepiride not fixed and no HbA1c stabilisation Imprecision:ok
Adverse events leading to withdrawal	300 (1) 24 weeks	dula:4.2% pla:0.0% NT	Not applicable
Diarrhea	300 (1) 24 weeks	dula:8.4% pla:0 **SS more diarrhea with dula**	⊕⊕⊖⊖ **LOW** Study quality:-1 unclear rando, allocation concealment, blinding Consistency: NA Directness: ok Imprecision: unable to assess, small placebo group (n=60)
Nausea	300 (1) 24 weeks	dula:10.5% pla:0 **SS more nausea with dula**	⊕⊕⊖⊖ **LOW** Study quality:-1 unclear rando, allocation concealment, blinding Consistency: NA Directness: ok Imprecision: unable to assess, small placebo group (n=60)
Vomiting	300 (1) 24 weeks	dula:4.2% pla: NR	Not applicable
Severe hypoglycaemia	300 (1) 24 weeks	dula:0 pla:0	Not applicable

Table 70

In this double blind RCT, 300 patients with type 2 diabetes, inadequately controlled by a sulfonylurea (≥ half-maximal dose) were randomized to dulaglutide 1.5 mg or placebo for 24 weeks, after switching their background SU to an equivalent dose of glimepiride (2 week lead-in period). The mean age was 58, mean duration of diabetes 7.6 years, mean baseline HbA1c was 8.4% and mean BMI was 31.5 kg/m^2. The number of patients with previous cardiovascular disease is not reported. Patients with mild or moderate renal impairment were allowed in the study, but it is unclear how many of these patients were actually included. The mean glimepiride dose at study entry was 4.8mg/d.

Our confidence in the estimate of the between-group differences is limited by questions about randomization, allocation concealment and blinding, by questions about the dose of glimepiride and by the lack of a HbA1c stabilization period after switching to glimepiride. The short duration of the trial is also an issue.

In patients who were inadequately controlled on glimepiride, at 24 weeks, the addition of dulaglutide 1.5 mg resulted in a statistically significant **decrease of HbA1c** compared to the addition of placebo.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on glimepiride, at 24 weeks
there was **no** statistically significant difference in *weight change* with the addition of dulaglutide 1.5 mg compared to the addition of placebo.
GRADE: LOW quality of evidence

Withdrawal from the study due to adverse events was seen in 4.2 % with dulaglutide 1.5 mg and 0 % with placebo.
GRADE: not applicable

Rates of **diarrhea** were 8.4% with dulaglutide 1.5 mg and 0% with placebo. The difference was statistically significant.
GRADE: LOW quality of evidence
Rates of **nausea** were 10.5% with dulaglutide 1.5 mg and 0 % with placebo. The difference was statistically significant.
GRADE: LOW quality of evidence
Rates of **vomiting** were 4.2% with dulaglutide 1.5 mg and not reported with placebo.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

5.6 Combination therapy with one or more oral antidiabetic drug

5.6.1 Dulaglutide + OAD versus placebo + OAD: evidence on blood pressure

5.6.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref	n:755	dulaglutide	Efficacy		RANDO:
Ferdinand	Race/Ethnicity:	1.5mg/w	**Change in 24h BP from**	SBP	Adequate
2014(32)	81% Caucasian	vs	**baseline at 16**	dula 1.5: −3.4±0.6	ALLOCATION CONC:
Design:		dulaglutide	**weeks(PO)**	dula 0.75: −1.7±0.6	Adequate
	Mean age: 56+/-10	0.75mg/w	MMRM	pla: −0.6±0.6	BLINDING :
RCT (DB) (PG)		vs			Participants: yes
non-	Prior/current	placebo		dula 1.5 vs pla	Personnel: unclear
inferiority	treatment:92% met,			LSMD −2.8 (95%CI −4.6, −1.0)	Assessors: unclear
	60% SU, 13% TZD,			p<0.001 for noninferiority	
	2.4% other	in addition to		p<0.001 for superiority	Remarks on blinding method:
	DMII duration:8.3y	this background		**Dula 1.5 superior to pla for SBP**	Measurements were blinded after
	Baseline HbA1c:7.9%	treatment:		**lowering at 16 weeks**	monitor calibration
	Mean BMI: 33.0kg/m2	Baseline			
Duration of	Previous CV event:	OAM were		dula 0.75 vs pla	FOLLOW-UP:
follow-up:26	8.1%	continued on		LSMD −1.1 (95%CI−2.8, 0.7)	Study completers:
w	Renal impairment: NR,	study. Dose		p<0.001 for non-inferiority	16 weeks: 87%
	but mean creatinine	adjustments		**dula 0.75 non-inferior to placebo for**	26 weeks: 83%
	clearance of	were allowed		**SBP change at 16 weeks**	
	participants	for glycemic			Reason described: yes
	120ml/min	management		DBP	
		although TZD		dula 1.5: −0.2±0.4	Hyperglycaemic uptitration of
		doses could only		dula 0.75: −0.1±0.4	OAM:
		be decreased;		pla: −0.6±0.4	Baseline OAM were continued on
	Inclusion	insulin initiation			study. Dose adjustments were
	≥18 years of age with	after			allowed for glycemic

	T2DM, a glycated hemoglobin A1c ≥7.0% and ≤9.5%, on ≥1 oral antihyperglycemic medication for ≥1 month (≥3 months if taking a thiazolidinedione), body mass index ≥23 kg/m2, and a stable body weight (±5% for ≥3 months), were included. Mean seated BP was required to be between >90/60 and <140/90 mm Hg, and patients with hypertension had to be taking ≤3 classes of antihypertensive medications (same regimen, ≥1 month). <u>Exclusion</u> a recent (<3 months) major cardiovascular event, mean seated HR<60 or >100 bpm, history of tachyarrhythmia,	randomization was permitted. <u>Stratification:</u> by site and hypertension status		dula 1.5 vs pla LSMD 0.3 (95%CI −0.8, 1.4) **dula 1.5 non-inferior to pla for DBP change at 16 weeks** dula 0.75 vs pla LSMD 0.4 (−0.7, 1.5)* **dula 0.75 noninferior for DBP change at 16 weeks**	management although TZD doses could only be decreased; insulin initiation after randomization was permitted. <u>Statistical method for drop out/missing data</u> : none
			Change in BP from baseline at 26weeks(SO)	SBP dula 1.5: −2.5±0.6 dula 0.75: −1.6±0.6 pla: 0.2±0.6 dula 1.5 vs pla LSMD −2.7 (95% CI −4.5, −0.8) p for non-inferiority <0.001 p for superiority 0.002 **dula 1.5 superior to pla for SBP change(lowering) at 26 weeks** dula 0.75 vs pla LSMD −1.7 (95%CI−3.5, 0.1) p for non-inferiority<0.001 **dula 0.75 non-inferior to pla for SBP change (lowering) at 26 weeks** DBP dula 1.5: 0.3±0.4 dula 0.75: −0.1±0.4 pla: −0.2±0.4 p for non-inferiority<0.001	<u>ITT</u>: no ITT only patients that completed 16 or 26 weeks were analysed SELECTIVE REPORTING: no Other important methodological remarks - 2-week placebo screening and run-in period before randomization - noninferiority margin of 3 mm Hg for SBP and 2.5mm HG for DBP - The treatment groups were similar at baseline, except for duration of diabetes mellitus and history of cardiovascular disease Sponsor: Eli Lilly and Company provided

	pancreatitis, clinically significant hepatic disease, renal impairment (estimated glomerular filtration rate ≤30 mL/min per 1.73 m2), and the use of any GLP-1 receptor agonist (past 3 months), any dipeptidyl peptidase-4 inhibitor (past 2 weeks), or insulin. Night or rotating shift workers, pregnant or nursing women, and women of childbearing potential not using approved means of contraception were also excluded			dula 1.5 vs pla LSMD 0.5 (95%CI −0.7, 1.7)* p for non-inferiority<0.001 **dula 1.5 non-inferior to pla for DBP change at 26 weeks** dula 0.75 vs pla LSMD 0.2 (95%CI−1.0, 1.3)* p for non-inferiority<0.001 **dula 0.75 non-inferior to pla for DBP change at 26 weeks** **No differences with regard to age (<65 and ≥65 years) were observed relative to treatment effects on mean 24-hour SBP or DBP (interaction P value, 0.271 and 0.555, respectively).** **When mean baseline 24-hour ABPM was dichotomized into BP≤130/80 versus >130/80 mm Hg, there was no subgroup by treatment interaction effect (interaction P values, 0.290 and 0.777, respectively).**
			Body weight change from baseline	NR for 26 weeks	
			HbA1c change from baseline	NR for 26 weeks	

			Safety		
			Death	0	
			Cardiovascular adverse events		
			Any adverse events	dula 1.5: dula 0.75: pla: 61.4%–64.8% 'similar across groups'	
			Serious adverse events		
			Adverse event leading to withdrawal		
			Any gastro-intestinal adverse event		
			Diarrhoea	dula 1.5:12.4% dula 0.75:9.1% pla: 7.6%	
			Nausea	dula 1.5:13.5% dula 0.75:7.1% pla: 6.0%	
			Vomiting	dula 1.5:7.6% dula 0.75:4.3% pla: 4.0%	
			Severe hypoglycaemia		
			Documented symptomatic hypoglycaemia		
			Injection site reactions		
			Thyroid cancer		

			Pancreatitis	0	

Table 71

5.6.1.2 *Summary and conclusions*

See . 5.8 Dulaglutide: other endpoints

5.7 Combination therapy with conventional insulin treatment

5.7.1 Dulaglutide + prandial insulin lispro vs insulin glargine + prandial insulin lispro

Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Blonde 2015(33) AWARD-4 Design: RCT (OL) (PG) non-inferiority Duration of follow-up:52 weeks	n:884 Race/Ethnicity:78% caucasian Mean age: 59y 28% ≥65y Prior/current treatment: 'conventional insulin treatment': basal only 62%; basal and prandial 38%; OAD use 80% ; biguanides 72%, SU29%,… DMII duration:12.5y Baseline HbA1c:8.45% Mean BMI: 32.5 Previous CV event: NR Renal impairment: NR	dulaglutide 1.5mg/w vs dula 0.75mg/w vs ins glargine daily in addition to this background treatment: prandial insulin lispro (all patients) + metformin ≥1500mg/d (76% of patients) total daily ins glar at 26 weeks: 64.07 units total daily lispro at 26 weeks	Efficacy		RANDO: Adequate ALLOCATION CONC: no BLINDING : Participants: no Personnel: no Assessors: unclear Remarks on blinding method: Participants and study investigators were not masked to treatment allocation, but were unaware of dulaglutide dose assignment FOLLOW-UP: <u>Study completers</u>: 26 weeks 82.1% 52 weeks 77% Reason described: yes
			Change in HbA1c from baseline at 26 weeks (PO) ANCOVA model with the last post-baseline HbA1c observation carried forward method, with treatment, country, and metformin use as fixed effects and baseline HbA1c as a covariate.	dula 1.5: –1·64% [95% CI –1·78 to –1·50] dula 0.75: –1·59% [95% CI –1·73 to –1·45] ins glar: –1·41% [95% CI –1·55 to –1·27], dula 1.5 vs ins glar adjusted MD –0·22% (95% CI –0·38 to –0·07) p=0.005 dula 0.75 vs ins glar adjusted MD: –0·17% (95%CI –0·33 to -0·02) p=0.015 p values reported but no mention of non-inferiority or superiority testing MMRM (sensitivity analysis) not reported. Since we would expect the MMRM to have less risk of bias and wider CI, this casts doubt on the actual results.	

	Inclusion 18 years or older and receiving one or two stable daily insulin doses (any combination of basal, basal with prandial, or premixed insulin, with or without OAD. HbA1c of 7·0% or more and 11·0% or less and a body-mass index (BMI) of 23–45 kg/m² Exclusion Diagnosis of type 1 diabetes mellitus. □ Multiple daily injection insulin regimen (≥3 insulin doses/day). □ Serious diabetes-related or other health concerns or risks including: o cardiovascular conditions such as acute myocardial infarction, New York Heart Association class III/IV heart failure, or stroke within 2 months	dula 1.5: 93.24u dula 0.75: 96.69U ins glar: 67.79 U SS less lispro with ins glar (at 52 weeks – 88.15 U; 95.00U and 69.12U resp.) Hyperglycaemia rescue protocol**:** in predefined situations: discontinue study and study medication Stratification: by country and metformin use.	**Change in HbA1c from baseline at 52 weeks (SO)**	dula 1.5: –1·48% (95% CI –1·64 to –1·32) dula 0.75: –1·42% (95%CI –1·58 to –1·26) ins glar: –1·23% (95%CI–1·39 to –1·07) dula 1.5 vs ins glar adjusted MD –0·25% (95%CI –0·42 to –0·07) p=0.005 dula 0.75 vs ins glar adjusted MD –0·19% (95%CI –0·37 to –0·02) p=0.014	Hyperglycaemic rescue: dula 1.5: 1 patient dula 0.75:4 patients ins glar: 2 patients Statistical method for drop out/missing data : LOCF Data handling for rescued patients: excluded from study ITT: yes. No definition given SELECTIVE REPORTING: no Other important methodological remarks non-inferiority margin 0.4% 9 week lead-in period on their present insulin regimen. Metformin was allowed; other oral antihyperglycaemia drugs were discontinued. Patients receiving metformin were to have used 1500 mg per day or more by week 2 of the lead-in period. The metformin dose then remained stable for at least 6 weeks before
			Body weight change from baseline at 26 weeks	dula 1.5: –0·87 kg (95% CI –1·40 to –0·34) dula 0.75: 0·18 kg (–0·35 to 0·71) ins glar: 2·33 kg (1·80–2·86) SS p<0.001 'similar differences were noted at 52 weeks' (displayed in figure)	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP (95%CI) dula 1.5: –0·26 (–2·10 to 1·58) dula 0.75: 1.04 (–0.78 to 2.86) ins glar: 1·98 (0·18 to 3·78) dula 1.5 and 0.75 vs ins glar NS 'The differences were significant at each visit (all p<0·05),except 52 weeks' DBP (95%CI) dula 1.5: –0·01 (–1·13 to 1·11) dula 0.75: 0·15 (–0·97 to 1·27)	

	prior to Visit 1 o significant gastric emptying abnormality acute or chronic hepatitis or symptoms of liver disease o acute or chronic pancreatitis o GFR ≤30 mL/min/1·73 m2 at screening o significant, uncontrolled endocrine abnormality o type 2A or type 2B multiple endocrine neoplasia or self or family history of medullary C-cell hyperplasia, focal hyperplasia, or carcinoma o serum calcitonin level of ≥20 pg/mL at Visit 1 o organ transplantation other than corneal transplants GLP-1 receptor agonist treatment (for example, exenatide or liraglutide) within 3			ins glar: –0·34 (–1·44 to 0·76) dula 1.5 and 0.75 vs ins glar NS	randomisation and during the treatment period. As a sensitivity analysis, we used a mixed-effects model repeated measures (MMRM) approach, which included factors of treatment, country, metformin use, baseline HbA1c, visit, and visit-by-treatment interaction in the model. Note: this was not reported Sponsor: Eli Lilly and Company
			Safety		
			Death number of patients	dula 1.5:1 dula 0.75:1 ins glar:3	
			Cardiovascular adverse events (independent adjudication)	dula 1.5:2% dula 0.75:2% ins glar:4% no statistical comparisons were done	
			Any adverse events (treatment emergent)	dula 1.5:74% dula 0.75:78% ins glar:70% dula 1.5 vs ins glar:NS **dula 0.75 vs ins glar: p=0.014 SS more AE with dula 0.75**	
			Serious adverse events (including severe hypoglycaemia)	dula 1.5: 9% dula 0.75: 15% ins glar: 18% **dula 1.5 vs ins glar:p=0.0013 SS less serious AE with dula 1.5** dula 0.75 vs ins glar: NS	
			Adverse event leading to withdrawal from study	dula 1.5: 7% dula 0.75: 5% ins glar: 4%	

	months prior to Visit 1. □ Treatment with weight loss medications within 3 months of Visit 1 or chronic (>2 weeks) systemic glucocorticoid therapy (excluding topical, intra-ocular, intranasal, or inhaled)			no statistical comparisons were done	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	dula 1.5:17% dula 0.75:16% ins glar:6% dula 1.5 vs ins glar: p<0.0001 dula 0.75 vs ins glar:p=0.0002 SS more diarrhoea with dula vs ins glar	
			Nausea	dula 1.5:26% dula 0.75:18% ins glar:3% p<0.0001 dula 1.5 vs ins glar: p<0.0001 dula 0.75 vs ins glar: p<0.0001 SS more nausea with dula vs ins glar	
			Vomiting	dula 1.5:12% dula 0.75:11% ins glar:2% dula 1.5 vs ins glar: p<0.0001 dula 0.75 vs ins glar: p<0.0001 SS more vomiting with dula vs ins glar	
			Severe hypoglycaemia based on the investigator's clinical judgement (but also described according to ADA criteria)	52 weeks dula 1.5:3.4% dula 0.75:2.4% % ins glar:5.1% dula 1.5 vs ins glar: NS dula 0.75 vs ins glar: NS	

			Documented symptomatic hypoglycaemia	26 weeks dula 1.5:78% dula 0.75:82.9% ins glar:82.4% dula 1.5 vs ins glar:NS dula 0.75 vs ins glar:NS 52 weeks dula 1.5: 80.8% dula 0.75: 85.6% ins glar: 83.7% dula 1.5 vs ins glar:NS dula 0.75 vs ins glar:NS	
			Injection site reactions Injection-site reaction was based on a Lilly search category that included specific MedDRA Preferred Terms subsidiary to the MedDRA HLT for injection-site reaction	dula 1.5: <1% dula 0.75: 1% ins glar: 0 no statistical comparisons were done	
			Thyroid cancer	dula 1.5:0 dula 0.75:0 ins glar:0	
			Pancreatitis (independent adjudication)	dula 1.5:0 dula 0.75:0 ins glar:0	

Table 72

In the case of persistent, severe hyperglycaemia where the investigator determined a new intervention was warranted; patients were required to discontinue administering all assigned study drugs (insulin glargine, insulin lispro and dulaglutide)

Total hypoglycaemia=plasma glucose concentrations of 3·9 mmol/L or less (or less than 3·0 mmol/L), or symptoms or signs, or both, attributable to hypoglycaemia.
Severe hypoglycaemia was determined by the investigator and defined as an episode requiring the assistance of another person to administer treatment (American Diabetes Association Workgroup on Hypoglycemia).
Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 2005; **28:** 1245–49.

5.7.1.1 *Summary and conclusions*

Dulaglutide 1.5 mg or dulaglutide 0.75 mg + prandial insulin lispro +/- metformin versus insulin glargine + prandial insulin lispro +/- metformin			
Bibliography: Blonde 2015(33) AWARD-4			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	884 (1) 26 weeks 52 weeks	dula 1.5: –1·64% dula 0.75: –1·59% ins glar: –1·41% treatment difference dula 1.5 vs ins glar **–0·22% (95%CI –0·38, –0·07) p=0.005** dula 0.75 vs ins glar **–0·17% (95%CI –0·33 to -0·02) p=0.015** **SS in favour of both doses of dulaglutide** these differences were maintained at 52 weeks	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 open label, no allocation concealment, inadequate handling of missing values (18%) and no reporting of sensitivity analysis Consistency: NA Directness: -1 different lispro doses at end of trial, population previously on different insulin treatment Imprecision :ok
Body weight change from baseline	884 (1) 26 weeks 52 weeks	dula 1.5: –0·87 kg dula 0.75:+0·18 kg ins glar: +2·33 kg dula 1.5 vs ins glar SS p<0.001 dula 0.75 vs ins glar SS p<0.001 'similar differences were noted at 52 weeks' (displayed in figure)	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 open label, no allocation concealment, inadequate handling of missing values (18%) and no reporting of sensitivity analysis Consistency: NA Directness: -1 different lispro doses at end of trial, population previously on different insulin treatment Imprecision :unable to assess
Adverse events leading to withdrawal	884 (1) 52 weeks	dula 1.5: 7% dula 0.75: 5% ins glar: 4% NT	Not applicable
Diarrhea	884 (1) 52 weeks	dula 1.5:17% dula 0.75:16% ins glar:6% dula 1.5 vs ins glar p<0.0001 dula 0.75 vs ins glar p=0.0002 **SS more diarrhea with both doses of dula vs ins glar**	⊕⊕⊖⊖ **LOW** Study quality:-2 open label, no allocation concealment Consistency:NA Directness: ok Imprecision: not assessable

Nausea	884 (1) 52 weeks	dula 1.5:26% dula 0.75:18% ins glar:3% dula 1.5 vs ins glar: p<0.0001 dula 0.75 vs ins glar: p<0.0001 **SS more nausea with both doses of dula vs ins glar**	⊕⊕⊖⊖ **LOW** Study quality:-2 open label, no allocation concealment Consistency:NA Directness: ok Imprecision: not assessable
Vomiting	884 (1) 52 weeks	dula 1.5:12% dula 0.75:11% ins glar:2% dula 1.5 vs ins glar: p<0.0001 dula 0.75 vs ins glar: p<0.0001 **SS more vomiting with both doses of dula vs ins glar**	⊕⊕⊖⊖ **LOW** Study quality:-2 open label, no allocation concealment Consistency:NA Directness: ok Imprecision: not assessable
Severe hypoglycaemia	884 (1) 52 weeks	dula 1.5:3.4% dula 0.75:2.4% ins glar:5.1% dula 1.5 vs ins glar: NS dula 0.75 vs ins glar: NS	⊕⊖⊖⊖ VERY **LOW** Study quality:-2 open label, no allocation concealment Consistency:NA Directness: ok Imprecision: -1 low event rates

Table 73

In this open label noninferiority RCT, 884 patients with type 2 diabetes, inadequately controlled by one or two stable insulin doses (62% basal only, 38% basal and prandial; 80% + OAD), entered a lead-in period to discontinue all OAD except for metformin ≥1500mg/d). After stabilization, they were randomized to dulaglutide 1.5mg once weekly, dulaglutide 0.75 mg once weekly or insulin glargine, all in combination with prandial insulin lispro.
Follow up was 52 weeks, but the primary outcome was measured at 26 weeks.
The mean age was 59 years, mean duration of diabetes 12.5 years, mean baseline HbA1c was 8.5% and mean BMI was 32.5 kg/m^2. It was not reported whether any of the included patients had a history of a cardiovascular event. Patients with mild or moderate renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.
At 26 weeks, the mean daily dose of insulin glargine was 64 units. The mean daily lispro dose with dulaglutide 1.5 mg was 93 units, with dulaglutide 0.75 it was 97 units and with insulin glargine it was 68 units.

Our confidence in the estimate of the between-group differences is limited by the open label design, the lack of allocation concealment, inadequate handling of missing values and the fact that the patients were previously on different background medication.

In patients who were inadequately controlled on 'conventional insulin treatment', at 26 weeks, the addition of dulaglutide 1.5 mg or 0.75 mg once weekly was **superior** to the addition of insulin glargine for the decrease of HbA1c.
These differences were maintained at 52 weeks.
GRADE: VERY LOW quality of evidence

In patients who were inadequately controlled on 'conventional insulin treatment', at 26weeks, there was a statistically significant difference in weight change with the addition of dulaglutide 1.5 mg or 0.75 mg once weekly compared to the addition of insulin glargine.
The weight in the dulaglutide 1.5 mg once weekly group was decreased compared to the insulin glargine group (in which the weight had increased from baseline).
There was more weight gain with insulin glargine than with dulaglutide 0.75 mg.
These differences were maintained at 52 weeks.
GRADE: VERY LOW quality of evidence

Withdrawal from the study due to adverse events was seen in 7% with dulaglutide 1.5 mg, 5% with dulaglutide 0.75 mg and 4% with insulin glargine.
GRADE: not applicable

Rates of **diarrhea** were 17% with dulaglutide 1.5 mg , 16% with dulaglutide 0.75 mg and 6% with insulin glargine. The difference between both doses of dulaglutide and insulin glargine was statistically significant.
Rates of **nausea** were 26% with dulaglutide 1.5 mg, 18% with dulaglutide 0.75 mg and 3% with insulin glargine. The difference between both doses of dulaglutide and insulin glargine was statistically significant.
Rates of vomiting were 12% with dulaglutide 1.5 mg, 11% with dulaglutide 0.75 mg and 2% with insulin glargine. The difference between both doses of dulaglutide and insulin glargine was statistically significant.
GRADE: LOW quality of evidence

Severe hypoglycemia occurred in 3.4% with dulaglutide 1.5 mg, 2.4% with dulaglutide 0.75 mg once and 5.1 % with insulin glargine. The difference was **not** statistically significant.
GRADE: VERY LOW quality of evidence

5.8 Dulaglutide: other endpoints from the RCTs

5.8.1 Blood pressure

Blood pressure change from baseline was reported in all of the 8 trials that were eligible for this review. The results can be found in the detailed 'clinical evidence profiles' in the full document (English).

4 of the trials that we included in this review compared dulaglutide to placebo (in addition to background antidiabetic treatment). 3 of these trials report statistically significant differences between dulaglutide and placebo at 24-26 weeks for systolic blood pressure, but not for diastolic blood pressure. At 52 weeks, the differences were not statistically significant.

The trials that compared dulaglutide to other active treatment did not find any statistically significant difference in blood pressure change at the end of the trials.

Karagiannis 2015(23) performed a meta-analysis of 5 trials that compared dulaglutide versus placebo (in the presence of any concomitant OAD – duration ≥ 12 weeks) and found a statistically significant difference in the systolic blood pressure change between dulaglutide and placebo (-2mmHg (95%CI -3.72 to -0.28). They found no statistically significant difference for diastolic blood pressure.

The quality of evidence is LOW because of the problems with trial quality that were already reported in the conclusion tables.

5.8.2 Injection site reactions

Injection site reactions (ISR) were reported in most of the trials that were eligible for this review. No statistical testing was performed. Injection site reactions were reported in +/-1% of patients on dulaglutide. The definition of what was considered an injection site reaction was not specified.

5.8.3 Cardiovascular adverse events (including heart failure)

To date, there are no results from trials that are designed to evaluate the cardiovascular safety of dulaglutide.

Cardiovascular adverse events were reported in most of the trials that were eligible for this review. There was an independent adjudication for cardiovascular events in these trials. Statistical tests were not performed and would be of little value due to the relatively short duration of the trials and the low event rate.

A prespecified meta-analysis of 9 dulaglutide trials by Ferdinand 2016(34) reported on cardiovascular safety. 6010 patients were included. The primary endpoint was a composite of first occurrence of **major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) or hospital admission for unstable angina**.

No statistically significant difference could be found between dulaglutide and all comparators (HR 0.57; 98.02%CI 0.30 to 1.10). The overall event rate was 0.66 events per 100 person-years with dulaglutide and 1.1 events per 100 person-years with all comparators.

When a separate analysis was done for dulaglutide versus placebo (added to existing OAD) or dulaglutide versus active treatment, again, no differences were found.
No statistically significant difference was found between dulaglutide and all comparators for hospital admission due to **heart failure**.

The quality of this evidence is LOW to VERY LOW, because these trials were not designed to evaluate cardiovascular safety, studies with different comparators and concomitant treatment were pooled, and event rates were low.

5.8.4 Pancreatitis and thyroid cancer

Because of the low event rate of pancreatitis and thyroid cancer, these outcomes will be discussed in the chapter 'rare safety outcomes'

6 Exenatide twice daily- evidence tables and conclusions

6.1 Monotherapy

6.1.1 Exenatide twice daily versus placebo

6.1.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Moretto 2008(35) Design: RCT (DB) (PG) Duration of follow-up: 24 weeks	n:233 Race/Ethnicity: 68% caucasian Mean age: 54 Prior/current treatment: diet and exercise DMII duration:2y Baseline HbA1c:7.8% Mean BMI: 31 Previous CV event: Renal impairment: <u>Inclusion</u> >18 years, type 2 diabetes, body mass index of 25 to 45 kg/m 2 (inclusive).	exenatide 5µg sc bid vs exentatide 10µg sc bid (5µg for the first 4 weeks) vs placebo in addition to individualized prestudy diet and exercise regimens <u>Hyperglycaemia protocol</u>**:**	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: unclear FOLLOW-UP: <u>Study completers</u>: 87% Reason described: yes <u>withdrawn from study due to loss of glycaemic control</u>: exe 5: 4% exe 10: 6% pla: 5%
			Change in HbA1c from baseline (PO) The ANCOVA model included effects for treatment, screening HbA1c subgroup, and HbAlc baseline values. Multiplicity of adjustments for change in HbAI1c was performed using the Fisher Protected Testing procedure	exe 5: -0.7% [SE 0.1] exe 10 : -0.9% [SE 0.1] pla: -0.2% [SE 0.1] **P = 0.003 and P < 0.001, respectively** **SS in favour of exe 5 and exe 10 compared to pla**	
			Body weight change from baseline	exe 5: -2.8 [0.3]kg exe 10 : -3.1 [0.3]kg pla: -1.4 [0.3]kg p= 0.004 and p<0.001 respectively	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP exe 5: -3.7 [1.2] exe 10 : -3.7 [1.2]	

	diet and exercise consistent with the local standards of medical care, in the opinion of the investigator,HbAI1c value at screening of between 6.5% and 10.0% (inclusive) <u>Exclusion</u> ever been treated with an antidiabetic agent; blood pressure >160/>110 mm Hg; history or presence of clinically significant cardiac disease within the year prior to inclusion; history of renal transplant or active renal or hepatic disease; received any medication for weight loss within 12 weeks prior to screening.	Patients with an HbA1c increase of 1.0% from baseline at any study visit or an HbA1c >10.5% at week >12 were to be discontinued from the study due to loss of glycemic control. Additionally, patients who had >4 fasting serum glucose (FSG) concentrations >260 mg/dL over 7 consecutive days on self-monitored blood glucose (SMBG) testing were to be discontinued from the study due to loss of glycemic control		pla: - 0.3 [1.2] DBP exe 5: -0.8 (0.7) exe 10 : -2.3 (0.7) pla: -0.3 (0.7) p= NS and p=0.046 respectively	<u>Statistical method for drop out/missing data</u> : LOCF <u>ITT</u>: all randomized patients who received >1 dose of study drug (99%) SELECTIVE REPORTING: no Other important methodological remarks 2 week placebo lead-in (single blind) Sponsor: Amylin Pharmaceuticals and Eli Lilly and Company
			Safety		
			Death	exe 5:0 exe 10 : 0 pla:0	
			Cardiovascular adverse events	0	
			Any adverse events	exe 5:21% exe 10 : 33% pla:19%	
			Serious adverse events	exe 5:0 exe 10 : 0 pla: 0	
			Adverse event leading to withdrawal number of patients	exe 5:0 exe 10 : 2 pla:0	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	exe 5:0 exe 10 : 3% pla:0	

		<u>Stratification:</u> by screening HbA1c values (<8% and >8%) within each investigative site			
			Nausea	exe 5: 3% exe 10 : 13% pla:0 P = 0.010 for the combined exenatide group vs placebo	
			Vomiting	exe 5:4% exe 10 : 4% pla:0%	
			Severe hypoglycaemia	exe 5:0 exe 10 : 0 pla:0	
			hypoglycaemia	exe 5:5% exe 10 : 4% pla:1% p=NS	
			Injection site reactions	NR	
			Thyroid cancer	NR	
			Pancreatitis	NR	

Table 74

Definition of Hypoglycemia
Hypoglycemia was defined as signs or symptoms associated with hypoglycemia, or an SMBG value <64 mg/dL, regardless of whether this concentration was considered to be associated with signs, symptoms, or treatment. Severe hypoglycemia was defined as an episode with signs or symptoms consistent with hypoglycemia during which the patient required the assistance of another person and that was associated with an SMBG value <54 mg/dL or prompt recovery after administration of oral carbohydrate, glucagon injection, or IV glucose.

6.1.1.2 *Summary and conclusions*

Exenatide 5µg twice daily or 10µg twice daily versus placebo			
Bibliography: Moretto 2008(35)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	233 (1) 24 weeks	exe 5: -0.7% exe 10 : -0.9% pla: -0.2% exe 5 vs pla **P = 0.003** **exe 10 vs pla** **and P < 0.001** **SS in favour of exenatide 5 and exe 10 compared to placebo**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 method of dealing with missing values (13% missing), unclear blinding Consistency: NA Directness: ok Imprecision: unable to assess
Body weight change from baseline	233 (1) 24 weeks	exe 5: -2.8 kg exe 10 : -3.1 kg pla: -1.4 kg exe 5 vs pla p= 0.004 exe 10 vs pla p<0.001	⊕⊕⊕⊖ **MODERATE** Study quality: -1 method of dealing with missing values (17% missing), unclear blinding Consistency: NA Directness: ok Imprecision: unable to assess
Adverse events leading to withdrawal	233 (1) 24 weeks	exe 5: 0 exe 10 : 3% pla: 0	Not applicable
Diarrhea	233 (1) 24 weeks	exe 5: 0 exe 10 : 3% pla: 0 NT	Not applicable
Nausea	233 (1) 24 weeks	exe 5: 3% exe 10 : 13% pla: 0 P = 0.010 for the combined exenatide group vs placebo	⊕⊕⊖⊖ **LOW** Study quality: -1 unclear blinding of assessors Consistency: NA Directness: ok Imprecision: -1 unable to assess + small groups
Vomiting	233 (1) 24 weeks	exe 5: 4% exe 10 : 4% pla: 0% NT	Not applicable
Severe hypoglycaemia	233 (1)	exe 5: 0 exe 10 : 0	Not applicable

	24 weeks	pla: 0	
	233 (1) 24 weeks		Not applicable

Table 75

In this double blind RCT, 233 patients with type 2 diabetes, inadequately controlled by diet and exercise, were randomized to exenatide 5µg twice daily or exenatide 10µg twice daily or placebo for 24 weeks. The mean age was 54 years, mean duration of diabetes 2 years, mean baseline HbA1c was 7.8% and mean BMI was 31kg/m^2. No patients with clinically significant cardiac or renal disease were allowed into the study.

Our confidence in the estimate of the between-group differences is limited by the method of dealing with missing values and the unclear blinding of assessors. It is difficult to perform a full grade analysis because no confidence intervals were reported, and because this is a single trial.

In patients who were inadequately controlled on diet and exercise, at 24 weeks, the addition of exenatide 5µg or 10µg twice daily resulted in a statistically significant **decrease of HbA1c** compared to the addition of placebo.
GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on diet and exercise, at 24 weeks, there was a statistically **significant difference in weight** change with the addition of exenatide compared to the addition of placebo.
There was more weight loss with both doses of exenatide than with placebo.
GRADE: MODERATE quality of evidence

Withdrawal from the study due to adverse events was seen in 3% with exenatide 10µg and 0% with exenatide 5µg and placebo.
GRADE: not applicable

Rates of diarrhea were 0% with exenatide 5 µg, 3% with exenatide 10µg and 0% with placebo.
Rates of nausea were 3% with exenatide 5µg, 13% with exenatide 10µg and 0% with placebo. The difference was statistically significant.
Rates of vomiting were 4% with exenatide 5µg, 4% with exenatide 10µg and 0% with placebo.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

6.2 Combination therapy with metformin

6.2.1 Exenatide twice daily + metformin versus placebo + metformin

6.2.1.1 *Clinical evidence profile*

Ref	n/Population	Comparison	Outcomes				Methodological
DeFronzo 2005 (36) Design: RCT (TB) (PG) duration: 30w (=4w acclimatization period* + 26w full dose treatment)	n= 336 mean age: 53±10y Prior R: metformin DMII duration: 5.9y Baseline HbA1c: 8.2±1.1% Baseline BMI: 34 previous CV event: Previous renal impairment: <u>Inclusion</u> - Type 2 diabetes - Age: 19-78y - Treated with metformin monotherapy (≥1500mg/d for 3m before screening) - FPG <13.3mmol/l - BMI 27-45 - Weight stable (±10%) for 3m - HbA1c 7.1-11.0% - No clinically significant abnormal laboratory test values <u>Exclusion</u> - Use of SU, meglit, TZD, α-	Exenatide 5µg SC twice daily for 4w, then 10µg SC twice daily for 26w added to metformin (≥1500mg/d) Vs Exenatide 5µg SC twice daily for 30w added to metformin (≥1500mg/d) Vs Placebo for 30w added to metformin (≥1500mg/d)	Efficacy				- Jadad score ○ RANDO: 1/2 ○ BLINDING: 1/2 ○ ATTRITION: 1/1 - ITT: defined as all randomised subjects who received at least one injection of medication starting from the evening of day 1 study completers: exe 5: 81.8% exe 10: 82.3% pla: 78.8% reason described: yes loss of glucose control: exe 5: 4.5% exe 10: 0.9% pla: 8% - Missing values: LOCF
				Placebo	Exenatide 5	Exenatide 10	
			Change from baseline HbA1c (PO)	+0.08%	-0.40%	-0.78%	
				SS, p<0.002			
			Change from baseline body weight (SO)	0	-1.6kg	-2.8kg	
				SS, p<0.001 vs placebo			
			change in SBP/DBP	'no changes observed between treatment arms'			
			Safety				
			Serious adverse events	3.5%	4.5%	2.7%	
			cardiovascular, hepatic, renal AE	'no increased incidence'			
			Nausea	23%	36%	45%	

	glucosidase inhibitors, exogenous insulin therapy, weight loss drugs, corticosteroids, transplantation medications, drugs affecting gastrointestinal motility or any study drug for 3m before screening	hyperglycaemia protocol: withdrawal from study at certain HbA1c values or FPG stratification according to baseline HbA1c	diarrhea	8%	12%	16%	4 week placebo lead-in period before randomisation - Sponsor: Amylin Pharmaceuticals and Eli Lily
			vomiting	4%	11%	12%	
			Hypoglycemia (mild-moderate)	5.3%	4.5%	5.3%	
			severe hypoglycemia	0	0	0	
			Adverse events leading to withdrawal	exe 5µg: 3.6% exe 10µg:7.1% pla: 0.9% NT			

Table 76

Any subject with either an HbA1c change of 1.5% from baseline at any clinic visit or an HbA1c 11.5% at week 18 or 24 could be terminated from the study for safety reasons at the investigator's discretion (loss of glucose control). Similarly, subjects could be withdrawn if fasting plasma glucose values were13.3 mmol/l (240 mg/dl) on two consecutive study visits or if recorded fingerstick fasting blood glucose values were 14.4 mmol/l (260 mg/dl) for at least 2 weeks, not secondary to a readily identified illness or pharmacological treatment.

For mild/moderate hypoglycemia, subjects reported symptoms consistent with hypoglycemia that may have been documented
by a plasma glucose concentration value _3.3 mmol/l. For severe hypoglycemia, subjects required the assistance of another person to obtain treatment for their hypoglycemia, including intravenous glucose or intramuscular glucagon.

6.2.1.2 *Summary and conclusions*

Exenatide 5 µg or 10 µg twice daily + metformin ≥1500mg/d versus placebo + metformin metformin ≥1500mg/d			
Bibliography: DeFronzo 2005 (36)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	336 (1) 30 w	exe 5µg:-0.4% exe 10µg:-0.78% pla:+0.08% **overall p<0.001** **SS 'for both exenatide treated arms'**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 poor method of dealing with missing values (19%) Consistency: NA Directness: ok Imprecision: unable to assess
Body weight change from baseline	336 (1) 30 w	exe 5µg:-1.6 kg exe 10µg: -2.8 kg pla: 0 exe 5 vs pla p<0.05 exe 10 vs pla **p<0.001** **SS more weight loss with exe**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 poor method of dealing with missing values (19%) Consistency: NA Directness: ok Imprecision: unable to assess
Adverse events leading to withdrawal	336 (1) 30 w	exe 5µg: 3.6% exe 10µg:7.1% pla: 0.9% NT	Not applicable
Diarrhea	336 (1) 30 w	exe 5µg:12% exe 10µg: 16% pla: 8% NT	Not applicable
Nausea	336 (1) 30 w	exe 5µg: 36% exe 10µg: 45% pla: 23% NT	Not applicable
Vomiting	336 (1) 30 w	exe 5µg: 11% exe 10µg: 12% pla: 4% NT	Not applicable
Severe hypoglycaemia	336 (1) 30 w	exe 5µg:0 exe 10µg:0 pla:0	Not applicable

Table 77

In this triple blind RCT, 336 patients with type 2 diabetes, inadequately controlled by metformin ≥1500mg/d, were randomized to exenatide 5µg or exenatide 10 µg twice daily or placebo for 30 weeks. The mean age was 53 years, mean duration of diabetes 5.9 years, mean baseline HbA1c was 8.2% and mean BMI was 34 kg/m^2.

Our confidence in the estimate of the between-group differences is limited by the method of dealing with missing values in this trial. We have problems assessing precision because no confidence intervals were calculated.

In patients who were inadequately controlled on metformin, at 30 weeks, the addition of exenatide 5 or 10µg twice daily resulted in a statistically **significant decrease of HbA1c** compared to the addition of placebo.
GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on metformin, at 30 weeks, there was a statistically significant difference in weight change with the addition of both doses of exenatie compared to the addition of placebo.
There was more **weight loss with exenatide** than with placebo.
GRADE: MODERATE quality of evidence

Adverse events were reported, but no statistical testing was performed or reported.
Withdrawal from the study due to adverse events was seen in 3.6 % with exenatide 5µg, 7.1% with exenatide 10µg and 0.9% with placebo.
GRADE: not applicable

Rates of diarrhea were 12% with exenatide 5 µg, 16% with exenatide 10µg and 8% with placebo.
Rates of nausea were 36% with exenatide 5 µg, 45% with exenatide 10µg and 23% with placebo.
Rates of vomiting were 11% with exenatide 5 µg, 12% with exenatide 10µg and 4% with placebo.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

6.2.2 Exenatide twice daily + metformin versus sulphonylurea + metformin

6.2.2.1 *Clinical evidence profile*

Ref	n/Population	Comparison	Outcomes		Methodological
Gallwitz 2012(37) and Simo 2015(38) (EUREXA) Design: OL RCT (PG) non-inferiority Duration: 3-4y	n=1029 mean age: 56y Prior R: metformin DMII duration:5.7y Baseline HbA1c: 7.5% baseline BMI :32.4kg/m2 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> Type 2 diabetes; BMI>=25; 18-85y; stable dose of metformin; subobtimal glycaemic control (HbA1c ≥ 6・5% and ≤9・0%) <u>Exclusion</u> CI for metformin or glimepiride; malignancy; renal or liver disease; haemoglobinopathy or	Exenatide injection 10µg twice daily (mean dose 17.35 µg/d) +metformin Vs Oral Glimepiride, max tolerated dose(mean dose 2.01mg/d) once daily +metformin (median metformin dose 2000mg/d) (Exenatide 5µg bid for 4 weeks, then 10µg bid)	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING:0/2 ○ ATTRITION: 1/1 FOLLOW-UP: <u>Discontinued treatment (not including treatment failure)</u>: exe:33.8% glim: 24.9% Reason described: yes <u>Statistical method for drop out/missing data</u>: MMRM (LOCF for some data, not clear which) <u>ITT</u> defined as patients receiving at least one dose of study treatment, and with baseline and at
			Median time to treatment failure (PE) (inadequate glycaemic control, HbA1c>9% after first 3m or >7% at two consecutive visits 3m apart after the first 6 months)	Exenatide: 180w Glimepiride: 142w **SS, p=0.032**	
			Treatment failure	Exenatide: 41% Glimepiride: 54% Risk diff=12.4% (95%CI 6.2, 18.6) **HR=0.75 (95%CI 0.62, 0.90)** **SS, p=0.002 for superiority** *'conclusions from the as-treated population were not different from those from the intention-to-treat analysis and are therefore not presented'* *'Risk of treat ment failure was signifi antly affected by baseline HbA1c concentration (HR 2·417, 95%*	

	clinically significant chronic anaemia; retinopathy or macular oedema; severe GI disease; use of drugs affecting GI motility, chornic systemic glucocorticoids, weight loss drugs; treamtent >2w with insulin, thiazolidinediones,alpha-glucosidase inhibitors, sulphonyluras or meglitinides	(Glimepiride 1 mg /d, increase every 4 weeks up to maximum tolerated dose) <u>Hyperglycaemia uptitration protocol:</u> <u>Hyperglycaemia rescue protocol</u>**:** <u>Stratification</u> by HbA1c		*CI 2·127–2·745; p<0·0001).* *'We noted no significant interactions of treatment with country, age or sex (data not shown).'*	leastone post-baseline HbA1c measurement were included exe:490/515 glim:487/515 <u>as-treated population</u> defined according to treatment actually received and included only patients with at least 6 months' follow-up for HbA1c. Other important methodological remarks non-inferiority of exenatide to glimepiride if the 97·5% CI for the hazard ratio (HR), , excluded 1.25, thus rejecting the hypothesis that risk of treatment failure with exenatide was more than 25% greater than that with glimepiride. If non-inferiority was shown, we tested
			Mean change in HbA1c ANCOVA with LOCF or MMRM	**from baseline to treatment failure or other endpoint** (ANCOVA) Exenatide: -0.36% Glimepiride: -0.21% **LS mean change between groups** **SS, p=0.002** at 12 months (MMRM) (patients remaining in study: 68% exe vs 77% glim) **LSMD NS** at 24 months (MMRM) (patients remaining in study: 47% exe vs 55% glim) **LSMD p=0.008 in favour of exenatide** at 36 months (MMRM) (patients remaining in study 37% exe and 41.0% glim) **LSMD p=0.035 in favour of exenatide**	
			Body weight change from	**at endpoint**	

			baseline	Exenatide: -3.32 kg Glimepiride: +1.15 kg difference between groups *'significant after* *4 weeks and at each time thereafter'* **SS, p<0.0001** **at 3 years** (Simo 2015,MMRM) **t**reatment difference **-5.2 kg (SE 0.46)** **p<0.0001**	superiority with 95% CI - Multicenter: 128 centers, 14 countries - - Sponsor: Eli Lilly, Amylin
			Blood pressure change from baseline (SystBP/DiastBP)	SBP exe: –1.9 mm Hg glim: 1.1 mm Hg difference between groups year 1 –3.1 mm Hg (95% CI –5.0,–1.2) p=0.001 year 3 –5.2 mm Hg (95%CI–7.6, –2.8) p<0.0001 SS in favour of exenatide DBP (Simo 2015) 3 years treatment difference -1.7 (SE 0.75) p= 0.023	
			Safety		

			Any adverse events	NR	
			Serious adverse events	exe : 14% glim : 13% NS	
			Adverse event leading to withdrawal	exe:49/490 glim: 17/487 p= 0.001	
			% of patients with - documented symptomatic hypoglycaemia (<3.9mmol/l) -Severe hypoglycemia	Exenatide 20% <1%	Glimepiride 47% p<0.0001 0% NS
			Death	Exenatide: n=5 Glimepiride: n=5	
			Pancreatitis Thyroid cancer Coronary artery disease Nephrolithiasis Gastro-intestinal: Nausea Diarrhoea Vomiting Dyspepsia Dropout due to GI events Dropout due to diarrhoea	Exenatide n=1 n=0 n=0 n=3 29% 12% 9% 5% 4% 3%	glimepiride n=1 n=1 n=4 n=0 2% TNR 7% TNR 2% TNR 4% TNR 0% TNR 0% TNR

Table 78

Classified hypoglycaemic episodes as recommended by the American Diabetes AssociationWorkgroup on Hypoglycemia

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Derosa 2011(39) Design: RCT (SB) (PG) Duration of follow-up: 52 weeks	n:111 Italy Mean age: 56 Prior/current treatment: metformin 1000 to 2000 mg/day DMII duration: Baseline HbA1c: exe: 8.7% (SD 0.7) glim: 8.8% (SD 0.8) Mean BMI: exe 28.4kg/m2 (SD 1.3) glim 28.5kg/m2 (SD 1.4) mean weight : exe : 80.2 (SD 7.5) glim: 81.4 (SD 8.1) Previous CV event: NR (excluded) Renal impairment: NR (excluded) <u>Inclusion</u> Caucasian type two diabetes, 18 years and	exenatide 5µg 2x/d for 1 month, then 10µg 2x/d Vs glimepiride 1mg 3x/d for 1 month, then 2mg 3x/d in addition to this background treatment: metformin 1000 to 2000 mg/day + controlled energy diet (600kcal daily deficit)	Efficacy		RANDO: Adequate ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: no Assessors: no/unclear Remarks on blinding method: blinding method for patients not described FOLLOW-UP: <u>Discontinued treatment</u>: exe: 8.8% glim: 9.3% Reason described: yes <u>Statistical method for drop out/missing data</u>: NR <u>ITT</u>: defined as patients who had received one or more doses of study medication, did not show any acute adverse reactions, and had a subsequent efficacy observation. SELECTIVE REPORTING: no, but inadequate reporting of adverse
			HbA1c ANCOVA	at 6 months exe: 7.9±0.5 glim: 8.1±0.6 between-group difference: NS at 12 months exe: 7.5±0.3 p<0.01 for change from baseline glim: 7.4±0.2 p<0.01 for change from baseline between-group difference: NS	
			Body weight	at 6 months exe: 77.6±7.0 p<0.05 vs baseline glim: 81.4±8.2 NS vs baseline at 12 months exe: 75.1±6.5 p< 0.001 vs baseline glim: 80.5±7.7 NS change from baseline between-group difference: NR	
			BMI	at 12 months exe: 26.6±0.9 p<0.001 vs baseline glim: 28.2±1.3	

	older, poor glycaemic control (HbA1c >8%) and over weight (BMI >= 25 and <30kg/m2), taking metformin at various doses and intolerant to metformin at the highest doses (1500 to 3000mg/day) <u>Exclusion</u> Age < 18 yrs, HbA1c <=8%, BMI <25 or >=30 kg/m2, Any liver disease, Any kidney disease, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, history of ketoacidosis, history of cerebrovascular condition, severe anemia, serious CVD (eg, NYHA classes II-IV CHF or a history of myocardial infarction or stroke) or cerebrovascular conditions < 6 months before enrolment			NS vs baseline **between-group difference for BMI: SS in favour of exenatide, p<0.001**	events Other important methodological remarks "every patient who had received at least one dose of the study medication underwent a tolerability observation to exclude the presence of acute adverse reactions" not 1 parameter defined as 'primary endpoint'. The main analyses of this trial were the changes from baseline for both individual drugs Sponsor: none
			Blood pressure change from baseline (SystBP/DiastBP)	NR	
			Safety		
			Death	NR	
			Cardiovascular adverse events	NR	
			Any adverse events	NR	
			Serious adverse events	NR	
			Adverse event leading to withdrawal	exe: 7.0% glim: 7.4%	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	NR withdrawal due to diarrhea exe: 1 patient	
			Nausea	NR withdrawal due to nausea: exe: 2 patients	
			Vomiting	NR withdrawal due to vomiting exe: 1 patient glim: 1 patient	
			Severe hypoglycaemia	NR	
			hypoglycaemia (FPG <60mg/dl) number of patients	exe:0 glim: 2 patients after 3 months and 1 patient after 6 months	

			Injection site reactions	NR	
			Thyroid cancer	NR	
			Pancreatitis	NR	

Table 79

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Derosa 2010(40) Design: RCT (SB) (PG) Duration of follow-up: 12 months	n:128 Italy Mean age: 57 Prior/current treatment: metformin 1500 +/- 500mg Mean DMII duration: Mean baseline HbA1c: exe: 8.8 % glib: 8.9 % Mean BMI: exe 28.7 kg/m2 glib 28.5 kg/m2 mean weight: exe: 82.0 glib: 82.4 Previous CV event: NR (exclusion) Renal impairment: NR (exclusion) <u>Inclusion</u> ≥18 years, poor glycemic control (expressed as HbA1c level >8.0%)	exenatide 10µg 2x/d (after 1 month of 5µg 2x/d) vs glibenclamide 5mg 3x/d (after 1 month of 2.5 mg 3x/d) in addition to this background treatment: metformin 1500 +/- 500mg + a controlled-energy diet (near 600 kcal daily deficit)	Efficacy		RANDO: Adequate? ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: no Assessors: no/unclear FOLLOW-UP: <u>Study completers</u>: 90.6% Reason described: yes <u>Statistical method for drop out/missing data</u>: NR <u>ITT</u>: 'Every patient who had received at least one dose of the study medication underwent a tolerability observation to exclude the presence of acute adverse reactions. After that an intention-to-treat analysis was conducted in patients who had received one or more doses of
			HbA1c at 12 months ANCOVA	exe: 7.3 (SD 0.3) P<0.001 versus baseline glib: 7.1 (SD 0.2) P<0.001 versus baseline exe vs glib NS	
			Body weight at 12 months	exe: 74.0 (SD 4.1) P<0.001 versus baseline glib: 86.7 (SD 11.2) p<0.05 versus baseline **exe vs glib** **P<0.001 in favour of exe**	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP DBP	
			Safety		
			Death	NR	
			Cardiovascular adverse events	NR	
			Any adverse events	NR	
			Serious adverse events	NR	
			Adverse event leading to withdrawal	NR	

	and overweight (BMI ≥25 and <30 kg/m2) receiving therapy with metformin 1,500+/-500mg/day. intolerant to metformin at maximum dosage (3,000mg=day) <u>Exclusion</u> history of ketoacidosis, unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy, impaired hepatic function, impaired renal function, or severe anemia, erious cardiovascular disease (e.g., NYHA class I–IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrollment		**Any gastro-intestinal adverse event**	NR	study medication, did not show any acute adverse reaction, and had a subsequent efficacy observation'. SELECTIVE REPORTING: yes incomplete reporting on adverse events Other important methodological remarks Author states that Bonferroni correction for multiple comparisons was used, BUT for all statistical analyses, P<0.05 was considered statistically significant. no primary outcome defined Sponsor: none
			Diarrhoea	NR withdrawal due to diarrhea exe: 2 patients glib: 1 patient	
			Nausea	NR withdrawal due to nausea: exe: 2 patients glib: 2 patients	
			Vomiting	NR withdrawal due to vomiting exe: 1 patient glib: 1 patient	
			Severe hypoglycaemia	NR	
			hypoglycaemia (FPG<60mg/dl)	exe:0 glim: 3	
			Injection site reactions	NR	
			Thyroid cancer	NR	
			Pancreatitis	NR	

Table 80

6.2.2.2 *Summary and conclusions*

Exenatide 10µg twice daily + metformin +/- 2000mg/d versus glimepiride metformin +/- 2000mg/d			
Bibliography: Gallwitz 2012(37) and Simo 2015(38) (EUREXA)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Median time to treatment failure (P0) (HbA1c>9% after first 3m or >7% at two consecutive visits 3m apart after the first 6 months)	1029 (1) 3-4 y	Exenatide: 180w Glimepiride: 142w **SS, p=0.032** **Treatment failure** Exenatide: 41% Glimepiride: 54% **HR=0.75 (95%CI 0.62, 0.90)** **SS, p=0.002 for superiority**	⊕⊖⊖⊖ **VERY LOW** Study quality:-2 open label, unbalanced and high drop out >20% Consistency: NA Directness: - 1 dose of glimepiride lower than usual Imprecision: ok
HbA1c change from baseline	1029 (1) 3-4 y 12 months* * combined GRADE for Gallwitz 2012, Derosa 2010 and Derosa 2011	from baseline to treatment failure or other endpoint Exenatide: -0.36% Glimepiride: -0.21% treatment difference **SS p=0.002** treatment difference NS	⊕⊖⊖⊖ **VERY LOW** Study quality:-2 open label, unbalanced and high drop out >20% Consistency: NA Directness: - 1 dose of glimepiride lower than usual Imprecision: ok ⊕⊕⊖⊖ **LOW *** Study quality:-2 open label, unbalanced and high drop out >20% Consistency: NA Directness: ok (if combined with Derosa 2010 and Derosa 2011 Imprecision: unable to assess
Body weight change from baseline	1029 (1) 3-4 y	**at endpoint** Exenatide: -3.32 kg Glimepiride: +1.15 kg difference between groups *'significant after 4 weeks and at each time thereafter'* **SS, p<0.0001** **at 3 years** **t**reatment difference **-5.2 kg (SE 0.46) p<0.0001**	⊕⊖⊖⊖ **VERY LOW** Study quality:-2 open label, unbalanced and high drop out >20% Consistency: NA Directness: -1 glimepiride dose Imprecision: unable to assess
Adverse events leading to withdrawal	1029 (1) 3-4 y	exe: 10% glim: 3.5% p= 0.001	⊕⊖⊖⊖ **VERY LOW** Study quality:-2 open label, unbalanced and high drop out >20% Consistency: NA Directness: -1 glimepiride dose Imprecision: unable to assess
Diarrhea	1029 (1) 3-4 y	exe:12% glim: 7% NT	Not applicable

Nausea	1029 (1) 3-4 y	exe: 29% glim:2% NT	Not applicable
Vomiting	1029 (1) 3-4 y	exe:9% glim:2% NT	Not applicable
Severe hypoglycaemia	1029 (1) 3-4 y	exe:<1% glim:0% NS	⊕⊖⊖⊖ **VERY LOW** Study quality:-2 open label, unbalanced and high drop out >20% Consistency: NA Directness: -1 glimepiride dose Imprecision: unable to assess, low event rates

Table 81

Exenatide 10µg 2x/d + metformin 1000-2000mg/d versus glimepride 2mg 3x/d + metformin 1000-2000mg/d			
Bibliography: Derosa 2011(39)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	111 (1) 6 months 12 months	at 6 months and at 12 months: between-group difference NS	**see Gallwitz for combined GRADE** Study quality: no blinding of personnel and possibly assessors Imprecision: unable to assess
Body weight change from baseline	111 (1) 6 months 12 months	between-group difference not reported	

Table 82

Exenatide 10µg 2x/d + metformin 1000-2000mg/d versus glibenclamide 5mg 3x/d + metformin 1000-2000mg/d			
Bibliography: Derosa 2010(40)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	128 (1) 12 months	between-group difference: NS	**see Gallwitz for combined GRADE** Study quality: no blinding of personnel and possibly assessors Imprecision: unable to assess
Body weight change from baseline	128 (1) 12 months	P<0.001 in favour of exe	⊕⊕⊖⊖ **LOW** Study quality: -1 no blinding of personnel and possibly assessors Consistency: ok Directness: ok Imprecision: -1 unable to assess, small trial

Table 83

In 3 RCTs, patients with type 2 diabetes, inadequately controlled by metformin, were randomized to exenatide 10µg twice daily or a sulphonylurea:

- In one open label, non-inferiority RCT by Gallwitz 2012(37)(EUREXA), 1029 patients were randomized to exenatide or glimepiride for 3 to 4 years. The primary endpoint was 'time to treatment failure' (defined as inadequate glycaemic control, HbA1c>9% after first 3m or >7% at two consecutive visits 3 months apart after the first 6 months). The mean age was 56 y, mean duration of diabetes 5.7 years, mean baseline HbA1c was 7.5% and mean BMI was 32 kg/m^2. The mean glimepiride dose was **2.01 mg** once daily.

- In one single blind RCT by Derosa 2011(39), 111 patients were randomized to exenatide 10µg 2x/d or glimepiride 2mg 3x/d for 52 weeks. The mean age was 56 y, mean duration of diabetes not reported, mean baseline HbA1c was 8.8% and mean BMI was 28 kg/m^2.

- In one single blind RCT Derosa 2010(40), 128 patients were randomized to exenatide 10µg 2x/d or glibenclamide 5mg 3x/d for 52 weeks. The mean age was 57 y, mean duration of diabetes not reported, mean baseline HbA1c was 8.9% and mean BMI was 29 kg/m^2.

Our confidence in the estimate of the between-group differences is hindered by the different study designs (EUREXA versus both Derosa trials), the non-blinding of personnel, the high drop-out rate in the largest study. Also, the mean HbA1c at study entry was much higher for both Derosa trials, compared to EUREXA and the SU dose in EUREXA much lower than in the Derosa trials.

In patients who were inadequately controlled on metformin, at a duration of 3-4 years, the addition of exenatide was **superior** to the addition of glimepiride for the endpoint **'treatment failure'** (HR 0.75; 95%CI 0.62 to 0.90).
GRADE: VERY LOW quality of evidence

In patients who were inadequately controlled on metformin, at 52 weeks, the addition of exenatide did **not** result in a statistically significant difference in **HbA1c change** compared to the addition of a sulfonylurea.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin, at 1 year and at 3 years, there was a statistically significant difference in weight change with the addition of exenatide compared to the addition of a sulfonylurea.
There was **more weight loss with exenatide** than with a sulfonylurea (in which there was weight gain versus baseline).
GRADE: LOW to VERY LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported.
Below are the data from Gallwitz 2012(37)

Withdrawal due to adverse events was seen in 10% with exenatide and 3.5% with glimepiride.
GRADE: not applicable

Rates of diarrhea were 12% with exenatide and 7% with glimepiride.
Rates of nausea were 29% with exenatide and 2% with glimepiride.
Rates of vomiting were 9% with exenatide and 2% with glimepiride.
GRADE: not applicable

Severe hypoglycemia occurred in <1% with exenatide and 0% with glimepiride. The difference was **not** statistically significant.
GRADE: VERY LOW quality of evidence

6.2.3 Exenatide twice daily + metformin versus lixisenatide + metformin

6.2.3.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Rosenstock 2013(41) GetGoal-X Design: RCT (OL) (PG) non-inferiority Duration of follow-up: 24w (main study)	n:639 Mean age: 54.7y Prior/current treatment: metformin +/ 2000mg Mean DMII duration: 6.8y Mean baseline HbA1c: 8.02% Mean BMI: 33.6% Previous CV event: NR Renal impairment: NR <u>Inclusion</u> 21–84 y, type 2 diabetes , ≥1.5 g/day metformin and HbA1c 7–10% <u>Exclusion</u>	Lixisenatide 20µg 1x/d (uptitrated from 10µg for 1 week and 15µg for 1 week), vs exenatide 10µg 2x/d (uptitrated from 5µg 2x/d for 1 month) in addition to this background treatment: Metformin +/- 2000mg <u>Stratification:</u> by screening values of HbA1c (<8%, ≥8%) and BMI (<30 kg/m2,	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: unclear FOLLOW-UP: <u>Study completers</u>: 86.4% at 24 weeks discontinued treatment: lixi: 12.9% exe: 14.2% Reason described: yes <u>Hyperglycaemic rescue</u>: NR <u>Statistical method for drop out/missing data</u>: LOCF
			Change in HbA1c from baseline at 24 weeks (PO) ANCOVA	lixi: -0.79% (SE 0.05) exe: -0.96% (SE 0.05) LSMD 0.17% (95% CI 0.033 to 0.297) **non-inferiority criterion met** **Lixi noninferior to exe when added to met**	
			Body weight change from baseline at 24 weeks (SO)	lixi: -2.96 (SE 0.23) kg exe: -3.98 (SE 0.23) kg LSMD 1.02 kg (95%CI 0.456 to 1.581) **SS in favour of exe** no p value reported (in figure: analysis with and without LOCF is SS)	
			Blood pressure change from baseline (SystBP/DiastBP)	The mean decreases in systolic blood pressure between baseline and end of treatment were –2.9 mmHg in the lixisenatide group and –2.5 mmHg in the exenatide group; for diastolic blood pressure, the mean decreases were –1.8 mmHg and –1.3 mmHg, respectively NT	
			Safety		

	use of glucose-lowering agents other than metformin within 3months before the time of screening; FPG at screening.13.9mmol/L (250 mg/dL); history of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery, or inflammatory bowel disease; history of metabolic acidosis, including diabetic ketoacidosis, within 1 year before screening; history within the previous 6 months of myocardial infarction, stroke, or heart failure requiring hospitalization; and clinically relevant history of gastrointestinal disease, with prolonged nausea and vomiting during the previous 6 months	≥30 kg/m2).	**Death**	lixi: 0.3% exe: 0.3%	<u>modified ITT</u>: defined as all randomized participants who received at least one dose of open-label investigational product and had both a baseline assessment and at least one postbaseline assessment SELECTIVE REPORTING: no predefined noninferiority criterion (<0.4% for the upper limit of the 95% CI). The 0.4% margin was selected in accordance with the Committee for Medicial Products for Human Use (CHMP)/International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use additional 52 week safety follow-up planned but never reported (searched pubmed and clinicaltrials.org) Sponsor: Sanofi
			Cardiovascular adverse events	NR	
			Any adverse events	lixi: 69.5% exe: 72.2%	
			Serious adverse events	lixi: 2.8% exe: 2.2%	
			Adverse event leading to withdrawal	lixi:10.4% exe: 13.0% (note: different numbers in on-line supplement: 9.1% vs 9.8%) In the lixisenatide group, 93% of patients (n = 295) demonstrated tolerance and continued with the target total daily dose of 20 mg at week 24 compared with 85% (n = 268) in the exenatide group.	
			Any gastro-intestinal adverse event	lixi:43.1% exe:50.6% NT 'less frequent with lixi'	
			Diarrhoea	lixi:10.4% exe:13.3%	
			Nausea	lixi:24.5% exe:35.1% $P < 0.05$	
			Vomiting	lixi:10.1% exe:13.3%	
			Severe hypoglycaemia	lixi:0 exe:0	

			Symptomatic hypoglycaemia	lixi:2.5% 8 events exe:7.9% 48 events P <0.05	
			Injection site reactions	lixi:8.5% exe:1.6%	
			Thyroid cancer	NR	
			Pancreatitis	lixi:0 exe:0	

Table 84

Symptomatic hypoglycemia was defined as symptoms consistent with hypoglycemia, with accompanying blood glucose ,3.3 mmol/L (60 mg/dL) and/or prompt recovery with oral carbohydrate, glucagon, or intravenous glucose. Severe hypoglycemia was defined as symptomatic hypoglycemia in which the subject required the assistance of another person and that was associated with either a plasma glucose level ,2.0 mmol/L (36 mg/dL) or, if no plasma glucose measurement was available, prompt recovery with intravenous glucose, glucagon, or oral carbohydrate administered by a third party.

6.2.3.2 *Summary and conclusions*

Lixisenatide 20µg once daily + metformin 2000mg/d versus exenatide 10µg twice daily + metformin 2000mg/d			
Bibliography: Rosenstock 2013(41) GetGoal-X			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	639 (1) 24 w	lixi: -0.79% exe: -0.96% treatment difference 0.17% (95% CI 0.03 - 0.30) **Lixi non-inferior to exe**	⊕⊕⊖⊖ **LOW** Study quality:-2 open label and inadequate dealing with missing values (15%), only ITT population analysed, wide non-inferiority marging Consistency: NA Directness: only 24 weeks Imprecision: ok
Body weight change from baseline	639 (1) 24 w	lixi: -2.96 kg exe: -3.98 kg treatment difference 1.02 kg (95%CI 0.46 to 1.58) **SS in favour of exe** no p value reported	⊕⊕⊖⊖ **LOW** Study quality: -1 open label and inadequate dealing with missing values Consistency: Directness: only 24 weeks Imprecision: ok
Adverse events leading to withdrawal	639 (1) 24 w	lixi:10.4% exe: 13.0% NT	Not applicable
Diarrhea	639 (1) 24 w	lixi:10.4% exe:13.3% NT	Not applicable
Nausea	639 (1) 24 w	lixi:24.5% exe:35.1% P < 0.05 **SS more nausea with exenatide**	Not applicable
Vomiting	639 (1) 24 w	lixi:10.1% exe:13.3% NT	Not applicable
Severe hypoglycaemia	639 (1) 24 w	lixi:0 exe:0	Not applicable

Table 85

In this open label non-inferiority RCT, 639 patients with type 2 diabetes, inadequately controlled by metformin +/- 2000 mg, were randomized to lixisenatide 20µg once daily or exenatide 10µg twice daily for 24 weeks. The mean age was 54.7y, mean duration of diabetes 6.8y, mean baseline HbA1c was 8.0% and mean BMI was 33.6% kg/m^2.

The authors planned an additional 52 week safety follow-up but this is not (yet?) published.

Our confidence in the estimate of the between-group differences is limited by the open label design and the inadequate dealing with missing values. The duration of this trial is only 24 weeks. We have no information whether these results are maintained over a longer period of time.

In patients who were inadequately controlled on metformin, at 24 weeks, the addition of lixisenatide was **non-inferior in reducing HbA1c** compared to the addition of exenatide.
Note that the upper limit of the confidence interval is 0.3%. The non-inferiority margin for this trial was established at 0.4% HbA1c.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin, at 24 weeks, there was a statistically significant difference in weight change with the addition of lixisenatide compared to the addition of exenatide.
There was **less weight loss with lixisenatide** than with exenatide.
GRADE: LOW quality of evidence

Withdrawal from the study due to adverse events was seen in 10.4% with lixisenatide and 13.0% with exenatide.
GRADE: not applicable

Rates of diarrhea were 10.4% with lixisenatide and 13.3% with exenatide.
GRADE: not applicable
Rates of nausea were 24.5% with lixisenatide and 35.1% with exenatide. The difference was statistically significant.
Rates of vomiting were 10.1% with lixisenatide and 13.3% with exenatide.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

6.2.4 Exenatide twice daily + metformin versus insulin aspart 70/30 + metformin

6.2.4.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Gallwitz 2011(42) Design: RCT (OL) (PG) non-inferiority Duration of follow-up: 26 weeks	n:363 Germany Mean age: 57y Prior/current treatment: Mean DMII duration: 5y Mean baseline HbA1c: 7.9% Mean BMI: 33.4kg/m2 Previous CV event: Renal impairment: <u>Inclusion</u> Metformin-treated adults with type 2 diabetes (A1C 6.5–10.0%) <u>Exclusion</u> NR	exenatide 10µg 2x/d (after 4 weeks of 5µg 2x/d) vs premixed insulin aspart 70/30 (PIA) 2x/d (mean final total dose (PIA) was 28.4 IU/day) PIA, titrated to glucose targets of 5.0–7.2 mmol/L (fasting) and ,10 mmol/L (2 h postprandial) after each main meal, without a structured insulin dosing algorithm.	Efficacy		RANDO: unclear ALLOCATION CONC: unclear BLINDING : Participants: no Personnel: no Assessors: /unclear Remarks on blinding method: not described FOLLOW-UP: <u>Study completers</u>: 74.9% Reason described: no <u>Uptitration of study medication</u>: PIA yes <u>Hyperglycaemic rescue</u>: NR <u>Statistical method for drop out/missing data</u>: MMRM
			Change in HbA1c from baseline (PO) MMRM	exe: -1.00% PIA: -1.14% treatment difference 0.14 (95% CI -0.003 to 0.291) **exe noninferior to PIA**	
			Body weight change from baseline (SO) MMRM	exe: -4.1 (SE 0.22)kg PIA: 1.0 (SE 0.22)kg P< 0.001 for group difference	
			Blood pressure change from baseline	NR	
			Safety		
			Death	NR	
			Cardiovascular adverse events	NR	
			Any adverse events	NR	
			Serious adverse events	NR	
			Adverse event leading to withdrawal	exe:7.2% PIA: 0.6% p = 0.0014	

		in addition to this background treatment: metformin +/- 2000mg/d Hyperglycaemia uptitration protocol: Hyperglycaemia rescue protocol: Stratification: baseline A1C (≤8.0 or >8.0%)	**Any gastro-intestinal adverse event**	NR	ITT: defined as all randomized patients who received the study drug (full analysis population). 353/364 SELECTIVE REPORTING: no complete reporting of adverse events Other important methodological remarks For noninferiority of exenatide BID, the upper limit of the 95% CI of the group difference in A1C change was required to be <0.4% (exenatide BID minus PIA;MMRM adjusting for baseline A1C). Only if noninferiority was shown, the second test on the risk for the first hypoglycemic episode (blood glucose ≤3.9 mmol/L or severe; Kaplan-Meier analysis) was done. This study was specifically designed to compare hypoglycemia with exenatide
			Diarrhoea	exe: 10.5% PIA: 8.1%	
			Nausea	exe:18.8% PIA: NR	
			Vomiting	exe: 9.9% PIA: NR	
			Severe hypoglycaemia	exe:0 PIA:0	
			first hypoglycemic episode (blood glucose≤3.9mmol/L or severe) Hypoglycemic episodes with blood glucose ≤3.0 mmol/L	exe: 8.0% (95% CI 4.7–13.4%) PIA: 20.5% (95% CI 15.0–27.7%) p<0.05 SS more hypoglycemia with PIA exe: 1.8% PIA: 6.3% NS (derived from figure)	
			Injection site reactions	NR	
			Thyroid cancer	NR	

			Pancreatitis	NR	twice daily (BID) versus premixed insulin aspart 70/30 BID Sponsor:

Table 86

Hypoglycemia= (blood glucose <3.9 mmol/L or severe episode. Severe episodes were defined as episodes requiring assistance of another person, with symptoms recovering after treatment Workgroup on Hypoglycemia, AmericanDiabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005;28:1245–1249

6.2.4.2 *Summary and conclusions*

Exenatide 10µg twice daily + metformin +/- 200mg/d versus premixed insulin aspart 70/30 twice daily + metformin +/- 2000mg/d			
Bibliography: Gallwitz 2011(42)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	363 (1) 26 weeks	exe: -1.00% PIA: -1.14% treatment difference 0.14 (95% CI -0.003 to 0.291) **exe non-inferior to PIA**	⊕⊕⊖⊖ **LOW** Study quality:-2 unclear rando and allocation concealment, open label, 25% attrition, attrition not described Consistency: NA Directness: only 26 weeks Imprecision: ok
Body weight change from baseline	363 (1) 26 weeks	exe: -4.1 kg PIA: 1.0 kg treatment difference P< 0.001 **SS in favour of exe**	⊕⊕⊖⊖ **LOW** Study quality:-2 unclear rando and allocation concealment, open label, 25% attrition, attrition not described Consistency: NA Directness: only 26 weeks Imprecision: unable to assess
Adverse events leading to withdrawal	363 (1) 26 weeks	exe:7.2% PIA: 0.6% p = 0.0014	⊕⊕⊖⊖ **LOW** Study quality:-2 unclear rando and allocation concealment, open label, 25% attrition, attrition not described Consistency: NA Directness: only 26 weeks Imprecision: unable to assess
Diarrhea	363 (1) 26 weeks	exe: 10.5% PIA: 8.1%	Not applicable
Nausea	363 (1) 26 weeks	exe:18.8% PIA: NR	Not applicable
Vomiting	363 (1) 26 weeks	exe: 9.9% PIA: NR	Not applicable
Severe hypoglycaemia	363 (1) 26 weeks	exe:0 PIA:0	Not applicable
	363 (1) 26 weeks		

Table 87

In this open label, non-inferiority RCT, 363 patients with type 2 diabetes, inadequately controlled by metformin +/- 2000mg/d, were randomized to exenatide 10µg 2x/d or premixed insulin aspart 70/30

(PIA) twice daily for 26 weeks. The mean age was 57 years, mean duration of diabetes 5 years, mean baseline HbA1c was 7.9% and mean BMI was 33.4 kg/m^2.

Our confidence in the estimate of the between-group differences is limited by the open label design, unclear randomization and allocation concealment and the incomplete reporting of drop-out.

In patients who were inadequately controlled on metformin, at 26 weeks, the addition of exenatide was **non-inferior for the decrease of HbA1c** compared to the addition of premixed insulin aspart 70/30. Note that the upper limit of the confidence interval is 0.29%. The non-inferiority margin for this trial was established at 0.4% HbA1c.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin, at 26 weeks, there was a statistically significant difference in weight change with the addition of exenatide compared to the addition of premixed insulin aspart 70/30.
There was **more weight loss with exenatide** than with premixed insulin aspart 70/30 (for which the weight had increased from baseline).
GRADE: LOW quality of evidence

Withdrawal from the study due to adverse events was seen in 7.2% with exenatide and 0.6% with premixed insulin aspart 70/30.
GRADE: LOW quality of evidence

Rates of diarrhea were 10.5% with exenatide and 8.1% with premixed insulin aspart 70/30.
Rates of nausea were 18.8% with exenatide and not reported with premixed insulin aspart 70/30.
Rates of vomiting were 9.9% with exenatide and not reported with premixed insulin aspart 70/30.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

6.3 Combination therapy with sulfonylurea

6.3.1 Exenatide twice daily + sulfonylurea versus placebo + sulfonylurea

6.3.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Buse 2004(43) Design: RCT (TB) (PG) Duration of follow-up: 30w	n: 377 Mean age: 55 Prior/current treatment: SU Mean DMII duration: exe 5:6.3y exe 10:6.6y pla: 5.7y Mean baseline HbA1c: 8.6% Mean BMI: 33kg/m2 Previous CV event: NR (excluded) Renal impairment: NR <u>Inclusion</u> 22–76 y, type 2 diabetes treated with at least the maximally effective dose of a	exenatide 5µg 2x/d vs exenatide 10µg 2x/d (after 4 weeks of 5µg 2x/d) vs placebo in addition to this background treatment: Sulphonylurea subjects had their SU dose adjusted before the placebo lead-in period to the maximally effective dose (4 mg/day glimepiride, 20	Efficacy		RANDO: unclear ALLOCATION CONC: unclear BLINDING : Participants: unclear Personnel: unclear Assessors: unclear Remarks on blinding method: no information on randomisation, allocation concealment or blinding FOLLOW-UP: <u>Study completers</u>: 69% exe 5: 76.0% exe 10: 70.5% pla: 60.2% Reason described: yes <u>Loss of glucose control (excluded from study)</u>:
			Change in HbA1c from baseline at 30 weeks (PO)	exe 5: -0.46% (SE 0.12) exe 10: -0.86% (SE 0.11) pla: +0.12% (SE 0.09) (adjusted P ≤ 0.0002 for pairwise comparisons	
			Body weight change from baseline (SO)	exe 5: -0.9kg (SE 0.3) exe 10: -1.6 kg (SE 0.3) pla: -0.6kg (SE 0.3) p<0.05 for exe 10 vs pla	
			Blood pressure change from baseline (SystBP/DiastBP)	'no adverse trends reported'	
			Safety		
			Death	NR	
			Cardiovascular adverse events	exe 5:0 exe 10:1 patient pla: 2 patients	
			Any adverse events	NR	
			Serious adverse events	exe 5: 3%	

	sulfonylurea as monotherapy ≥ 3 months. fasting plasma glucose concentration <240 mg/dl, BMI 27–45 kg/m2, and HbA1c 7.1–11.0%, inclusive, stable weight (+/-10%), no abnormal laboratory test values ; female: postmenopausal or surgically sterile or using contraceptives for at least 3 months before screening and continuing throughout the study <u>Exclusion</u> metformin, thiazolidinediones, meglitinides, alpha glucosidase inhibitors, exogenous insulin therapy, or weight-loss drugs within3months. steroids, drugs that affect gastrointestinal motility,	mg/day glipizide, 10 mg/ day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/ day chlorpropamide, or 500 mg/day tolazamide) progressive 50% reductions in sulfonylurea dose, eventual discontinuation in the event of a documented episode of hypoglycemia (glucose <60 mg/dl), or two undocumented but suspected episodes of hypoglycemia <u>Hyperglycaemia</u>		exe 10: 4% pla: 8%	exe 5: 5.6% exe 10:4.7% pla:16.3% <u>Statistical method for drop out/missing data</u>: LOCF <u>ITT</u>: defined as all randomized subjects who received at least one injection of randomized medication starting from the evening of day 1. SELECTIVE REPORTING: safety was deemed a primary aim of the study, but no statistical testing reported Other important methodological remarks - 4 week placebo lead-in - SU: 45% glipizide, 33% glyburide, 20% glimepiride, 1% tolazamide, and 0.3% chlorpropamide - no information given about number of patients in whom SU dose was reduced after hypoglycemia
			Adverse event leading to withdrawal	exe 5: 7.2% exe 10: 10.1% pla: 3.3% NT	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	exe 5: 11% exe 10: 9% pla: 4% NT	
			Nausea	exe 5: 39% exe 10: 51% pla: 7% NT	
			Vomiting	exe 5: 10% exe 10: 13% pla: 2% NT	
			Severe hypoglycaemia	0	
			Mild to moderate hypoglycaemia	exe 5: 14% exe 10: 36% pla: 3% NT	
			Injection site reactions	NR	
			Thyroid cancer	NR	

	transplantation medications, or any investigational drug. Subjects were excluded if they had evidence of clinically significant comorbid conditions.	rescue protocol: yes (excluded from study if exceeding certain HbA1c values or FPG values)see below Stratification: according to screening HbA1c values (<9.0% and ≥9.0%)	**Pancreatitis**	NR	Sponsor: Amylin Pharmaceuticals and Eli Lilly

Table 88

Any subject with either an HbA1c change of 1.5% from baseline at any clinic visit before study termination or an HbA1c >11.5% at week 18 or 24 could be withdrawnfrom the study (loss of glucose control). Similarly, subjects could be withdrawn if they had fasting plasma glucose values >240 mg/dl on two consecutive study visits or consistently recorded finger-stick fasting blood glucose values>260 mg/dl for at least 2 weeks, not secondary to a readily identified illness or pharmacological treatment.

The intensity of hypoglycemic episodes was defined as mild/ moderate or severe. For mild/moderate hypoglycemia, subjects reported symptoms consistent with hypoglycemia that may have been documented by a plasma glucose concentration value (_60 mg/dl).
For severe hypoglycemia, subjects required the assistance of another person to obtain treatment for their hypoglycemia, including intravenous glucose or intramuscular glucagon.

6.3.1.2 *Summary and conclusions*

Exenatide 5µg or 10µg twice daily + sulphonylurea versus placebo + sulfonylurea			
Bibliography: Buse 2004(43)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	377 (1) 30 w	exe 5: -0.46% exe 10: -0.86% pla: +0.12% treatment difference not reported **P ≤ 0.0002 for pairwise comparisons, SS**	⊕⊕⊖⊖ **LOW** Study quality:-1 attrition 30% and inadequate method of dealing with missing values, unclear blinding, rando Consistency: ok Directness: ok, but only 30 weeks Imprecision: -1 unable to assess
Body weight change from baseline	377 (1) 30 w	exe 5: -0.9kg exe 10: -1.6 kg pla: -0.6kg exe 10 vs pla **p<0.05** exe 5 vs pla NS	⊕⊕⊖⊖ **LOW** Study quality: -1 attrition 30% and inadequate method of dealing with missing values, unclear blinding, rando Consistency: ok Directness: ok, but only 30 weeks Imprecision: -1 unable to assess
Adverse events leading to withdrawal	377 (1) 30 w	exe 5: 7.2% exe 10: 10.1% pla: 3.3% NT	Not applicable
Diarrhea	377 (1) 30 w	exe 5: 11% exe 10: 9% pla: 4% NT	Not applicable
Nausea	377 (1) 30 w	exe 5: 39% exe 10: 51% pla: 7% NT	Not applicable
Vomiting	377 (1) 30 w	exe 5: 10% exe 10: 13% pla: 2% NT	Not applicable
Severe hypoglycaemia	377 (1) 30 w	0	Not applicable

Table 89

In this triple blind RCT, 377 patients with type 2 diabetes, inadequately controlled by a sulphonylurea, were randomized to exenatide 5µg twice daily, exenatide 10µg twice daily or placebo for 30 weeks. The mean age was 55y, mean duration of diabetes 6y, mean baseline HbA1c was 8.6% and mean BMI was 33 kg/m^2. Participants were on the maximally effective dose of sulphonylurea at the time of randomization. 45% of participants were on glipizide, 33% on glyburide and 20% on glimepiride.

Our confidence in the estimate of the between-group differences is limited by the large drop-out throughout the study (overall 31%) and drop out was higher in the placebo group. It is difficult to make a full grade assessment because of incomplete reporting of confidence intervals.

In patients who were inadequately controlled on a sulphonylurea, at 30 weeks, the addition of exenatide resulted in a statistically significant **decrease of HbA1c** compared to the addition of placebo.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on a sulphonylurea, at 30 weeks, there was a statistically significant difference in weight change with the addition of exenatide 10µg compared to the addition of placebo.
There was **more weight loss with exenatide 10 µg** than with placebo.
There was **no** statistically significant difference in weight change with the addition of **exenatide 5µg** compared to the addition of placebo.
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported.

Withdrawal from the study due to adverse events was seen in 7.2% with exenatide 5µg, 10.1% with exenatide 10µg and 3.3% with placebo.
GRADE: not applicable

Rates of diarrhea were 11% with exenatide 5µg and 9% with exenatide 10µg and 4% with placebo.
Rates of nausea were 39% with exenatide 5µg, 51% with exenatide 10µg and 7% with placebo.
Rates of vomiting were 10% with exenatide 5µg, 13% with exenatide 10µg and 2% with placebo.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

6.4 Combination therapy with metformin or sulfonylurea or both

6.4.1 Exenatide twice daily + lifestyle modification + MET and/or SU versus placebo + lifestyle modification + MET and/or SU

6.4.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Apovian 2010(44) Design: RCT (DB) (PG) Duration of follow-up: 24 weeks	n: 196 Race/Ethnicity: Mean age: 54.8y Prior/current treatment: MET or SU DMII duration:5.5y Baseline HbA1c:7.6% Mean BMI: 33.8kg/m2 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> 18-75 years of age with type 2 diabetes, treated for at least 6 weeks with a stable dose of metformin or a sulfonylurea, hemoglobin A1c	exenatide uptitrated from 5µg 2x/d to 10µg 2x/d vs placebo in addition to this background treatment:lifestyle program: goals of 600 kcal/day deficit and physical activity of at least 2.5 hours/week + met or SU or both continuation	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: unclear FOLLOW-UP: <u>Study completers</u>: 73% Reason described: yes balanced across groups: yes 1 patient in placebo group excluded because of loss of glycaemic control Six participants treated with exenatide plus lifestyle modification and one participant treated with placebo plus
			Change in HbA1c from baseline (SO) MMRM	exe: -1.21% (SE 0.09) pla: -0.73%(SE 0.09) p<0.001 **SS in favour of exe**	
			Body weight change from baseline to week 24 (PO) MMRM	exe: -6.16 (SE 0.54) kg pla:-3.97 (SE 0.52)kg P=0.003 **SS in favour of exe**	
			Blood pressure change from baseline (SystBP/DiastBP) 'exploratory endpoint'	SBP exe: -9.44 (SE 1.40) pla:-1.97 (SE 1.40) p<0.001 **SS in favour of exe** DBP exe: -2.22 (SE 1.00) pla: 0.47 (SE 0.99) p=0.04 **SS in favour of exe**	
			Safety		
			Death	NR	
			Cardiovascular adverse events	NR	
			Any adverse events	NR	

	(HbA1c) 6.6%-10.0%, body mass index 25-39.9 kg/m2, and history of stable body weight (not varying by 5% for at least 6 months before screening) Exclusion use of exogenous insulin, alpha-glucosidase inhibitors, a thiazolidinedione, weight loss agents within 6 months before study entry, evidence of poorly controlled hypertension within the previous 3 months, or history or presence of cardiac disease within 3 years of screening.	Hyperglycaemia rescue protocol: **NR** Stratification: by baseline oral therapy One confirmed hypoglycemic event (documented blood glucose 60 mg/dL) or 2 unconfirmed hypoglycemic events allowed sulfonylurea dose to be decreased 50%; additional episodes allowed further decrease or discontinuation.	**Serious adverse events** number of events	exe:2 pla:2	lifestyle modification reduced their dose of sulfonylurea (P =0.104). Statistical method for drop out/missing data : MMRM modified ITT: described as all randomized participants who received at least one dose of study medication and had baseline and at least one postbaseline measurement (>99% in ITT) SELECTIVE REPORTING: unclear definitions of hypoglycaemia Other important methodological remarks : aim of the study was weight loss endpoint Sponsor: Eli lily and company
			Adverse event leading to withdrawal	exe:4.2% pla:5.1% NS	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	NR	
			Nausea	exe:44.8% pla:19.4% p<0.001 **SS more nausea with exe**	
			Vomiting	exe:22% pla: 9% p=0.017 **SS more vomiting with exe**	
			Severe hypoglycaemia	0	
			hypoglycaemia events per person-year no definition stated	exe:7.1 (SE 1.4) pla: 4.6 (SE 1.4) NS	
			Injection site reactions	NR	
			Thyroid cancer	NR	
			Pancreatitis	NR	

Table 90

Lifestyle modification program: A registered dietitian instructed participants on individualized diet and activity plans that included a balanced macronutrient-content, calorie-restricted diet (600 kcal/day deficit) and an increase in moderately intense physical activity to achieve a minimum of 150 minutes per week

Subgroup analysis by oral agent

metformin subgroup, exenatide vs placebo:- 0.57 +/- 0.15% greater decrease in HbA_{1c} than placebo (P = .0002).

metformin plus sulfonylurea subgroup , exenatide vs placebo: -0.53 +/-0.22% greater decrease in HbA_{1c} (P =.02).

sulfonylurea subgroup (n=22) no statistically significant difference in HbA_{1c} -0.17 +/-0.26% (P =.52)

6.4.1.2 *Summary and conclusions*

Exenatide 10µg twice daily + lifestyle modification +/MET +/- SU versus placebo + lifestyle modification + MET +/- SU			
Bibliography: Apovian 2010(44)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (SO)	196 (1) 24 weeks	exe: -1.21% pla: -0.73% p<0.001 **SS in favour of exe**	⊕⊕⊖⊖ **LOW** Study quality: -1 drop out 27% Consistency: NA Directness: background therapy varied, only 24 weeks Imprecision: -1 unable to assess
Body weight change from baseline (PO)	196 (1) 24 weeks	exe: -6.16 kg pla:-3.97 kg P=0.003 **SS in favour of exe**	⊕⊕⊖⊖ **LOW** Study quality: -1 drop out 27% Consistency: NA Directness: background therapy varied, only 24 weeks Imprecision: -1 unable to assess
Adverse events leading to withdrawal	196 (1) 24 weeks	exe:4.2% pla:5.1% NS	⊕⊕⊖⊖ **LOW** Study quality: -1 drop out 27% Consistency: NA Directness: background therapy varied, only 24 weeks Imprecision: -1 unable to assess
Diarrhea	196 (1) 24 weeks	NR	Not applicable
Nausea	196 (1) 24 weeks	exe:44.8% pla:19.4% p<0.001 **SS more nausea with exe**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 drop out 27% Consistency: consistent with other studies Directness: see above. Only 24 weeks Imprecision: unable to assess
Vomiting	196 (1) 24 weeks	exe:22% pla: 9% p=0.017 **SS more vomiting with exe**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 drop out 27% Consistency: consistent with other studies *Directness:* see above. Only 24 weeks Imprecision: unable to assess
Severe hypoglycaemia	196 (1) 24 weeks	0	Not applicable

Table 91

In this double blind RCT, 196 patients with type 2 diabetes, inadequately controlled by metformin or sulfonylurea or both, were randomized to exenatide 10µg twice daily or placebo for 24 weeks. Patients in both groups received an intensive lifestyle modification program (diet and exercise). The primary aim of the study was the outcome weight loss.

The mean age was 54.8y, mean duration of diabetes 5.5y, mean baseline HbA1c was 7.6% and mean BMI was 33.8 kg/m^2.

Our confidence in the estimate of the between-group differences is limited by a drop-out of 27% and by the relatively short duration of the study.

In patients who were inadequately controlled on metformin or sulphonylurea or both, at 24 weeks, the addition of exenatide 10µg twice daily + lifestyle modification resulted in a statistically significant **decrease of HbA1c** compared to the addition of placebo + lifestyle modification.
GRADE: LOW quality of evidence

These results were consistent across subgroups by oral background therapy for MET and MET + SU, but not for SU only (possibly due to lack of power)
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin or sulphonylurea or both, at 24 weeks, there was a statistically significant difference in weight change with the addition of exenatide 10µg twice daily + lifestyle modification compared to the addition of placebo + lifestyle modification.
There was **more weight loss with exenatide** 10µg twice daily than with placebo.
GRADE: LOW quality of evidence
These results were consistent across subgroups by oral background therapy for MET and MET + SU, but not for SU only (possibly due to lack of power)

Rates of adverse events can be found in the table above.
The authors state that the treatment effect was consistent among subgroups of background treatment (MET, SU, MET + SU).

6.4.2 Exenatide twice daily +metformin +/- sulfonylurea versus liraglutide + metformin +/- sulfonylurea

6.4.2.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Buse 2009(45) LEAD-6 Design: RCT (OL) (PG) non-inferiority Duration of follow-up: 26w	n: 464 Mean age: 57y Prior/current treatment: max tolerated dose of MET, SU or both Mean DMII duration: 8.2y Mean baseline HbA1c: 8.2% Mean BMI: 32.9kg/m2 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> 18–80 years with type 2 diabetes were eligible if their HbA1c value was 7–11% and if they had a body-mass index (BMI)	liraglutide 1.8mg 1x/d (increased from 0.6mg week 1 to 1.2mg week two) vs exenatide 10µg 2x/d (5µg 2x/d for the initial 4 weeks) in addition to this background treatment: MET+SU 63% SU: 10% MET: 27% <u>if unacceptable hypoglycaemia:</u> sulphonylurea doses could be reduced to no	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: no/unclear FOLLOW-UP: <u>Discontinued treatment</u>: lira: 14.2% exe: 19.5% Reason described: yes 1 person in lira group discontinued due to 'ineffective therapy' SU dose decrease: *' most patients could continue sulphonylurea treatment at the dose used in the period before enrolment (liraglutide*
			Change in HbA1c from baseline at 26 weeks(PO) ANCOVA	lira: –1·12% [SE 0·08] exe: –0·79% [0·08] estimated treatment difference : –0·33 (95% CI –0·47 to –0·18) p<0.0001 per-protocol population HbA1c: liraglutide –1·16% [0·09] exenatide–0·87% [0·09]; ETD –0·29%; 95% CI –0·45 to –0·13; p<0·0001) *'Differences in HbA1c values between treatment groups did not depend on baseline therapy, BMI, country, sex, ethnic origin, or age because the interaction effects were not significant (p>0·05)'* the difference was greatest for patients with baseline HbA1c of 10% or more (liraglutide –2·4% [SE 0·21] vs exenatide –1·2% [0·37]).	
			Body weight change from baseline	lira: –3·24 kg exe: –2·87 kg	

	of 45·0 kg/m² or less on stable treatment with maximally tolerated doses of metformin, sulphonylurea, or both, for 3 months or more. <u>Exclusion</u> previous insulin treatment (except shortterm treatment for intercurrent illness), previous exposure to exenatide or liraglutide, impaired liver or renal function, clinically significant cardiovascular disease, retinopathy or maculopathy requiring acute treatment, uncontrolled hypertension (≥180/100 mm Hg), or cancer.	less than 50% of the starting dose* <u>Stratification:</u> by previous oral antidiabetic therapy		ETD –0·38 kg; 95% CI –0·99 to 0·23	*89% and exenatide 85%)' – per protocol population* <u>Statistical method for drop out/missing data</u>: LOCF (MMRM as a sensitivity analysis – data not reported) <u>ITT</u>: no definition. Number analysed = number randomised SELECTIVE REPORTING: unclear reporting of severe-serious adverse events (confusing). Other important methodological remarks - non-inferiority margin 0.4% - it is unclear whether the subgroup analyses were prespecified Sponsor: Novo Nordisk A/S
			Blood pressure change from baseline (SystBP/DiastBP)	SBP lira: –2·51 (1·15) exe: –2·00 (1·18) NS DBP lira: –1·05 (0·71) exe: –1·98 (0·71) NS	
			Safety		
			Death	NR	
			Cardiac disorders	lira:0.4% exe:0.9%	
			Any adverse events	lira:74.9% exe:78.9%	
			Serious adverse events	lira: 5.1% exe:2.6%	
			Adverse event leading to withdrawal	lira:9.9% exe:13.4%	
			Any gastro-intestinal adverse event	lira: 45.5% exe: 42.7%	
			Diarrhoea	lira:12.3% exe:12.1%	
			Nausea	lira: 25.5% exe: 28.0%	
			Vomiting	lira:6.0% exe:9.9%	
			Major hypoglycaemia	lira:0 exe:2 episodes	
			Minor hypoglycaemia	lira: 26%	

				exe: 34% event rate 1·932 vs 2·600 events per participant per year; rate ratio 0·55, 95% CI 0·34 to 0·88; p=0·0131) The proportion of patients who had episodes of minor hypoglycaemia was lower in the subgroups using metformin as background therapy (6% and 11% for liraglutide and exenatide groups, respectively) than in those taking a sulphonylurea with or without metformin (33% and 42%, respectively).	
			Injection site reactions	NR	
			Thyroid cancer	lira:1? (unclear reporting) exe:	
			Pancreatitis	lira:1 (mild – no pancreatic enzymes reported) exe:0	

Table 92

Major hypoglycaemic episodes were defined as requiring third-party assistance with food only, glucagon, or intravenous glucose. Minor episodes were defined as those that the participant could self-treat and for which the plasma glucose concentration was less than 3·1 mmol/L. At glucose concentrations of 3·1 mmol/L or more, or in the absence of glucose measurements, episodes were regarded as symptoms only.

6.4.2.2 *Summary and conclusions*

Liraglutide 1.8mg once daily +/- MET +/- SU versus exenatide 10µg twice daily +/- MET +/- SU			
Bibliography: Buse 2009(45) LEAD-6			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	464 (1) 26 weeks	lira: –1·12% exe: –0·79% treatment difference : –0·33% (95%CI –0·47 to -0·18) p<0.0001	⊕⊕⊖⊖ **LOW** Study quality: -1 open label, inadequate method of dealing with missing values (17% missing) Consistency: NA Directness: -1 background therapy varied, only 26 weeks Imprecision: ok
Body weight change from baseline	464 (1) 26 weeks	lira: –3·24 kg exe: –2·87 kg treatment difference –0.38kg (95%CI –0.99 to 0.23)	⊕⊕⊖⊖ **LOW** Study quality: -1 open label, inadequate method of dealing with missing values (17% missing) Consistency: NA Directness: -1 background therapy varied, only 26 weeks Imprecision: ok
Adverse events leading to withdrawal	464 (1) 26 weeks	lira:9.9% exe:13.4%	Not applicable
Diarrhea	464 (1) 26 weeks	lira:12.3% exe:12.1%	Not applicable
Nausea	464 (1) 26 weeks	lira: 25.5% exe: 28.0%	Not applicable
Vomiting	464 (1) 26 weeks	lira:6.0% exe:9.9%	Not applicable
Severe hypoglycaemia	464 (1) 26 weeks	lira:0 exe:2	Not applicable
			Not applicable

Table 93

In this open label, non-inferiority RCT, 464 patients with type 2 diabetes, inadequately controlled by metformin + sulphonylurea (63%) or metformin only (27%) or sulphonylurea only (10%) were randomized to liraglutide 1.8 mg daily or exenatide 10µg twice daily for 26 weeks. The mean age was 57y, mean duration of diabetes 8.2y, mean baseline HbA1c was 8.2% and mean BMI was 33 kg/m^2. Patients with clinically significant cardiovascular disease or renal impairment were **not** allowed in the study.

Our confidence in the estimate of the between-group differences is mainly limited by the open label design, the method of dealing with missing values and the short duration of the trial (no information beyond 26 weeks).

In patients who were inadequately controlled on MET + SU or MET or SU, at 26 weeks, the addition of liraglutide 1.8 mg once daily was **superior** to the addition of exenatide 10µg twice daily for the **decrease of HbA1c.**
GRADE: LOW quality of evidence

In patients who were inadequately controlled on MET + SU or MET or SU, at 26 weeks,, there was **no** statistically significant **difference in weight change** with the addition of liraglutide 1.8 mg once daily compared to the addition of exenatide 10µg twice daily.
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported.

Withdrawal from the study due to adverse events was seen in 9.9% with liraglutide 1.8 mg once daily and 13.4% with exenatide 10µg twice daily.
GRADE: not applicable

Rates of diarrhea were 12.3% with liraglutide 1.8 mg once daily and 12.1% with exenatide 10µg twice daily.
Rates of nausea were 25.5% with liraglutide 1.8 mg once daily and 28.0% with exenatide 10µg twice daily.
Rates of vomiting were 6.0% with liraglutide 1.8 mg once daily and 9.9% with exenatide 10µg twice daily.
GRADE: not applicable

Severe hypoglycemia occurred in 0 patients with liraglutide 1.8 mg once daily and there were 2 events with exenatide 10µg twice daily.
GRADE: not applicable

6.5 Combination therapy with metformin + sulfonylurea

6.5.1 Exenatide twice daily + metformin + sulfonylurea versus placebo + metformin + sulfonylurea

6.5.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Kendall 2005(46) Design: RCT (DB) (PG) Duration of follow-up: 30 weeks	n:733 USA Mean age: 55 Prior/current treatment: metformin + sulfonylurea Mean DMII duration: 8.7 to 9.4y Mean baseline HbA1c: 8.5% Mean BMI: 33.6 Previous CV event: NR (excluded) Renal impairment: NR <u>Inclusion</u> 22–77 y, type 2 diabetes treated with metformin and a	exenatide 5µg 2x/d vs exenatide 10µg 2x/d (after 4 weeks of 5µg 2x/d) vs placebo in addition to this background treatment: normal dose of metformin + sulfonylurea, randomization to MAX dose or MIN recommended dose of SU	Efficacy		RANDO: unclear ALLOCATION CONC: unclear BLINDING : unclear unclear unclear Remarks on blinding method: no description of randomisation and blinding FOLLOW-UP: <u>Study completers</u>: 81% exe 5: 84.1% exe 10: 82.2% pla: 76.1% Reason described: yes <u>Uptitration of study medication</u>: SU in the MIN group could be uptitrated according to FPG above a certain level before week
			Change in HbA1c from baseline at 30 weeks (PO)	exe 5: -0.55%(SE 0.07) exe 10: -0.77(SE 0.08) pla: +0.23% (SE 0.07) exe 5 vs pla adjusted reduction -0.8% exe 10 vs pla adjusted reductuion -1.0% adjusted P< 0.0001 vs. Placebo for both comparisons MAX SU dose vs MIN SU dose (HbA1c change from baseline) p<0.001 for between-group differences more HbA1c reduction with higher dose SU	
			Body weight change from baseline	exe 5: -1.6(SE 0.2) kg exe10: -1.6(SE 0.2) kg pla: -0.9(SE 0.2) kg P ≤ 0.01 for each exe dose vs placebo	
			Blood pressure change from baseline	NR	

	sulfonylurea. FPG 13.3 mmol/l, BMI 27–45 kg/m2, HbA1C value of 7.5–11.0%. metformin 1,500 mg/day, sulfonylurea maximally effective dose for 3 months before screening, weight stable (10%) for 3 months before screening, no clinically relevantabnormal laboratory test values <u>Exclusion</u> other clinically significant medical conditions; used thiazolidinediones, meglitinides, -glucosidase inhibitors, exogenous insulin, or weight loss drugs within the prior 3 months, corticosteroids, drugs known to affect gastrointestinal motility, transplantation medications, or any investigational drug	sulfonylurea dose could be reduced by 50%, regardless of the subject's assigned sulfonylurea management group, in the event of one documented hypoglycemic event (blood glucose concentration 3.3 mmol/l) or two undocumented suspected hypoglycemic events. Further 50% reductions, including complete cessation of sulfonylurea dose, were allowed upon repetition of the previous criteria	Safety		12 <u>Loss of glucose control</u>: exe 5: 1.2% exe 10: 0.8% pla: 2.4% <u>Statistical method for drop out/missing data</u>: LOCF <u>ITT</u>: defined as all randomized subjects who received at least one injection of randomized medication starting from the evening of day 1. SELECTIVE REPORTING: reporting of AE a bit sparse, considering it was defined as a 'primary outcome' Other important methodological remarks - 4-week, single-blind, placebo lead-in period - To standardize sulfonylurea use in the clinical trial, subjects were randomized (one for one) to either maximally effective sulfonylurea dose (MAX group; 4 mg/day
			Death	NR	
			Cardiovascular adverse events	'no evidence of CV toxicity'	
			Any adverse events	NR	
			Serious adverse events	exe 5: 6% exe10: 5% pla: 6% NR	
			Adverse event leading to withdrawal	exe 5:5.7% exe10:9.1% pla:4.5% NT	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	exe 5: 10.2% exe10: 17.4% pla: 6.5% NT	
			Nausea	exe 5: 39.2% exe10: 48.5% pla: 20.6% NT	
			Vomiting	exe 5: 14.7% exe10: 13.7% pla: 4.5% NT	
			Severe hypoglycaemia	exe 5:1 patient exe10:0 pla:0	

		<u>Stratification:</u> according to screening A1C values (<9.0 and ≥9.0%)	**Mild/moderate hypoglycaemia**	exe 5: 19% exe10: 28% pla: 13% 'higher in each exenatide treatment arm compared with the placebo arm' MAX SU group exe 5:22% exe 10:35% pla: 15% MIN SU group exe 5 : 16% exe 10 : 21% pla : 10% 'lower incidence in MIN group'	glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glibenclamide [glyburide], 6 mg/day micronized glibenclamide, 350 mg/day chlorpropamide, 500 mg/day tolazamide, or 1,500 mg/day tolbutamide) or to minimum recommended dose (MIN group; 1 mg/day glimepiride, 5 mg/day glipizide, 5 mg/day glipizide XL, 1.25 mg/ day glibenclamide, 0.75 mg/day micronized glibenclamide, 100 mg/ day chlorpropamide, 100 mg/day tolazamide, or 250 mg/day tolbutamide). The assignment to the sulfonylurea management group was not blinded primary outcome measures: HbA1c and safety In the MAX group, all treatment arms maintained relatively constant dosage levels of sulfonylurea throughout the study In the MIN group, sulfonylurea dose was 64% of MAX sulfonylurea dose across all treatment arms at study outset
			Injection site reactions	NR	
			Thyroid cancer	NR	
			Pancreatitis	NR	

					(baseline). By week 2, MIN subjects reduced the dose of sulfonylurea to a nadir of 30% of MAX dose across treatment arms. This low dose was maintained for several weeks, then sulfonylurea doses gradually increased throughout the remainder of the study. At week 30, subjects on placebo reached 94% of MAX dose compared with 79% of MAX dose in the exenatide arms. For the two sulfonylurea dosing groups, there were similar overall effects on A1C when comparing exenatide treatment arms with placebo, but the MAX group had a slightly greater reduction in A1C from baseline (P 0.0001 for pairwise comparisons; Table 2). However, the overall incidence of hypoglycemia was lower in the MIN group, with a small attenuation of the effects on glycemic control. Sponsor: Amylin Pharmaceuticals and Eli Lilly

For mild/moderate hypoglycemia, subjects reported symptoms consistent with hypoglycemia that may have been documented by a plasma glucose concentration value (<3.33 mmol/l). For severe hypoglycemia, subjects required the assistance of another person to obtain treatment for their hypoglycemia, including intravenous glucose or intramuscular glucagon.

6.5.1.2 *Summary and conclusions*

Exenatide 5µg or 10µg twice daily + metformin + sulphonylurea versus placebo + metformin + sulphonylurea			
Bibliography: Kendall 2005(46)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	733 (1) 30 w	exe 5: -0.55% exe 10: -0.77% pla: +0.23% treatment difference exe 5 vs pla -0.8% exe 10 vs pla -1.0% P< 0.0001 vs. Placebo for both comparisons	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear rando and blinding, inadequate method of dealing with missing values, (19% missing) Consistency: NA Directness: ok Imprecision: unable to assess
Body weight change from baseline	733 (1) 30 w	exe 5: -1.6kg exe10: -1.6kg pla: -0.9kg P ≤ 0.01 for each exe dose vs placebo	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear rando and blinding, inadequate method of dealing with missing values, (19% missing) Consistency: NA Directness: ok Imprecision: unable to assess
Adverse events leading to withdrawal	733 (1) 30 w	exe 5: 5.7% exe10: 9.1% pla: 4.5% NT	Not applicable
Diarrhea	733 (1) 30 w	exe 5: 10.2% exe10: 17.4% pla: 6.5% NT	Not applicable
Nausea	733 (1) 30 w	exe 5: 39.2% exe10: 48.5% pla: 20.6% NT	Not applicable
Vomiting	733 (1) 30 w	exe 5: 14.7% exe10: 13.7% pla: 4.5% NT	Not applicable
Severe hypoglycaemia	733 (1) 30 w	exe 5:1 patient exe10:0 pla:0	Not applicable
	733 (1) 30 w		Not applicable

In this double blind RCT, 733 patients with type 2 diabetes, inadequately controlled by metformin ≥1500mg/d + a sulphonylurea, were randomized to exenatide 5µg twice daily, exenatide 10µg twice daily or placebo for 30 weeks. The mean age was 55y, mean duration of diabetes 9y, mean baseline HbA1c was 8.5% and mean BMI was 33.6 kg/m^2.

In patients who were inadequately controlled on metformin + a sulphonylurea, at 30 weeks, the addition of exenatide 5µg or exenatide 10µg resulted in a statistically significant **decrease of HbA1c** compared to the addition of placebo (which was increased from baseline).
GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on metformin + a sulphonylurea, at 30 weeks, there was a statistically significant difference in weight change with the addition of exenatide 5µg or exenatide 10µg compared to the addition of placebo.
There was **more weight loss with exenatide 5µg or exenatide 10µg** than with placebo.
GRADE: MODERATE quality of evidence

Adverse events were reported, but no statistical testing was performed or reported.

Withdrawal from the study due to adverse events was seen in 5.7% with exenatide 5µg, 9.1% with exenatide 10µg and 4.5% with placebo.
GRADE: not applicable

Rates of diarrhea were 10.2% with exenatide 5µg, 17.4% exenatide 10µg and 6.5% with placebo.
Rates of nausea were 39.2% with exenatide 5µg, 48.5% with exenatide 10µg and 20.6% with placebo.
Rates of vomiting were 14.7% with exenatide 5µg, 13.7% with exenatide 10µg and 4.5 % with placebo.
GRADE: not applicable

There was 1 patient with severe hypoglycaemia with exenatide 5µg.
GRADE: not applicable

6.5.2 Exenatide twice daily + metformin + sulfonylurea versus biphasic insulin aspart (30% aspart) + metformin + sulfonylurea

6.5.2.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Nauck 2007(47) Design: RCT (OL) (PG) non-inferiority Duration of follow-up: 52 weeks	n: 505 Mean age: 59 Prior/current treatment: 'optimally effective ' metformin and sulfonylurea Mean DMII duration:10y Mean baseline HbA1c: 8.6% Mean BMI: 30.4 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> between 30 and 75 years of age and suboptimal glycaemic control despite receiving optimally	exenatide 10µg 2x/d (after 4 weeks of 5µg 2x/d) vs biphasic insulin aspart (BIAsp)(30% rapid actin insulin aspart) 2x/d (titrated) *At the end of the study, 80% of exenatide-treated patients were using the 10 µg twice-daily dose. The mean dose of premixed insulin increased from 15.7±9.5 U/day at week 2 to*	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: no/unclear FOLLOW-UP: <u>Discontinued treatment</u>: exe: 21.3% BIAsp: 10.1% Reason described: yes <u>Uptitration of study medication</u>: yes for insulin <u>Statistical method for drop out/missing data</u>: MMRM
			Change in HbA1c from baseline at 52 weeks (PO) MMRM	exe: −1.04±0.07% BIASP: −0.89±0.06% difference −0.15% (95%CI −0.32 to 0.01) (identical results for per-protocol and ITT population) **non-inferiority of exe versus BIASP** *'Observed reductions in HbA1c were similar in exenatide-treated patients with stable and reduced sulfonylurea doses (descriptive mean±SD change: −0.99±1.31%; −0.93±1.13%, respectively)'*	
			Body weight change from baseline at 52 weeks	exe: -2.5 (SE0.2) kg BIASP: + 2.9 (SE 0.2) between-group difference −5.4 kg (95% CI−5.9 to −5.0) p<0.001 **SS in favour of exe**	
			Blood pressure change	SBP	

	effective metformin and sulfonylurea therapy for at least 3 months. , HbA1c levels ≥7.0 and ≤11.0%, BMI ≥25 and ≤40 kg/m2 <u>Exclusion</u> more than three episodes of severe hypoglycaemia within 6 months prior to screening; (2) any prescription drug to promote weight loss within 3 months; or (3) had been treated with insulin, thiazolidinediones, alpha-glucosidase inhibitors or meglitinides for longer than 2 weeks within 3 months, less than 5 years of remission history from any malignancy, NYHA class III or IV, renal transplant, liver disease, … see clinicaltrials.gov for more details:	*24.4±15.6 U/day at week 52.* in addition to this background treatment: metformin + sulfonylurea <u>dose adjustment</u> exe: If frequent nausea (daily episodes for >1 week duration), patients had the option to decrease their dose to 5 µg twice daily <u>in case of hypoglycaemia</u> investigators reduced the sulfonylurea dose by approximately 50% for patients on exenatide or	**from baseline (SystBP/DiastBP)**	exe: −5 (SD 15) mmHg; SS vs baseline BIASP: 1 (SD 16) mmHg NS vs baseline DBP exe: −2 (SD 10) mmHg; SS vs baseline BIASP: 1 (SD 10) mmHg NS vs baseline NT	<u>ITT</u>: defined as patients who received at least one dose of study medication and had at least one post-baseline measurement of HbA1c (99%) <u>per-protocol sample</u> defined as patients who had at least 12 weeks of exposure to study medication and no violations of screening criteria or discontinuation criteria. (222+224/505) SELECTIVE REPORTING: no Other important methodological remarks The non-inferiority margin for the difference in HbA1c change between treatments was predefined as 0.4% The margin of 0.4% was selected on the assumption that HbA1c differences of less that 0.3% are of questionable clinical relevance and that the benefit of weight reduction may account for an additional 0.1% of HbA1c difference.
			Safety		
			Death	exe: 0.8% BIASP: 0.4% NT	
			Cardiac disorders angina pectoris, myocardial infarction, atrial fibrillation, coronary artery disease, acute coronary syndrome, atrial flutter and bundle branch block left	exe: 4.0% BIASP: 2.0% NT	
			Any adverse events	exe: 70.8% BIASP: 49.6% NT	
			Serious adverse events	exe: 7.5% BIASP: 4.4% NT	
			Adverse event leading to withdrawal	exe:8% BIASP:0 NT 'a greater proportion'	

	NCT00082407	adapted the insulin dose for patients on insulin *Approximately 33% of exenatide-treated patients and 5% of patients treated with premixed insulin had their sulfonylurea dose reduced during the study.* <u>Stratification:</u> by site and based on screening values of HbA1c (≤9.0 and >9.0%)	***Any gastro-intestinal adverse event***	*'The incidence of gastrointestinal adverse events was higher with exenatide than with premixed insulin'*	A forced titration schedule was not used in this trial. Investigators were instructed to adjust insulin doses to achieve an optimal balance between glycaemic control and risk of hypoglycaemia as dictated by best clinical practice (investigator's judgement). Predefined subgroup analyses were completed to determine the influence of baseline characteristics, sulfonylurea dose reduction, and antibody status on changes in HbA1c and fasting serum glucose no information on metformin and SU dose Sponsor: Eli Lilly and Company and Amylin Pharmaceuticals
			Diarrhoea	exe:9.5% BIASP:2.0% NT	
			Nausea	exe: 33% BIASP: 0.4% NT	
			Vomiting	exe:15.0% BIASP: 3.2% NT	
			Severe hypoglycaemia (assessed by investigator)	exe:0 BIASP:0	
			overall hypoglycaemia a sign or symptom of hypoglycaemia or noted a blood glucose level <3.4 mmol/l (60 mg/dl)	exe:4.7 (SE 0.7) events/patient-year BIASP:5.6 (SE 0.7) events/patient-year NT 'The overall hypoglycaemia rates were decreased following sulfonylurea dose reductions in exenatide-treated patients (mean±SD: before sulfonylurea reduction, 26.9±43.3 events/patient-year; after sulfonylurea reduction, 6.1±8.3 events per patient-year).'	
			Injection site reactions	exe:1.6% BIASP:0.4% NT	

			Thyroid cancer	NR	
			Pancreatitis	NR	

Table 94

A hypoglycaemic episode was defined as any time a patient experienced a sign or symptom of hypoglycaemia or noted a blood glucose level <3.4 mmol/l (60 mg/dl) during selfmonitoring, whether or not this level was associated with signs, symptoms or treatment. The severity (mild, moderate or severe) and timing (nocturnal or daytime) of each hypoglycaemic event and whether it could be attributed to therapy (yes or no) were assessed by the investigator

In addition to biases intrinsic to open-label studies , multiple factors could have influenced the comparatively low endpoint mean insulin dose observed in this trial. For example, a forced titration schedule was not used in this trial In addition, a fear of hypoglycaemic episodes or pronounced increases in body weight may have precluded the use of higher insulin doses. It should also be considered that all patients in the current trial remained on both metformin and sulfonylurea, whereas in the previous premixed insulin trials, metformin and sulfonylurea therapy were stopped or only metformin was continued

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Bergenstal 2009(48) Design: RCT (OL) (PG) Duration of follow-up: 24 weeks	n: 372 Mean age: 52 Prior/current treatment: MET + SU Mean DMII duration: 9y Mean baseline HbA1c: 10.2% Mean BMI: 34kg/m2 Previous CV event: Renal impairment: <u>Inclusion</u> type 2 diabetes for >6 months, aged 18-80 years, Hba1c >=8%, were insulin naïve and had received therapy with metformin (atleast 1500 mg/day) and a sulfonylurea (at least half the max dose) for 3 months before screening <u>Exclusion</u>	exenatide 10µg 2x/d (5µg 2x/d for 4w) vs Biphasic insulin aspart 30 1x/d (mean dose 44.9U) (started with 12 U) vs Biphasic insulin aspart 30 2x/d (mean dose 96.1 U) (started with 12 U divided in 2 doses) in addition to this background treatment: metformin ≥1500mg + SU (at least half the max dose)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: unclear Remarks on blinding method: (vrij te omschrijven, schrappen als nvt) FOLLOW-UP: <u>Discontinued treatment</u>: 29.8% in exenatide group 16.1% in BIAsp 30 qd 19.4% in the BIAsp 30 bid Reason described: yes <u>drop out due to unsatisfactory effect:</u> <u>exe:3.2%</u> <u>biasp qd:0.8%</u> <u>biasp bd: 0%</u> <u>Statistical method for drop out/missing data</u>: LOCF
			Change in HbA1c from baseline at 24 weeks (PO)	exe: - 1.75 (SD 1.57) BIAsp qd: -2.34 (SD 1.51) BIAsp bd: -2.76 (SD 1.79) exe vs BIAsp qd: MD=-0.67 (95% CI: -0.99, -0.35) p<0.001 exe vs BIAsp bd : MD=-0.91 (CI: -1.23, -0.59) p<0.001 **BIAsp both schedules superior to exe**	
			Body weight change from baseline	exe:-1.9 kg (SD 3.8) BIAsp qd: +2.8kg (SD 3.6) BIAsp bd: +4.1 kg (SD 5.4) NT	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP DBP	
			Safety		
			Death	1 in BIASP bid group	
			Cardiovascular adverse events		
			Any adverse events	exe: 7.3% BIAsp qd: 0.8% BIAsp bd:	

	Significant cardiac disease within 12 months prior to the study, hepatic or renal insufficiency, use of thiazolidinediones, alpha glucosidase inhibitors or meglitinides within the 6 months prior to the study or were receiving a weight reducing diet	subjects in exenatide and BIAsp 30 qd group continued SU. **Subjects in BIAsp30 bid discontinued SU** Hyperglycaemia uptitration protocol: Hyperglycaemia rescue protocol**:** Stratification:			ITT: defined as participants who were exposed to at least one dose of study medication and had one post-dosing and post-baseline primary efficacy measurement, was used to evaluate primary and secondary analyses Per protocol population (PP), defined as participants who completed the study without protocol violations, were used to evaluate the primary efficacy analysis. SELECTIVE REPORTING: yes/no (describe if yes) Other important methodological remarks Subjects initiated insulin therapy with 12 U before supper in the BIAsp 30 QD group, and with 12 U divided equally between pre-breakfast and pre-supper in the BIAsp 30 BID group. Subjects randomized to BIAsp 30 treatment were instructed to adjust their insulin dose every 3–4 days based on an insulin titration
			Serious adverse events	exe: BIAsp qd: BIAsp bd:	
			Adverse event leading to withdrawal	exe: 7.3% BIAsp qd: 0.8% BIAsp bd: 4.8%	
			Any gastro-intestinal adverse event	exe: BIAsp qd: BIAsp bd:	
			Diarrhoea	exe: BIAsp qd: BIAsp bd:	
			Nausea	exe:29.0% BIAsp qd: 8.9% BIAsp bd: 8.1%	
			Vomiting	exe: BIAsp qd: BIAsp bd:	
			Severe hypoglycaemia defined as symptoms associated with a BG reading <3.1 mmol/l and requiring third party assistance) (number of patients)	(number of patients) exe:0 BIAsp qd:3.2% BIAsp bd: 4.8%	
			all hypoglycaemic events defined as any symptom of	exe:2 9.0% BIAsp qd: 55.6% BIAsp bd: 61.3%	

			hypoglycaemia with a confirmed blood glucose meter reading (3.1 mmol/l) or any asymptomatic reading <3.1 mmol/l which was handled by the participant themselves) + as symptoms associated with a BG reading <3.1 mmol/l and requiring third party assistance)		algorithm (Table 1). Insulin dose titration was based on the average selfmonitored blood glucose (SMBG) results for the 3 days preceding the visit The clinical hypothesis of this trial was that the glycemic control achieved with BIAsp 30 BID plus metformin would be superior to that with exenatide BID in combination with metformin and a sulfonylurea after 24 weeks of treatment; and the glycemic control achieved with BIAsp 30 QD in combination with metformin and a sulfonylurea would be either non-inferior or superior to that with exenatide BID plus metformin and a sulfonylurea after 24 weeks of treatment. non-inferiority margin <0.4% HbA1c Sponsor: Novo Nordisk
			Injection site reactions		
			Thyroid cancer		
			Pancreatitis		

Table 95

6.5.2.2 *Summary and conclusions*

Two RCTs (one with three arms) examine the comparison between exenatide 10µg twice daily and biphasic insulin aspart in patients that are inadequately controlled on metformin + sulphonylurea. Both are of low quality when considered individually. The comparisons are described in detail below. There are some differences as to duration and as to dosing schedule of insulin and the possible discontinuation of SU in the insulin arm.

There is conflicting evidence regarding HbA1c (exenatide favoured in 1 trial, biphasic insulin aspart favoured in the other trial).
GRADE: *VERY LOW quality of evidence*

Weight loss versus baseline is seen with exenatide, weight gain is seen with biphasic insulin aspart
GRADE: LOW quality of evidence

Exenatide 10µg twice daily + metformin + sulphonylurea versus biphasic insulin aspart 2x/d+ metformin + sulphonylurea			
Bibliography: Nauck 2007(47)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	505 (1) 52 w	exe: −1.04% BIASP: −0.89% treatment difference −0.15% (95%CI −0.32 to 0.01) **non-inferiority of exe versus BIAsp**	⊕⊕⊖⊖ **LOW** Study quality: -1 open label, unbalanced drop-out Consistency: NA Directness: -1 titration of insulin not optimal Imprecision: ok
Body weight change from baseline	505 (1) 52 w	exe: -2.5 kg BIASP: + 2.9 kg treatment difference −5.4 kg (95% CI−5.9 to −5.0) p<0.001 **SS in favour of exe**	⊕⊕⊖⊖ **LOW** Study quality: -1 open label, unbalanced drop-out Consistency: NA Directness: -1 titration of insulin not optimal Imprecision: ok
Adverse events leading to withdrawal	505 (1) 52	exe:8% BIASP:0 NT	Not applicable
Diarrhea	505 (1) 52 w	exe:9.5% BIASP:2.0% NT	Not applicable
Nausea	505 (1) 52 w	exe: 33% BIASP: 0.4% NT	Not applicable
Vomiting	505 (1) 52 w	exe:15.0% BIASP: 3.2% NT	Not applicable
Severe hypoglycaemia	505 (1) 52 w	exe:0 BIASP:0	Not applicable

Table 96

In this open label non-inferiority RCT, 505 patients with type 2 diabetes, inadequately controlled by 'optimally effective' metformin + a sulphonylurea, were randomized to exenatide 10µg twice daily or biphasic insulin aspart (30% aspart) twice daily for 52 weeks. The mean age was 59y, mean duration of diabetes 10y, mean baseline HbA1c was 8.6% and mean BMI was 30.4 kg/m^2. At the end of the trial, the mean dose of premixed insulin was 24.4 units/day.

Our confidence in the estimate of the between-group differences is limited by the open label design, unbalanced drop-out and the relatively low dose of insulin used in this trial.

In patients who were inadequately controlled on metformin + sulphonylurea at 52 weeks, the addition of exenatide 10µg was **non-inferior for the decrease of HbA1c** compared to the addition of biphasic insulin aspart 30.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin + sulphonylurea at 52 weeks, there was a statistically significant difference in weight change with the addition of exenatide 10µg compared to the addition of biphasic insulin aspart 30.
There was **more weight loss with exenatide 10µg** than with biphasic insulin aspart 30 (in which the weight had increased from baseline).
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported.
For rates of adverse events: see table
GRADE: not applicable

Exenatide 10µg twice daily + metformin + sulphonylurea versus biphasic insulin aspart twice daily + metformin			
Bibliography: Bergenstal 2009(48)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	248 for this comparison (1) 24 w	exe: - 1.75% BIAsp bd: -2.76% exe vs BIAsp bd treatment difference 0.91 (CI: -1.23, -0.59) p<0.001 **BIAsp bid superior to exe**	⊕⊕⊖⊖ **LOW** Study quality: -2 open label, unbalanced drop-out (more with exe), inadequate dealing with missing values (> 20%) Consistency: NA Directness: ok Imprecision: ok
Body weight change from baseline	248 for this comparison (1) 24 w	exe:-1.9 kg BIAsp bd: +4.1 kg NT	Not applicable
Adverse events leading to withdrawal	248 for this comparison (1) 24 w	exe: 7.3% BIAsp bd: 4.8%	Not applicable
Diarrhea		NR	Not applicable
Nausea	248 for this comparison (1) 24 w	exe: 29% BIASP: 8.1% NT	Not applicable
Vomiting		NR	Not applicable
Severe hypoglycaemia	248 for this comparison (1) 24 w	exe:0 BIAsp bd: 4.8%	Not applicable

Table 97

This was a three arm study, comparing exenatide to two dosing schedules of biphasic insulin aspart 30.

In this open label non-inferiority RCT, 248 patients with type 2 diabetes, inadequately controlled by metformin + a sulphonylurea, were randomized to exenatide 10µg twice daily (in addition to metformin and SU) or to biphasic insulin aspart (30% aspart) twice daily (in addition to metformin. **SU was stopped**) for 24 weeks. The mean age was 52y, mean duration of diabetes 9y, mean baseline HbA1c was 10.2% and mean BMI was 34 kg/m^2. At the end of the trial, the mean dose of premixed insulin was 96.1 units/day.

Our confidence in the estimate of the between-group differences is limited by the open label design, unbalanced drop-out and inadequate dealing with missing values.

In patients who were inadequately controlled on metformin + sulphonylurea at 24 weeks, the addition of addition of **biphasic insulin aspart 30** twice daily to MET (SU was stopped) **was superior** to the addition of exenatide 10µg twice daily to MET+ SU.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin + sulphonylurea at 24 weeks, a **weight loss with the addition of exenatide 10µg** bid to MET + SU compared to the addition of biphasic insulin aspart 30 bid to MET (SU was stopped), in which there was weight gain.
GRADE: not applicable

Adverse events were reported, but no statistical testing was performed or reported.
For rates of adverse events: see table
GRADE: not applicable

Exenatide 10µg twice daily + metformin + sulphonylurea versus biphasic insulin aspart once daily + metformin + sulphonylurea			
Bibliography: Bergenstal 2009(48)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	248 for this comparison (1) 24 w	exe: - 1.75 % BIAsp qd: -2.34 % exe vs BIAsp qd: treatment difference -0.67 (95% CI: -0.99, -0.35) p<0.001 **BIAsp qd superior to exe**	⊕⊕⊖⊖ **LOW** Study quality: -2 open label, unbalanced drop-out (more with exe), inadequate dealing with missing values (> 20%) Consistency: NA Directness: ok Imprecision: ok
Body weight change from baseline	248 for this comparison (1) 24 w	exe:-1.9 kg BIAsp qd: +2.8kg NT	Not applicable
Adverse events leading to withdrawal	248 for this comparison (1) 24 w	exe: 7.3% BIAsp qd: 0.8%	Not applicable
Diarrhea		NR	Not applicable
Nausea	248 for this comparison (1) 24 w	exe: 29% BIASP qd: 8.9% NT	Not applicable
Vomiting		NR	Not applicable
Severe hypoglycaemia	248 for this comparison (1) 24 w	exe:0 BIAsp qd: 3.2%	Not applicable

Table 98

This was a three arm study, comparing exenatide to two dosing schedules of biphasic insulin aspart 30.

In this open label non-inferiority RCT, 248 patients with type 2 diabetes, inadequately controlled by metformin + a sulphonylurea, were randomized to exenatide 10µg twice daily (in addition to metformin and SU) or to biphasic insulin aspart (30% aspart) once daily (in addition to metformin + SU) for 24 weeks. The mean age was 52y, mean duration of diabetes 9y, mean baseline HbA1c was 10.2% and mean BMI was 34 kg/m^2. At the end of the trial, the mean dose of premixed insulin was 44.9 units/day.

Our confidence in the estimate of the between-group differences is limited by the open label design, unbalanced drop-out and inadequate dealing with missing values.

In patients who were inadequately controlled on metformin + sulphonylurea at 24 weeks, the addition of addition of **biphasic insulin aspart 30** once daily to MET + SU **was superior** to the addition of exenatide 10µg twice daily to MET+ SU.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin + sulphonylurea at 24 weeks, a **weight loss was seen with the addition of exenatide 10µg** bid to MET + SU compared to the addition of biphasic insulin aspart 30 bid to MET (SU was stopped), in which weight gain was observed.
GRADE: not applicable

Adverse events were reported, but no statistical testing was performed or reported.
For rates of adverse events: see table
GRADE: not applicable

6.5.3 Exenatide + metformin + sulfonylurea versus insulin glargine + metformin + sulfonylurea

6.5.3.1 *Clinical evidence profile*

Ref	n/Population	Comparison	Outcomes		Methodological
Heine 2005(49) Design: RCT OL PG non-inferiority Setting: outpatient study centers follow-up: 26 weeks	n=551 mean age 59y therapy at baseline: 'maximally effective' MET + SU mean HbA1c 8.2 mean BMI 31gk/m^2 mean DMII duration: 9.5y Previous CV event: NR Renal impairment: NR <u>Inclusion</u> - Type 2 diabetes with inadequate glycemic control (HbA1c 7.0% to 10.0%) on max. effective dose of metformin and a SU - BMI 25-45kg/m^2 and stable body weight 3 months before screening <u>Exclusion</u> - > 3 episodes of severe hypoglycemia before	Exenatide 10 µg 2*/d (after 5µg 2x/d for 4 weeks) vs insulin glargine 10U/d starting dose titrated to <100mg/dl FGP (average dose 25 U/d) in addition to ongoing metformin + sulphonylurea <u>in case of hypoglycemia:</u> 50% reduction in SU dose recommended	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING: 0/2 ○ ATTRITION: 1/1 - FU: 80.6% exenatide (due to AE) and 90.3% insulin ITT: any patient who had at least 1 postbaseline measurement of the dependent variable (hemoglobin A1c level), 99% in ITT analysis per protocol : patients who had at least 12 weeks of exposure to study medication, had no violations of the inclusion or exclusion criteria obtained at screening, and met no discontinuation criteria FOLLOW-UP: <u>Discontinued treatment</u>: exe:19.4%
			Change in HbA1c from baseline at week 26 (PO) MMRM	Exenatide: -1.11% Insuline glargine: -1.11% Difference 0.017% (95%CI: -0.123 to 0.157) NS For the per-protocol sample, the change in hemoglobin A1c level was -1.16% and -1.14% for exenatide and insulin glargine, respectively (difference, -0.016 percentage point [CI, -0.161 to 0.129 percentage point]) **non-inferiority of exenatide vs ins glargine**	
			Body weight change from baseline (SO)	Exenatide: -2.3kg Insuline glargine: + 1.8kg **Difference -4.1kg (95%CI: -4.6 to -3.5)** **SS**	
			Safety		
			Death	NR	
			Cardiovascular adverse events	NR	

	screening - Malignant disease - Heart failure NYH 3-4 - Serum creat > 1.5mg/dl men or 1.2mg/dl women - Liver disease - Systemic glucocorticoid therapy - Prior treatment with insulin/thiazolidinediones, α-glucosidase inh, meglitinides				ins glar: 9.7% Reason described: yes <u>Uptitration of study medication</u>: yes, for ins glargine <u>loss of glucose control</u>: exe: n=4 ins glar: n=0 <u>Statistical method for drop out/missing data</u>: MMRM SELECTIVE REPORTING: no Other important methodological remarks Noninferiority margin for the difference between treatments (exenatide minus insulin glargine) was defined as 0.4% no information on number of patients who had their SU dose lowered because of hypoglycaemia. no information on baseline an end-of-trial MET or SU
			Any adverse events	NR	
			Serious adverse events	NR	
			Adverse event leading to withdrawal	exe: 9.5% ins glar:0.7%	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	Exenatide: 8.5% Insuline glargine: 3.0% **P = 0.006**	
			Nausea	Exenatide: 57.1% Insuline glargine: 8.6% **p<0.001**	
			Vomiting	Exenatide: 17.4% Insuline glargine: 3.7% **P<0.001**	
			Severe hypoglycaemia	exe:n=4 ins glar:n=4	
			total hypoglycaemia	exe: 7.3 events/patientyear ins glar:6.3 events/patientyear NS *Patients in the exenatide group experienced a lower incidence of nocturnal hypoglycemic events (0.9 event/patient-year vs. 2.4 events/patient-year; difference,* *1.6 events/patient-year [CI,* *2.3 to*	

				0.9 events/patient-year]) but a higher incidence of daytime hypoglycemia (6.6 events/patient-year vs. 3.9 events/patientyear; difference, 2.7 events/patient-year [CI, 0.4 to 4.9 events/patient-year]).	dose - Low insulin doses - Sponsor: Amylin Pharmaceuticals and Eli Lilly
			Injection site reactions	NR	
			Thyroid cancer	NR	
			Pancreatitis	NR	

Table 99

Patients were asked at each visit whether they had experienced hypoglycemia since their previous visit. Severity of each event (mild, moderate, or severe) and its attribution to therapy (yes or no) were assessed by the investigator. Symptomatic hypoglycemia was defined as a blood glucose measurement less than 3.4 mmol/L (<60 mg/dL) or hypoglycemia accompanied by such symptoms as sweating, shaking, pounding heart, or confusion. Severe hypoglycemia was defined as a hypoglycemic episode in which the patient required assistance from another person and had a blood glucose mmeasurement less than 2.8 mmol/L (_50 mg/dL) or had promptly recovered after an oral carbohydrate or glucagon injection or intravenous glucose

6.5.3.2 *Summary and conclusions*

Exenatide 10µg twice daily + metformin + sulphonylurea versus insulin glargine + metformin + sulfonylurea			
Bibliography: Heine 2005(49)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	551 (1) 26 w	Exe: -1.11% Ins glar: -1.11% treatment difference 0.017% (95%CI: -0.123 to 0.157) **exenatide non-inferior to insulin glargine**	⊕⊕⊖⊖ **LOW** Study quality: -1 open label, unbalanced drop-out, but <20% Consistency:NA Directness: - 1 relatively low dose of insulin Imprecision: ok
Body weight change from baseline	551 (1) 26 w	Exe: -2.3kg Ins glar: + 1.8kg treatment difference **-4.1kg (95%CI: -4.6 to -3.5)** **SS**	⊕⊕⊖⊖ **LOW** Study quality: -1 open label, unbalanced drop-out, but <20% Consistency: NA Directness: - 1 relatively low dose of insulin Imprecision: ok
Adverse events leading to withdrawal	551 (1) 26 w	exe: 9.5% ins glar:0.7%	Not applicable
Diarrhea	551 (1) 26 w	Exe: 8.5% Ins glar: 3.0% **P = 0.006**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label, unbalanced drop-out, but <20% Consistency: NA Directness: -relatively low dose of insulin but ok Imprecision: not assessable
Nausea	551 (1) 26 w	Exe: 57.1% Ins glar: 8.6% **p<0.001**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label, unbalanced drop-out, but <20% Consistency: NA Directness: - 1 relatively low dose of insulin Imprecision: not assessable
Vomiting	551 (1) 26 w	Exe: 17.4% Ins glar: 3.7% **P<0.001**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label, unbalanced drop-out, but <20% Consistency: NA Directness: - Imprecision: not assessable
Severe hypoglycaemia	551 (1) 26 w	exe:n=4 ins glar:n=4	Not applicable

Table 100

In this open label, non-inferiority RCT, 551 patients with type 2 diabetes, inadequately controlled by metformin + sulphonylurea were randomized to exenatide 10µg twice daily or insulin glargine for 26 weeks. The mean age was 59y, mean duration of diabetes 9.5y, mean baseline HbA1c was 8.2% and mean BMI was 31kg/m^2. At 26 weeks, the mean dose of insulin glargine was 25.0 U/d.

Our confidence in the estimate of the between-group differences is limited by the open label design, the unbalanced drop out and the relatively low dose of insulin glargine.

In patients who were inadequately controlled on metformin + a sulphonylurea, at 26 weeks, the addition of exenatide was **non-inferior for the decrease of HbA1c** compared to the addition of insulin glargine.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin + a sulphonylurea, at 26 weeks, there was a statistically significant difference in weight change with the addition of exenatide compared to the addition of insulin glargine.
The **weight in the exenatide group was decreased** compared to the insulin glargine group (in which the weight had increased from baseline).
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported.

Withdrawal from the study due to adverse events was seen in 9.5% with exenatide and 0.7% with insulin glargine.
GRADE: not applicable

Rates of diarrhea were 8.5% with exenatide and 3.0% with insulin glargine. The difference was statistically significant.
Rates of nausea were 57.1% with exenatide and 8.6% with insulin glargine. The difference was statistically significant.
Rates of vomiting were 17.4% with exenatide and 3.7% with insulin glargine. The difference was statistically significant.
GRADE: MODERATE quality of evidence

There were 4 patients with severe hypoglycemia in each group.
GRADE: not applicable

6.6 Combination therapy with metformin + pioglitazone

6.6.1 Dulaglutide + metformin + pioglitazone versus exenatide + metformin + pioglitazone

See Dulaglutide 5.4.2

6.7 Combination therapy with OAD

6.7.1 Exenatide twice daily +/- OAD versus exenatide once weekly +/- OAD

6.7.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Blevins 2011(50) DURATION-5 Design: RCT (OL) (PG) Duration of follow-up: 24 weeks	n: 254 Mean age: 56y Prior/current treatment: • Drug naïve (19%) • One OAD (47%) • Multiple OAD(35%) Mean DMII duration: 7y Mean baseline HbA1c: 8.4% Mean BMI: 33 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> • Type 2 diabetes • Otherwise healthy	Exenatide 2 mg 1x/week vs Exenatide 10µg twice daily in addition to this background treatment: +/- OAD (metformin, SU, thiazolidinedione, or a combination of these medications) <u>Hyperglycaemia uptitration protocol:</u> No protocol	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: no FOLLOW-UP: <u>Study completers</u>: 81% <u>Discontinued treatment</u>: ExW: 23% ExBid: 16% Reason described: yes <u>Uptitration of study medication</u>: Not applicable
			Change in HbA1c from baseline (PO)	ExW: -1.6% ExBid: -0.9% **ExW vs ExBid: -0.7% (-0.9 to -0.4)** **P<0.0001=> SS in favour of exeW**	
			Body weight change from baseline	ExW: -2.3 kg ExBid: -1.4 kg ExW vs ExBid: -0.95kg (-1.9 to to 0.01) => NS	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP ExW: -2.9 mmHg ExBid: -1.2 mmHg NT DBP ExW:+0.2 mmHg ExBid: -0.1 mmHg NT	
			Safety		
			Death	ExW: 0 ExBid: 1 case NT	

	• Treated with diet and exercise alone or with a stable, maximally effective regimen of metformin, SU, thiazolidinedione, or a combination of these medications. • HbA1c 7.1-11% • FPG <280 mg/dL • BMI 25-45 • <u>Exclusion</u> • Use of concomitant weight –loss agents • Supplementary lifestyle modification programs	<u>Hyperglycaemia rescue protocol</u>**:** No protocol <u>Stratification:</u> • According to concomitant SU use at screening • Baseline HbA1c <9 or ≥9	**Cardiovascular adverse events**	ExW: 0 ExBid: 1 myocardial infarction NT	<u>Hyperglycaemic rescue</u>: Withdrawn due to loss of glucose control ExW: 2% ExBid: 3% <u>Statistical method for drop out/missing data</u>: LOCF <u>Data handling for rescued patients</u>: LOCF <u>ITT</u>: defined as all randomized patients receiving at least one dose of randomized study medication SELECTIVE REPORTING: no Other important methodological remarks • Noninferiority of ExW to ExBid was demonstrated if the upper limit of the two-sided 95% CI for the treatment difference fell beneath 0.4% • Sensitivity analysis with MRMM analysis performed for primary outcome; similar
			Any adverse events	NR	
			Serious adverse events	ExW: 2% ExBid: 4% NT	
			Adverse event leading to withdrawal	ExW: 5% ExBid: 5% NT	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	ExW: 9% ExBid: 4% NT	
			Nausea	ExW: 14% ExBid: 35% NT	
			Vomiting	ExW: 9% ExBid: 5% NT	
			Severe hypoglycaemia	No events	
			Documented symptomatic hypoglycaemia *"minor hypoglycaemia": events with symptoms consistent with hypoglycemia accompanied by a blood glucose concentration*	ExW: 5% ExBid: 3% NT	

			less than 54 mg/dL before treatment.		result Sponsor: Amylin Pharmaceuticals, Eli Lilly & Co
			Injection site reactions	ExW: 13% ExBid: 10% NT	
			Thyroid cancer	No events	
			Pancreatitis	1 clinical diagnosis of acute pancreatitis (in ExW), MRI did not confirm diagnosis	

Table 101

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Drucker 2008(51) DURATION-1 Design: RCT (OL) (PG) non-inferiority Duration of follow-up: 30w	n:303 Mean age: 55 y Prior/current treatment: 0, 1 or 2 OAD (MET, SU, TZD) Mean DMII duration: 6.7y Mean baseline HbA1c: 8.3% Mean BMI: 35kg/m2 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> 16 years of age, with type 2 diabetes treated for at least 2 months before screening. Entry criteria included a baseline HbA1c of 7·1–11·0%, fasting plasma glucose of less than 16 mmol/L, body-mass index of 25–45 kg/m²,	exenatide LR 2 mg 1x/w vs exenatide 10µg 2x/d (after 28 days of 5µg 2x/d) in addition to this background treatment: 15% no OAD 36% MET only 28% MET+ SU (total 73% MET; 37% SU, 16% TZD) <u>SU titration</u> in patients treated with sulphonylurea, a decrease up to minimum labelled dose was required until week 10. Subsequently, the	Efficacy		RANDO: Adequate/inadequate/unclear ALLOCATION CONC: Adequate/inadequate/unclear BLINDING : Participants: no Personnel: no Assessors: no Remarks on blinding method: (it is clearly stated that nobody was blinded to treatment, However, blinding to the HbA1c and fasting plasma glucose results were maintained by sponsor personnel throughout the 30-week assessment period, such that individual patient data were anonymised through scrambling before review FOLLOW-UP: <u>Discontinued treatment</u>: exe QW: 13.5% exe BID: 11.6% Reason described: yes
			Change in HbA1c from baseline (PO) ANOVa	exe QW: 1·9 (0·1%) exe BID: 1·5 (0·1%) mean difference in HbA1c change at endpoint –0·33 (95% CI –0·54 to –0·12) non-inferiority for exe QW superiority for exe QW p= 0.0023 'Hb*A1c reductions were consistent across all treatment background therapies, for patients in both treatment groups. Reductions in HbA1c did not vary notably with sex or age (>65 years vs <65 years)'* no calculations reported
			Body weight change from baseline ANCOVA	exe QW: –3·7 [SE 0·5] kg exe BID: –3·6 [0·5] kg 95% CI –1·3 to 1·1, intention to treat, p=0·89
			Blood pressure change from baseline (SystBP/DiastBP)	SBP exe QW: –4·7 (SE 1·1) exe BID: –3·4 (SE 1·1) 'similar' DBP exe QW: –1·7 (SE 0·7) exe BID: –1·7 (SE 0·7)

	and therapy with diet modification and exercise, or pharmacological treatment with metformin, a sulphonylurea, a thiazolidinedione, or any combination of two of these agents. <u>Exclusion</u> use of meglitinides, α-glucosidase inhibitors, insulin therapy, weight-loss drugs, corticosteroids, drugs known to affect gastrointestinal motility, or any investigational drug; any previous exposure to exenatide or a GLP-1 analogue; or evidence of clinically significant medical conditions that might preclude safe participation in the study.	sulphonylurea dose was up-titrated, based on daily glucose measurements, to reach FPG of 6 mmol/L or less <u>Hyperglycaemia protocol:</u> Patients who had a loss of glucose control, predefined as a 1·5% increase from baseline in HbA1c value or an HbA1c of 11·5% or higher at or after week 14, were withdrawn from the study <u>Hyperglycaemia rescue protocol</u>**:**		'similar'	<u>Statistical method for drop out/missing data</u>: LOCF <u>ITT</u>: defined as all randomised patients who received at least one injection of exenatide 97.3% SELECTIVE REPORTING: some adverse events not clearly reported? Other important methodological remarks - 3day lead in with exe 5µg 2x/d (after randomization) - non-inferiority margin of 0.4% in HbA1C change difference - non-inferiority testing on ITT population with LOCF Sponsor: Amylin Pharmaceuticals and Eli Lilly and Company
			Safety		
			Death	NR	
			Cardiovascular adverse events	NR	
			Any adverse events	NR	
			Serious adverse events	exe QW:5.4% exe BID: 3.4%	
			Adverse event leading to withdrawal	exe QW: 6.1% exe BID: 4.8%	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	exe QW:13.5% exe BID: 13.1%	
			Nausea	exe QW:26.4% exe BID: 34.5%	
			Vomiting	exe QW:10.8% exe BID: 18.6%	
			Major hypoglycaemia	exe QW:0 exe BID: 0	
			Minor hypoglycaemia	non SU background	

		<u>Stratification:</u> according to concomitant sulphonylurea use at screening and HbA1c strata (<9·0% vs ≥9·0%)		exe QW: 0 exe BID: 1.1% SU background exe QW: 14.5% exe BID: 15.4%	
			Injection site reactions	**pruritis** exe QW:17.6% exe BID: 1.4% **bruising** exe QW:4.7% exe BID: 10.3%	
			Thyroid cancer	NR	
			Pancreatitis	exe QW:0 exe BID: 0	

Table 102

Minor hypoglycaemia was defined as patients reporting symptoms consistent with hypoglycaemia, and a plasma glucose concentration of less than 3 mmol/L. Major hypoglycaemia was defi ned as loss of consciousness, seizure, or coma which resolved after administration of glucagon or glucose, or required third-party assistance to resolve, and a glucose concentration of less than 3 mmol/L.

There were no substantial changes in sulphonylurea dose from randomisation to 30 weeks. The mean screening sulphonylurea dose for patients receiving exenatide once a week was 57% of maximum labelled daily dose; at 30 weeks, the mean dose was reduced to 52%. For exenatide twice a day, mean screening sulphonylurea dose was 49%, and at 30 weeks was 64% of maximum labelled daily dose.

6.7.1.2 *Summary and conclusions*

Exenatide LR 2mg once weekly +/- OAD versus exenatide 10µg twice daily +/- OAD				
Bibliography: Drucker 2008(51) DURATION-1, Blevins 2011(50) DURATION-5				
Outcomes	**N° of participants (studies) Follow up**	**Results**		**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	557 (2) 24 to 30 weeks	DURATION 1 exe QW: -1.9 % exe BID: -1.5 % treatment difference –0·33 (95% CI –0·54 to –0·12) **ExeQW superior to exe BID**	DURATION 5 1.6% -0.9% -0.7% (-0.9 to -0.4)	⊕⊕⊖⊖ **LOW** Study quality: -1 open label, inadequate dealing with missing values Consistency: ok Directness: -1 any oad as background therapy Imprecision: ok
Body weight change from baseline	557 (2) 24 to 30 weeks	treatment difference DURATION 1 -0.1 kg (95% CI–1·3 to 1·1) DURATION 5 -0.95kg (95%CI-1.9 to 0.01) NS		⊕⊕⊖⊖ **LOW** Study quality: -1 open label, inadequate dealing with missing values Consistency: ok Directness: -1 any oad as background therapy Imprecision: ok
Adverse events leading to withdrawal	557 (2) 24 to 30 weeks	DURATION 1 exe QW: 6.1% exe BID: 4.8%	DURATION 5 5% 5%	Not applicable
Diarrhea	557 (2) 24 to 30 weeks	DURATION 1 exe QW:13.5% exe BID: 13.1%	DURATION 5 9% 4%	Not applicable
Nausea	557 (2) 24 to 30 weeks	DURATION 1 exe QW:26.4% exe BID: 34.5%	DURATION 5 14% 35%	Not applicable
Vomiting	557 (2) 24 to 30 weeks	DURATION 1 exe QW:10.8% exe BID: 18.6%	DURATION 5 9% 5%	Not applicable
Severe hypoglycaemia	557 (2) 24 to 30 weeks	no events in both trials		Not applicable

Table 103

Two RCTs compared exenatide 10µg twice daily to exenatide 2mg once weekly in patients with type 2 diabetes inadequately controlled on diet + exercise and/or ≥ 1 OAD.
In the first, open label, non-inferiority RCT by Drucker 2008(51) DURATION-1, 303 patients were randomized to exenatide LR 2mg once weekly or exenatide 10µg twice daily for 30 weeks. The mean age was 55y, mean duration of diabetes 6.7y, mean baseline HbA1c was 8.3% and mean BMI was 35 kg/m^2.
In the second, open label, non-inferiority RCT by Blevins 2011(50) DURATION-5, 254 patiens were randomized and followed for 24 weeks. The mean age was 56y, mean duration of diabetes 7y, mean baseline HbA1c was 8.4% and mean BMI was 33 kg/m^2.

Our confidence in the estimate of the between-group differences is mainly limited by the open label design and the inadequate method of dealing with missing values.
The interpretation of these results is further limited because of the inclusion of patients with any background oral antidiabetic therapy. Based on these results, it is difficult to make statements about the combination of a glp-1 receptor agonist with a specific oral antidiabetic agent.

In patients who were inadequately controlled on diet and exercise or ≥1 OAD, at 24 to 30 weeks, the addition **of exenatide LR 2mg once weekly was superior** to the addition of exenatide 10µg twice daily for the decrease of HbA1c.
GRADE: LOW quality of evidence

IIn patients who were inadequately controlled on diet and exercise or ≥1 OAD, at 24 to 30 weeks, there was **no** statistically significant **difference in weight change** with the addition of exenatide LR 2mg once weekly compared to the addition of exenatide 10µg twice daily.
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported.
Rates of adverse events can be found in the table.
There were no events of severe hypoglycemia.
GRADE: not applicable

6.7.2 Exenatide twice daily + OAD versus insulin glargine + OAD

6.7.2.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Davies 2009(52) HEELA Design: RCT (OL) (PG) Duration of follow-up: 26 w	n: 235 Mean age: 56.5% Prior/current treatment: MET, SU, TZD Mean DMII duration: 8.7y Mean baseline HbA1c: 8.57% Mean BMI: 34.1kg Previous CV event: 15.8% Renal impairment: NR <u>Inclusion</u> (BMI) >27 kg/m2] , elevated cardiovascular risk (either a previous cardiovascular event, peripheral	exenatide 10µg x2/d (after 4 weeks of 5µg 2x/d) vs insulin glargine (10IU/d), titrated to FPG ≤ 100mg/dl (The median dose of insulin glargine at endpoint was 34.0 (interquartile range: 24.0–52.0) IU/day and the mean (s.d.) dose was 38.7 (23.5) IU/day.) in addition to this background treatment:	Efficacy		RANDO: unclear ALLOCATION CONC: unclear BLINDING : Participants: no Personnel: no Assessors: no/unclear FOLLOW-UP: <u>Study completers</u>: exe: 83.9% ins glar: 89.7% Reason described: yes <u>Statistical method for drop out/missing data</u>: LOCF <u>ITT</u>: defined as randomized patients who received at least one dose of study drug SELECTIVE REPORTING: no
			Composite: HbA1C ≤7.4% AND weight gain ≤ 1kg) at 26 weeks (PO)	exe: 53.4% ins glar: 19.8% **odds ratio (OR):** **4.71 (95% CI: 2.62–8.46)** **p < 0.001** (similar results when 5 patients with missing values were excluded)	
			Change in HbA1c from baseline at 26 weeks	exe: −1.25 (SE 0.09) ins glar: −1.26 (SE 0.09) LS mean difference 0.01%, (95% CI: −0.24 to +0.27%) p = 0.924	
			Body weight change from baseline at 26 weeks	exe: −2.73 (SE 0.31) ins glar: +2.98 (SE 0.31) **LS mean difference** **−5.71 kg (95% CI: −6.58 to −4.84 kg)** **p < 0.001**	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP exe: −2.9 (SE 1.2) ins glar: 0.7 (SE 1.2) **LS mean difference −3.6 mmHg;** **p = 0.034**	

	vascular disease, or an abnormal risk factor [low-density lipoprotein (LDL) >3.0 mmol/l, high-density lipoprotein (HDL) <1.0 mmol/l (men) or <1.3 mmol/l (women), triglyceride >1.7 mmol/l, systolic blood pressure (BP) >130 mmHg, diastolic BP >80 mmHg or increased waist circumference (European: >94 cm, men, >80 cm, women; Asian: >90 cm, men, >80 cm, women) and type 2 diabetes inadequately controlled (HbA1c 7.5–10.0%) on two or three oral antidiabetes drugs (OADs – MET, SU, TZD) <u>Exclusion</u> history of malignancy, Class III or IV heart disease, uncontrolled hypertension (systolic BP ≥180 mmHg,	2 OAD 58.5% 3 OAD: 40.6% metformin and sulphonylurea (42.3%) metformin, sulphonylurea and thiazolidinedione (40.6%) (85% on SU) one or more confirmed or suspected hypoglycaemic event occurred, when the sulphonylurea dose could be reduced <u>Stratification:</u> according to the number (two or three) of OADs		DBP exe: −0.5 (0.7) ins glar: 0.9 (0.7) NS	Other important methodological remarks - Sponsor: Eli Lilly and Company
			Safety		
			Death	NR	
			Acute MI	exe:n=1 ins glar:n=0	
			Any adverse events	exe:89.8% ins glar: 81.0% NS	
			Serious adverse events	exe: n=5 ins glar: n= 5	
			Adverse event leading to withdrawal	exe: n= 7 ins glar: n:=4	
			Any gastro-intestinal adverse event	exe: 70.3% ins glar:21.6%	
			Diarrhoea	exe: 18.6% ins glar: 12.1%	
			Nausea	exe: 48.3% ins glar:2.6%	
			Vomiting	exe: ins glar:	
			Severe hypoglycaemia	exe: 4.2% ins glar: 5.3% 0.80, 95% CI: 0.24–2.71, p = 0.716	
			Documented	exe: 31.4%	

	diastolic BP ≥105 mmHg), renal transplantation or dialysis, chronic renal impairment (serum creatinine ≥135 µmol/l for males and ≥110 µmol/l for females) or liver disease (serum alanine aminotransferase >3 × upper limit of normal).		**symptomatic hypoglycaemia** Episodes confirmed by blood glucose <3.4 mmol/l	ins glar: 36.8% 0.78, 95% CI: 0.45–1.35, p = 0.369	
			Injection site reactions	NR	
			Thyroid cancer	NR	
			Pancreatitis	NR	

Table 104

For mean selfmonitored fasting plasma glucose levels ≥10 mmol/l, the increase in insulin glargine dosage was 8 IU/day; for fasting plasma glucose levels of 7.8–9.9 mmol/l, the increase in insulin glargine dosage was 6 IU/day and for fasting plasma glucose levels of 6.7–7.7 or 5.6–6.6 mmol/l, the increase in insulin glargine dosage was 4 or 2 IU/day respectively, as detailed previously [15]

Hypoglycaemic episodes were recorded and defined as incidents in which a patient experienced a sign or symptom associated with hypoglycaemia or who had a blood glucose <3.4 mmol/l (<60 mg/dl) even if it was not associated with a sign, symptom or treatment. Severe hypoglycaemia was defined as an episode with symptoms consistent with hypoglycaemia in which the patient required the assistance of a third party and also had an associated blood glucose level <2.8 mmol/l (50 mg/dl) and/or prompt recovery after oral carbohydrate, glucagon or intravenous glucose, and/or resulted in coma.

6.7.2.2 *Summary and conclusions*

Exenatide 10µg twice daily + OAD versus insulin glargine + OAD			
Bibliography: Davies 2009(52) HEELA			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Composite: HbA1C ≤7.4% AND weight gain ≤ 1kg) at 26 weeks (PO)	235 (1) 26 weeks	exe: 53.4% ins glar: 19.8% **odds ratio (OR):** **4.71 (95% CI: 2.62–8.46)** **p < 0.001**	⊕⊕⊖⊖ **LOW** Study quality: -1 open label, unclear rando and blinding, inadequate method of dealing with missing values (but only 15% missing) Consistency:NA Directness: -1 any OAD background, only 26 weeks Imprecision: ok
HbA1c change from baseline (PO)	235 (1) 26 weeks	exe: −1.25% ins glar: −1.26% treatment difference 0.01% (95%CI −0.24 to 0.27%) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 open label, inadequate method of dealing with missing values (but only 15% missing) Consistency:NA Directness:-1 any OAD background, only 26 weeks Imprecision: ok
Body weight change from baseline	235 (1) 26 weeks	exe: −2.73 kg ins glar: +2.98 kg **treatment difference** **−5.71kg (95%CI−6.58 to −4.84)** **p < 0.001**	⊕⊕⊖⊖ **LOW** Study quality: -1 open label, inadequate method of dealing with missing values (but only 15% missing) Consistency:NA Directness:-1 any OAD background, only 26 weeks Imprecision: ok
Adverse events leading to withdrawal	235 (1) 26 weeks	exe: n= 7 ins glar: n:=4	Not applicable
Diarrhea	235 (1) 26 weeks	exe: 18.6% ins glar: 12.1%	Not applicable
Nausea	235 (1) 26 weeks	exe: 48.3% ins glar:2.6%	Not applicable
Vomiting		NR	
Severe hypoglycaemia	235 (1) 26 weeks	exe: 4.2% ins glar: 5.3% 0.80 (95% CI: 0.24–2.71) p = 0.716	⊕⊖⊖⊖ **VERY LOW** Study quality: -1 open label, inadequate method of dealing with missing values (but only 15% missing) Consistency:NA Directness:-1 any OAD background, only 26 weeks Imprecision: -1 wide CI

Table 105

In this open label RCT,235 patients with type 2 diabetes, inadequately controlled by 2 or 3 OAD, were randomized to exenatide 10µg twice daily or insulin glargine for 26 weeks. The mean glargine dose at the end of the trial was 38.7 IU/d. The mean age was 56.5y, mean duration of diabetes 8.7y, mean baseline HbA1c was 8.6% and mean BMI was 34.1 kg/m^2. 15.8% of participants had had a previous cardiovascular event. Patients with chronic renal impairment (serum creatinine ≥135 µmol/l for males and ≥110 µmol/l forfemales) were not allowed in the study.

Our confidence in the estimate of the between-group differences is limited by the open label design, by the unspecified background OAD and by the relatively short study duration.

In patients who were inadequately controlled on 2 or 3 OAD, at 26 weeks, a composite endpoint of **HbA1C ≤7.4% AND weight gain ≤ 1kg** was achieved more often with the addition of exenatide 10µg twice daily compared to the addition of insulin glargine. The difference was statistically significant.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on 2 or 3 OAD, at 26 weeks, the addition of exenatide 10µg twice daily did **not** result in a statistically significant **difference in HbA1c** compared to the addition of insulin glargine.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on 2 or 3 OAD, at 26 weeks, there was a statistically **significant difference in weight change** with the addition of exenatide 10 µg twice daily compared to the addition of insulin glargine.
the weight in the exenatide group was decreased compared to the insulin glargine group (in which the weight had increased from baseline).
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported.
The rates can be found in the table above.

Severe hypoglycemia occurred in 4.2% with exenatide and 5.3% with insulin glargine. The difference was **not** statistically significant.
GRADE: VERY LOW quality of evidence

6.8 Combination therapy with insulin glargine

6.8.1 Exenatide twice daily + insulin glargine +/- MET or PIO versus placebo + insulin glargine +/- MET or PIO

6.8.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref: Buse 2011(53) Design: RCT (DB) (PG) Duration of follow-up: 30 weeks	n: 261 Mean age: 59 y Prior/current treatment: insulin glargine at a minimum of 20 U/d without any other insulin, alone or in combination with a stable dose of metformin or pioglitazone (or both) Mean DMII duration: 12y Mean baseline HbA1c: 8.4% Mean BMI: 33 Previous CV event: NR Renal impairment: NR	Exenatide 10 µg twic daily vs Placebo in addition to this background treatment: Insulin glargine with or without metformin or pioglitazone (or both agents) <u>Hyperglycaemia uptitration protocol:</u> No protocol <u>Hyperglycaemia</u>	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: <u>Study completers</u>: 82% <u>Discontinued treatment</u>: ExBid: 19% Pla: 18% Reason described: yes <u>Uptitration of study medication</u>: Not applicable <u>Hyperglycaemic rescue</u>: ExBid: 0%
			Change in HbA1c from baseline (PO)	ExBid: -1.74% Pla: -1.04% **ExBid vs pla: -0.69% (-0.93 to -0.46); p<0.001 => SS**	
			Body weight change from baseline	ExBid: -1.8 kg Pla: +1.0 kg **ExBid vs pla: -2.7 kg (-3.7 to -1.7); p<0.001 => SS**	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP ExBid: -2.7 mmHg Pla: +1.7 mmHg **ExBid vs pla: -4.4 mmHg (-7.8 to -1.0); p=0.01 => SS** DBP ExBid: -1.7 mmHg Pla: +1.7 mmHg **ExBid vs pla: -3.4 mmHg (-5.2 to -1.6); p<0.001 => SS**	
			Safety		

	Inclusion • ≥18 years old • Type 2 diabetes • Had been receiving insulin glargine at a minimum of 20 U/d without any other insulin, alone or in combination with a stable dose of metformin or pioglitazone (or both) for at least 3 months • HbA1c 7.1 to 10.5% • BMI ≤45 • Stable body weight Exclusion • Clinically significant hematologic, oncologic, renal, cardiac, hepatic, or gastrointestinal disease • In weight loss program in 3 months before study • Systemic	rescue protocol: No protocol	**Death**	ExBid: 0% Pla: 1% (one death, myocardial infarction) NT	Pla: 2% Statistical method for drop out/missing data: MRMM Data handling for rescued patients: excluded, MRMM ITT: no; analysis included data from all participants who received the study drug and had measurements at postbaseline visits. SELECTIVE REPORTING: no Other important methodological remarks At randomization, participants with HbA1c ≤8% decreased their dose of insulin glargine by 20%. These doses were maintained for 5 weeks, after which participants began titration to achieve a FG <100 mg/dL Sponsor: Eli Lilly and Amylin Pharmaceuticals
			Cardiovascular adverse events	NR	
			Any adverse events	NR	
			Serious adverse events	ExBid: 6% Pla: 9% NT	
			Adverse event leading to withdrawal	ExBid: 9% Pla: 1% **P< 0.01 => SS**	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	ExBid: 18% Pla: 8% NT	
			Nausea	ExBid: 41% Pla: 8% **Between-group difference: 32% (23 to 42) => SS**	
			Vomiting	ExBid: 18% Pla: 4% **Between-group difference: 10% (2 to 18) => SS**	
			Severe hypoglycaemia	ExBid: 0% Pla: 1% **Between-group difference: 14% (7 to 21) => SS**	

	glucocorticoid therapy in last 8 weeks • More than 1 episode of major hypoglycemia in last 6 months • Irregular sleep-wake cycle • History of pancreatitis		**Documented symptomatic hypoglycaemia** *("minor hypoglycemia: signs or symptoms associated with hypoglycemia and fingerstick blood glucose level <3 mmol/L (<54 mg/dL) that were either self-treated or resolved on their own)*	ExBid: 25% Pla: 29% NT	
			Injection site reactions	NR	
			Thyroid cancer	No events	
			Pancreatitis	No events	

Table 106

6.8.1.2 *Summary and conclusions*

Exenatide twice daily + insulin glargine +/- MET +/- PIO vs placebo + insulin glargine +/- MET +/- PIO			
Bibliography: Buse 2011(53)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	261 (1) 30 weeks	Exe: -1.74% Pla: -1.04% treatment difference: **-0.69% (95%CI-0.93 to -0.46); p<0.001** **SS in favour of exenatide**	⊕⊕⊕⊖ **MODERATE** Study quality: ok, but 18% attrition Consistency: NA Directness: -1 background therapy varied, ins glar dose was decreased by 20% at study entry for patients with HbA1C<8, nonaggressive titration, duration Imprecision: ok
Body weight change from baseline	261 (1) 30 weeks	Exe: -1.8 kg Pla: +1.0 kg treatment difference: **-2.7 kg (-3.7 to -1.7)** **p<0.001** **SS in favour of exenatide**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 background therapy varied, ins glar dose decreased by 20% at study entry for patients with HbA1C<8, nonaggressive titration, duration Imprecision: ok
Adverse events leading to withdrawal	261 (1) 30 weeks	ExBid: 9% Pla: 1% **P< 0.01 => SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 background therapy varied, ins glar dose decreased by 20% at study entry for patients with HbA1C<8, nonaggressive titration, duration Imprecision: unable to assess
Diarrhea	261 (1) 30 weeks	ExBid: 18% Pla: 8% NT	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 background therapy varied, ins glar dose decreased by 20% at study entry for patients with HbA1C<8, nonaggressive titration Imprecision: ok
Nausea	261 (1) 30 weeks	ExBid: 41% Pla: 8% **Between-group difference: 32% (23 to 42) => SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 background therapy varied, ins glar dose decreased by 20% at study entry for patients with HbA1C<8, nonaggressive titration, duration Imprecision: ok
Vomiting	261 (1) 30 weeks	ExBid: 18% Pla: 4% **Between-group difference: 10% (2 to 18) => SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 background

			therapy varied, ins glar dose decreased by 20% at study entry for patients with HbA1C<8, nonaggressive titration, duration Imprecision: ok
Severe hypoglycaemia	261 (1) 30 weeks	ExBid: 0% Pla: 1% **Between-group difference: 14% (95% CI 7 to 21) => SS**	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -1 background therapy varied, ins glar dose decreased by 20% at study entry for patients with HbA1C<8, nonaggressive titration, duration Imprecision: -1 low event rates

Table 107

In this double blind, RCT, 464 patients with type 2 diabetes, inadequately controlled by insulin glargine (minimum 20U/d), alone or in combination with a stable dose of metformin or pioglitazone or both, were randomized to exenatide 10µg twice daily or placebo for 30 weeks. Insulin glargine in both groups was to be titrated to achieve a FGL<100mg/dl.
The mean age was 59y, mean duration of diabetes 12y, mean baseline HbA1c was 8.4% and mean BMI was 33 kg/m^2. Participants with clinically significant cardiac or renal disease were excluded from the trial.

Our confidence in the estimate of the between-group differences is somewhat limited by the different possible background treatments, by some issues with the insulin glargine titration and by the relatively short duration of the trial.

In patients who were inadequately controlled on insulin glargine +/- MET +/- PIO, at 30 weeks, the addition of exenatide 10µg twice daily resulted in a statistically **significant decrease of HbA1c** compared to the addition placebo.
GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on insulin glargine +/- MET +/- PIO, at 30 weeks, there was a statistically **significant difference in weight change** with the addition of exenatide 10µg twice daily compared to the addition of placebo.
The weight in the exenatide 10µg twice daily group was decreased compared to the placebo group (in which the weight had increased from baseline).
GRADE: MODERATE quality of evidence

Withdrawal from the study due to adverse events was seen in 9% with exenatide 10µg twice daily and 1% with placebo.
GRADE: MODERATE quality of evidence

Rates of diarrhea were 18% with exenatide 10µg twice daily and 8 % with placebo. The difference was statistically significant.

Rates of nausea were 41% with exenatide 10µg twice daily and 8% with placebo. The difference was statistically significant.
Rates of vomiting were 18% with exenatide 10µg twice daily and 4% with placebo. The difference was statistically significant.
GRADE: MODERATE quality of evidence

Severe hypoglycemia occurred in 0% with exenatide 10µg twice daily and 1% with placebo. The difference was statistically significant.
GRADE: LOW quality of evidence

6.8.2 Exenatide twice daily + insulin glargine +metformin versus mealtime insulin lispro + insulin glargine +metformin

6.8.2.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref : Diamant 2014(54) Design: RCT (OL) (PG) Non-inferiority trial Duration of follow-up: 30 weeks	n: 627 Mean age: 60 y Prior/current treatment: insulin glargine and metformin +/- SU Mean DMII duration: 12 y Mean baseline HbA1c: 8.2% Mean BMI: 32 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> • ≥18 years • Type 2 diabetes • Treated with insulin glargine and metformin +/- SU	Exenatide 10-20µg/day vs mealtime lispro (titrated to premeal glucose 5.6-6.0 mmol/L) thrice daily in addition to this background treatment: insulin glargine + metformin <u>Hyperglycaemia uptitration protocol:</u> No protocol <u>Hyperglycaemia rescue protocol</u>**:** No protocol	Efficacy		RANDO: Adequate ALLOCATION CONC: unclear BLINDING : Participants: no Personnel: no Assessors: no FOLLOW-UP: <u>Study completers</u>: 86% <u>Discontinued treatment</u>: Exenatide: 17% Insulin lispro: 14% Reason described: yes <u>Uptitration of study medication</u>: Not applicable <u>Hyperglycaemic rescue</u>: Exenatide: 1% Insulin lispro: 0%
			Change in HbA1c from baseline (PO)	Exenatide: -1.13% Insulin lispro: -1.10% Exenatide vs insulin lispro: LS mean -0.04% (-0.18 to 0.11) *in per protocol population* non-inferiority of exenatide compared to insulin lispro (both in per protocol and ITT population)	
			Body weight change from baseline	*in per protocol population* Exenatide: -2.5 kg Insulin lispro: +2.1 kg Exenatide vs insulin lispro: **LS mean: -4.6 kg (-5.2 to -3.9)** **P<0.001 => SS**	
			Blood pressure change from baseline (SystBP/DiastBP)	*in per protocol population* SBP Exenatide: -4.1 mmHg Insulin lispro: +0.4 mmHg **Exenatide vs insulin lispro:** **LS mean: -4.5 mmHg (-7.0 to -2.0)**	

	• HbA1c 7-10% • BMI 25-45 <u>Exclusion</u> • Use of other glucose-lowering agents Clinical history, condition, or concomitant medication that could confound efficay or safety (incl. creatinine clearance <30 ml/min, clinically significant cardiac, hepatic, gastrointestinal disease)			**P<0.001 => SS** DBP Exenatide: -0.6 Insulin lispro: -0.1 Exenatide vs insulin lispro: LS mean: -0.5 mmHg (-2.1 to 1.1)	<u>Statistical method for drop out/missing data</u>: MRMM <u>Data handling for rescued patients</u>: exclusion <u>ITT</u>: defined as all randomized subjects receiving at least one dose of study drug grouped according to randomized treatment, regardless of the study drug actually received SELECTIVE REPORTING: yes, incomplete reporting of safety endpoints Other important methodological remarks • 12 weeks prior basal insulin optimalization phase which identified patients requiring additional therapy by failure to reach HbA1c 7.0% or less on titrated basal insulin and metformin • SU discontinued at entry • Daily glargine was reduced 10% or more in patients allocated to exenatide with HbA1c of ≤8.0%
			Safety		
			Death	Exenatide: 1/315 Insulin lispro: 0/312 NT	
			Cardiovascular adverse events *Acute myocardial infarction*	Exenatide: 0% Insulin lispro: 1% NT	
			Any adverse events	Exenatide: 72% Insulin lispro: 56% NT	
			Serious adverse events	Exenatide: 6% Insulin lispro: 7% NT	
			Adverse event leading to withdrawal	Exenatide: 5 % Insulin lispro: 2% NT	
			Any gastro-intestinal adverse event	Exenatide: 47% Insulin lispro: 13% NT	

			Diarrhoea	Exenatide: 11% Insulin lispro: 5% NT	• Daily glargine was reduced by ½ or 1/3, at the investigator's discretion, in patients randomized to lispro • Noninferiority was assessed using an HbA1c non-inferiority margin of 0.4% Sponsor: Eli Lilly and Company and Amylin Pharmaceuticals
			Nausea	Exenatide: 32% Insulin lispro: 2% NT	
			Vomiting	Exenatide: 12% Insulin lispro: 1% NT	
			Severe hypoglycaemia	Exenatide: 1% Insulin lispro: 2% NT	
			Documented symptomatic hypoglycaemia *Minor hypoglycemia: symptoms of hypoglycemia, self-treated, and finger stick blood glucose <54 mg/dL*	Exenatide: 30% Insulin lispro: 41% NT	
			Injection site reactions	NR	
			Thyroid cancer	No events	
			Pancreatitis	No events	

Table 108

6.8.2.2 *Summary and conclusions*

Exenatide 10µg twice daily + insulin glargine +/- metformin versus **mealtime insulin lispro** + insulin glargine +/- metformin			
Bibliography: Diamant 2014(54)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	627 (1) 30 weeks	Exenatide: -1.13% Insulin lispro: -1.10% treatment difference -0.04% (95%CI-0.18 to 0.11) **non-inferiority of exenatide compared to insulin lispro**	⊕⊕⊖⊖ **LOW** Study quality: -1 open label Consistency: NA Directness: -1 insulin titration, only 30 weeks Imprecision: ok
Body weight change from baseline	627 (1) 30 weeks	Exenatide: -2.5 kg Insulin lispro: +2.1 kg treatment difference **-4.6 kg (95% CI-5.2 to -3.9)** **P<0.001** **SS in favour of exenatide**	⊕⊕⊖⊖ **LOW** Study quality: -1 open label Consistency: NA Directness: -1 insulin titration, only 30 weeks Imprecision: ok
Adverse events leading to withdrawal	627 (1) 30 weeks	Exenatide: 5 % Insulin lispro: 2% NT	Not applicable
Diarrhea	627 (1) 30 weeks	Exenatide: 11% Insulin lispro: 5% NT	Not applicable
Nausea	627 (1) 30 weeks	Exenatide: 32% Insulin lispro: 2% NT	Not applicable
Vomiting	627 (1) 30 weeks	Exenatide: 12% Insulin lispro: 1% NT	Not applicable
Severe hypoglycaemia	627 (1) 30 weeks	Exenatide: 1% Insulin lispro: 2% NT	Not applicable

Table 109

In this open label, non-inferiority RCT, 627 patients with type 2 diabetes, inadequately controlled by insulin glargine and metformin +/- SU, were randomized to exenatide 10µg twice daily or mealtime insulin lispro for 30 weeks. SU was discontinued. The mean age was 60y, mean duration of diabetes 12y, mean baseline HbA1c was 8.2% and mean BMI was 32 kg/m^2. Patients with clinically significant cardiac disease were not allowed into the study. Patients with creatinine clearance ≥ 30 ml/min were allowed into the study but it is unclear how much patients with renal impairment were included.

Our confidence in the estimate of the between-group differences is mainly limited by the open label design and the relatively short duration of the study.

In patients who were inadequately controlled on insulin glargine and metformin +/- SU, at 30 weeks, the addition of exenatide 10µg twice daily resulted was **non-inferior** for the **decrease of HbA1c** compared to the addition of mealtime insulin lispro.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on insulin glargine and metformin +/- SU, at 30 weeks, there was a statistically **significant difference in weight change** with the addition of exenatide 10µg twice daily compared to the addition of mealtime insulin lispro.
The weight in the exenatide 10µg twice daily group was decreased compared to the mealtime insulin lispro group (in which the weight had increased from baseline).
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported.

Withdrawal from the study due to adverse events was seen in 5% with exenatide 10µg twice daily and 2% with mealtime insulin lispro.
GRADE: not applicable

Rates of diarrhea, nausea, vomiting and severe hypoglycaemia can be found in the table above.
GRADE: not applicable

6.9 Triple therapy versus sequential therapy

6.9.1 Metformin + pioglitazone + exenatide twice daily versus metformin, later + SU, later + insulin glargine

6.9.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Abdul-ghani 2015(55) EDICT Design: RCT (OL) (PG) Duration of follow-up: 2 years (total study will be 3 years)	n: 249 Mean age: 46y Prior/current treatment: drug naive Mean DMII duration: 5 months Mean baseline HbA1c: 8.6% Mean BMI: 36.5 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> • 30-75 years • BMI 24-50 • Drug naive • Recently (<2y) diagnosed	Metformin 2000 mg + pioglitazone 30 mg+ exenatide 2 x 10µg (triple R/) vs metformin, sequential addition of sulfonylurea and glargine insulin (conventional R/) (see hyperglycaemia uptitration protocol for dosage) <u>Hyperglycaemia uptitration protocol:</u> In triple R/: if at months, HbA1c was >6.5%, pioglitazone was increased to 45 mg.	Efficacy		RANDO: Unclear (method of randomization not clear) ALLOCATION CONC: Unclear (not mentioned) BLINDING : Participants: no Personnel: no Assessors: no FOLLOW-UP: <u>Study completers</u>: 70% <u>Discontinued treatment</u>: Triple R/: 33% Conventional R/: 25% Reason described: no <u>Uptitration of study medication</u>: At 24 months, 100% of
			Change in HbA1c from baseline (PO)	Triple R/: NR Conventional R/: NR **Triple vs conventional: 0.6%** **P=0.0001 => SS in favour of triple R/**	
			Body weight change from baseline	Triple R/: -1.2 kg Conventional R/:+ 4.1 kg **Triple vs conventional: 5.3 kg** **P<0.01=> SS in favour of triple R/**	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP Triple R/: -9.7 mmHg Conventional R/: -3.6 mmHg Triple vs conventional: NS DBP Triple R/: NR Conventional R/: NR	
			Safety		

	• Stable body weight <u>Exclusion</u> • Haematocrit levels <34% • Medications known to affect glucose metabolism • Previous treatment with any antidiabetic agent • Evidence of diabetic proliferative retinopathy	Participants receiving conventional therapy were started on metformin 1000mg/day. If, at 1month, fasting plasma glucose (FPG) concentration was >6.1 mmol/l (110mg/dl), metformin was increased to 2000mg and glipizide started at 5mg/day. If, at 2months, FPG was >6.1 mmol/l (110mg/dl) or HbA1c was >6.5%, glipizide was increased to 10mg and then to 20mg. If, at 3months, FPGwas >6.1 mmol/l (110mg/dl) or HbA1c >6.5%, glargine insulin was started at 10 units before breakfast, and escalatedweekly by 1–5units (based onFPGandHbA1c levels) to 60 units/day to maintain FPG at <6.1 mmol/l (110mg/dl).	**Death**	Triple R/: 0% Conventional R/: 2% NT	participants of triple therapy group was taking all 3 agents. At 24 months, in the conventional therapy group, 19% was taking metformin only 53% was taking metformin+ glipizide 28% was taking Met+glip+glarg <u>Hyperglycaemic rescue</u>: NR <u>Statistical method for drop out/missing data</u>: LOCF <u>Data handling for rescued patients</u>: excluded, LOCF <u>ITT</u>: No, only randomized participants who received therapy adn completed at least 6 months of follow-up were included in the analysis. SELECTIVE REPORTING: yes, incomplete and unclear reporting of all endpoints Sponsor: Funded by grants from the ADA, Amylin Pharmaceuticals,
			Cardiovascular adverse events	NR	
			Any adverse events	Triple R/: 90% Conventional R/: 87% NT	
			Serious adverse events	NR	
			Adverse event leading to withdrawal	Triple R/: 6% Conventional R/: 2% NT	
			Any gastro-intestinal adverse event	Triple R/: 33% Conventional R/: 25%	
			Diarrhoea	NR	
			Nausea	Triple R/: 25% Conventional R/: NR, described as less than triple R/	
			Vomiting	NR	
			Severe hypoglycaemia	No events	
			Documented symptomatic hypoglycaemia *Blood glucose <60 mg/dL, with or without symptoms,*	Triple R/: 14%; 0.3 events/ participant/ year Conventional R/: 46%; 2.2 events/ participant/ year **Triple vs Conventional: P<0.0001 =>**	

		<u>Hyperglycaemia rescue protocol</u>**:** If HbA1c increased to >6.5% on two consecutive visits 3 months apart, rescue therapy was started (short-acting insulin). Rescue therapy in the triple therapy arm was glargine insulin. The first HbA1c value to exceed 6.5% was censored and carried forward for analysis.	*or hypoglycaemia symptoms that subsided after glucose ingestion*	**SS in favour of triple**	BristolMyers, Squibb, Astra Zeneca, Eli Lilly
			Injection site reactions	NR	
			Thyroid cancer	NR	
			Pancreatitis	NR	

Table 110

6.9.1.2 *Summary and conclusions*

triple therapy with MET+ PIO+ EXE vs sequential therapy with MET, then + SU, then + glargine in new-onset diabetes			
Bibliography: Abdul-ghani 2015(55) EDICT			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	249 (1) 2 years	Triple R/: NR Conventional R/: NR **Triple vs conventional: 0.6%** **P=0.0001 => SS in favour of triple R/**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 open label, inadequate method of dealing with missing values (30% missing) Consistency: NA Directness: -1 very low targets for HbA1c Imprecision: -1 unable to assess
Body weight change from baseline	249 (1) 2 years	Triple R/: -1.2 kg Conventional R/:+ 4.1 kg **Triple vs conventional: 5.3 kg** **P<0.01** **SS in favour of triple R/**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 open label, inadequate method of dealing with missing values (30% missing) Consistency: NA Directness: -1 very low targets for HbA1c Imprecision: -1 unable to assess
Adverse events leading to withdrawal	249 (1) 2 years	Triple R/: 6% Conventional R/: 2% NT	Not applicable
Diarrhea	249 (1) 2 years	Triple R/: 33% Conventional R/: 25%	Not applicable
Nausea	249 (1) 2 years	NR	Not applicable
Vomiting	249 (1) 2 years	Triple R/: 25% Conventional R/: NR, described as less than triple R/	Not applicable
Severe hypoglycaemia	249 (1) 2 years	NR	Not applicable

Table 111

In this open label RCT, 249 patients with new onset type 2 diabetes, were randomized to triple therapy with metformin 2000mg/d + pioglitazone 30mg/d + exenatide 10µg 2x/d or sequential therapy starting with metformin and adding SU and then insulin glargine if insufficient control f2 years. The mean age was 46y, mean duration of diabetes 5 months, mean baseline HbA1c was 8.6% and mean BMI was 36.5 kg/m^2.

Our confidence in the estimate of the between-group differences is limited by the open label design, the inappropriate method of dealing with missing values (30% missing), the very strict HbA1c targets and some issues with selective reporting.

In patients with new onset diabetes, at 2 years, triple therapy with metformin, pioglitazone and exenatide resulted in a **statistically significant decrease of HbA1c** compared to a sequential therapy starting with metformin and adding SU and then insulin glargine in case of insufficient control.
GRADE: VERY LOW quality of evidence

In patients with new onset diabetes, at 2 years , there was a statistically significant difference in **weight change** with triple therapy with metformin, pioglitazone and exenatide compared to a sequential therapy starting with metformin and adding SU and then insulin glargine in case of insufficient control.
The weight in the triple therapy group was decreased compared to the sequential therapy group (in which the weight had increased from baseline).
GRADE: VERY LOW quality of evidence

Adverse events were not consistently reported. The rates of adverse events can be found in the table above.

7 Exenatide once weekly– evidence tables and conclusions

7.1 Monotherapy

7.1.1 Exenatide once weekly versus metformin

7.1.1.1 *Clinical evidence profile: exenatide once weekly versus metformin, pioglitazone, sitagliptin*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Russell-Jones 2012 DURATION-4(56) Design: RCT (DB) (PG) non-inferiority trial Duration of follow-up: 26 weeks + 10 weeks open label for	n:820 Mean age: 54y Prior/current treatment: drug-naieve Mean DMII duration: 2.7y Mean baseline HbA1c: 8.5% Mean BMI: 31kg/m2 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> Adults with type 2 diabetes, HbA1c 7.1–11.0%, BMI 23–45	Exenatide once weekly 2.0mg vs metformin 2,000mg/d vs pioglitazone 45mg/d vs sitagliptin 100mg/d MET and PIO dosages were increased in weekly increments up to target doses of 2,000 and 45 mg/day, respectively.	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: unclear Personnel: unclear Assessors: unclear dummy injection and dummy pills, but dosing of different oral therapy may give a clue as to the drug used. FOLLOW-UP: <u>Study completers</u>: 84.9% at 26 weeks 89.8% at additional 10 week safety follow up Reason described: yes
			Change in HbA1c from baseline at 26 weeks (PO) MMRM	exe: -1.53% (SE 0.07%) met: -1.48% (SE 0.07%) pio: -1.63% (SE 0.08%) sita: -1.15% (SE 0.08%) exe vs met 98.3% CI -0.26 to 0.17 **exe once weekly non-inferior to met** exe vs pio 98.3% CI -0.15 to 0.35 exe once weekly not non-inferior to pio exe vs sita 98.3% CI-0.62 to-0.13 **exe once weekly non-inferior to sita** **exe once weekly superior to sita** Findings from original (excluding drop	

extra safety data	kg/m2, and history of stable weight. <u>Exclusion</u> treated with any antihyperglycemic drug for >7 days within 3 months of screening.	MET could be increased up to 2,500 mg/day based on glycemic control <u>Stratification:</u> by country		outs before 8 weeks) and modified primary analyses were consistent	<u>Uptitration of study medication</u>: By week 12, 87% of patients taking MET and 75% taking PIO had been titrated to or above target doses for each agent (PIO 45mg/day,MET 2,000mg/day, respectively). At week 16–26, patients were on stable doses: PIO (≤45 mg/day) 88% and MET (≤2,000 mg/day) 76%. <u>Hyperglycaemic rescue</u>: excluded from study if loss of glucose control exe:1.2% met:1.2% pio:3.1% sita:1.8% <u>Statistical method for drop out/missing data</u>: MMRM <u>Data handling for rescued patients</u>: rescued patients were excluded <u>ITT</u>: defined as randomized patients who received at least one dose of the study drug
			Body weight change from baseline	exe:-2kg (SE 0.2) met:-2kg (SE 0.2) pio:+1.5kg (SE0.3) sita:-0.8 kg (SE 0.3) exe vs met P = 0.892 NS exe vs pio **P<0.001** **SS in favour of exe** exe vs sita **P<0.001** **SS in favour of exe**	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP exe: -1.3 mmHg (SE 0.8 mmHg) met: NR pio: -1.7 mmHg (SE 1.0mmHg) sita: -1.8 mmHg (SE 1.0 mmHg) DBP exe: NR met: NR pio: -2.5 mmHg (SE 0.6 mmHg) sita: NR	
			Safety		
			Death	NR	
			Cardiovascular adverse events	NR	

					SELECTIVE REPORTING: yes no information on all adverse events Other important methodological remarks A predefined noninferiority margin of 0.3% and sample size of 444 patients would provide 74% power to test the noninferiority of EQW versus MET, and a sample size of 370 would provide 65% power to test the noninferiority of EQW versus PIO (and SITA). Bonferroni-Hommel gate-keeping procedure was used to test hypotheses. upward shift inHbA1c, observed in the EQW group between weeks 16 and 26 (Fig) Sponsor: Amylin Pharmaceuticals (San Diego, CA) and Eli Lilly (Indianapolis, IN).
			Any adverse events	NR	
			Serious adverse events	exe:1.6% met:5.3% pio:5.5% sita:1.8%	
			Adverse event leading to withdrawal	exe:2.4% met:2.4% pio:3.1% sita:0.6%	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	exe:10.9% met:12.6% pio:3.7% sita:5.5%	
			Nausea	exe:11.3% met:6.9% pio:4.3% sita:3.7%	
			Vomiting	exe: 4.8% met:3.3% pio:3.1% sita:1.8%	
			Severe hypoglycaemia	exe:0 met:0 pio:0 sita:0	

			hypoglycaemia unconfirmed by glucose measurement	exe:5.2% met:4.1% pio:3.7% sita:3.1%	
			minor hypoglycaemia	exe 2.0% rest: NR	
			Injection site nodules	exe:10.5% met:10.2% pio:3.7% sita:6.7% Injection site nodules were more commonly reported with active EQW and placebo injection administered in the MET arm compared with placebo injection administered in the PIO and SITA arms.	
			Thyroid cancer	NR	
			Pancreatitis	exe:0 met:0 pio:0 sita:1	

Table 112

Minor hypoglycemia was defined as signs or symptoms associated with blood glucose<3.0 mmol/L (either self-treated or resolved independently).
Major hypoglycemia was classified as symptoms resulting in loss of consciousness or seizure that showed prompt recovery after administration of glucose, or documented blood glucose ,3.0 mmol/L that required the assistance of another person because of severe impairment in consciousness or behavior.
A subset, defined as symptoms of hypoglycemia, was not confirmed by blood glucose measurement.

First, patients were enrolled based on specific criteria and were followed according to the study schedule, which may not reflect real-world use. Second, no specific compliance data were collected; however, patient-reported outcomes indicated that both oral and injectable therapies were associated with increases in treatment satisfaction and quality of life in these previously drug-naive patients. Additionally, 26 weeks is too short a study duration to evaluate long-term glycemic control, weight loss, and b-cell

preservation (25). For example, potential implications of the upward shift inHbA1c, observed in the EQW group between weeks 16 and 26 (Fig. 2A), cannot be assessed further without additional data points.

7.1.1.2 *Summary and conclusions*

Exenatide once weekly versus metformin			
Bibliography: Russell-Jones 2012 DURATION-4(56)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	494 (1) 26 weeks	exe vs met treatment difference 98.3% CI -0.26 to 0.17 **exe once weekly non-inferior to met**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear blinding, very long titration period of metformin Consistency: NA Directness: ok Imprecision: ok
Body weight change from baseline	494 (1) 26 weeks	exe vs met treatment difference P = 0.892 NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear blinding, very long titration period of metformin Consistency: NA Directness: ok Imprecision: not evaluable
Adverse events leading to withdrawal	494 (1) 26 weeks	exe: 2% met: 2% NT	Not applicable
Diarrhea	494 (1) 26 weeks	exe: 11% met: 13% NT	Not applicable
Nausea	494 (1) 26 weeks	exe: 11% met: 7% NT	Not applicable
Vomiting	494 (1) 26 weeks	exe: 5% met: 3% NT	Not applicable
Severe hypoglycaemia	494 (1) 26 weeks	No events	Not applicable

Table 113

In this double blind non-inferiority RCT, 820 drug-naive patients with type 2 diabetes were randomized to exenatide 2 mg once weekly (n=248), metformin 2000 mg/d (n=246), pioglitazone 45 mg/day (n=163), or sitagliptin 100 mg/d (n=163) for 26 weeks.
The mean age was 54, mean duration of diabetes 2.7 years, mean baseline HbA1c was 8.5% and mean BMI was 31 kg/m^2. It was not reported how many participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

Our confidence in the estimate of the between-group differences is limited by unclear blinding (dummy injection and dummy pills were utilised, but dosing of different oral therapy may give a clue

as to the drug used) and the long titration period of metformin (87% had been titrated to target doses by week 12).

In drug-naive patients, at 26 weeks, exenatide once weekly was non-inferior compared to metformin 2000 mg/day for the lowering of HbA1c.

GRADE: MODERATE quality of evidence

In drug-naive patients, at 26 weeks, there was **no** statistically significant difference in weight change with the addition of exenatide once weekly compared to the addition of metformin 2000 mg/day.

GRADE: MODERATE quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 2% with exenatide once weekly and 2% with metformin.
GRADE: not applicable

Rates of diarrhea were 11% with exenatide once weekly and 13% with metformin.
Rates of nausea were 11% with exenatide once weekly and 7% with metformin.
Rates of vomiting were 5% with exenatide once weekly and 3% with metformin.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

7.1.2 Exenatide once weekly versus pioglitazone

7.1.2.1 *Clinical evidence profile*

See 7.1.1.1.

7.1.2.2 *Summary and conclusions*

Exenatide once weekly versus metformin			
Bibliography: Russell-Jones 2012 DURATION-4(56)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	411 (1) 26 weeks	exe vs pio treatment difference 98.3% CI -0.15 to 0.35 exe once weekly not non-inferior to pio	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear blinding, very long titration period of pioglitazone Consistency: NA Directness: ok Imprecision: ok
Body weight change from baseline	411 (1) 26 weeks	exe vs pio treatment difference **P<0.001** **SS in favour of exenatide**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear blinding, very long titration period of pioglitazone Consistency: NA Directness: ok Imprecision: not evaluable
Adverse events leading to withdrawal	411 (1) 26 weeks	exe: 2% pio: 3% NT	Not applicable
Diarrhea	411 (1) 26 weeks	exe: 11% pio: 4% NT	Not applicable
Nausea	411 (1) 26 weeks	exe: 11% pio: 4% NT	Not applicable
Vomiting	411 (1) 26 weeks	exe: 5% pio: 3% NT	Not applicable
Severe hypoglycaemia	411 (1) 26 weeks	No events	Not applicable

Table 114

In this double blind non-inferiority RCT, 820 drug-naive patients with type 2 diabetes were randomized to exenatide 2 mg once weekly (n=248), metformin 2000 mg/d (n=246), pioglitazone 45 mg/day (n=163), or sitagliptin 100 mg/d (n=163) for 26 weeks.
The mean age was 54, mean duration of diabetes 2.7 years, mean baseline HbA1c was 8.5% and mean BMI was 31 kg/m^2. It was not reported how many participants had had a previous myocardial

infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

Our confidence in the estimate of the between-group differences is limited by unclear blinding (dummy injection and dummy pills were utilised, but dosing of different oral therapy may give a clue as to the drug used) and the long titration period of pioglitazone (75% had been titrated to target doses by week 12).

In drug-naive patients, at 26 weeks, exenatide once weekly was non-inferior compared to pioglitazone 45 mg/day for the lowering of HbA1c.

GRADE: MODERATE quality of evidence

In drug-naive patients, at 26 weeks, there was a statistically significant difference in weight change with the addition of exenatide once weekly compared to the addition of pioglitazone.
The weight in the exenatide once weekly group was decreased compared to the pioglitazone group (in which the weight had increased from baseline).

GRADE: MODERATE quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 2% with exenatide once weekly and 3% with pioglitazone.
GRADE: not applicable

Rates of diarrhea were 11% with exenatide once weekly and 4% with pioglitazone.
Rates of nausea were 11% with exenatide once weekly and 4% with pioglitazone.
Rates of vomiting were 5% with exenatide once weekly and 3% with pioglitazone.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

7.1.3 Exenatide once weekly versus sitagliptin

7.1.3.1 *Clinical evidence profile*

See 7.1.1.1.

7.1.3.2 *Summary and conclusions*

Exenatide once weekly versus metformin			
Bibliography: Russell-Jones 2012 DURATION-4(56)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	411 (1) 26 weeks	exe vs sita treatment difference 98.3% CI-0.62 to-0.13 **exe once weekly non-inferior to sita** **exe once weekly superior to sita**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 unclear blinding Consistency: NA Directness: ok Imprecision: ok
Body weight change from baseline	411 (1) 26 weeks	exe vs sita treatment difference **P<0.001** **SS in favour of exe**	⊕⊕⊕⊖ **MODERATE** Study quality: 1 unclear blinding Consistency: NA Directness: ok Imprecision: not evaluable
Adverse events leading to withdrawal	411 (1) 26 weeks	exe: 2% sita: 1% NT	Not applicable
Diarrhea	411 (1) 26 weeks	exe: 11% sita: 6% NT	Not applicable
Nausea	411 (1) 26 weeks	exe: 11% sita: 4% NT	Not applicable
Vomiting	411 (1) 26 weeks	exe: 5% sita: 2% NT	Not applicable
Severe hypoglycaemia	411 (1) 26 weeks	No events	Not applicable

Table 115

In this double blind non-inferiority RCT, 820 drug-naive patients with type 2 diabetes were randomized to exenatide 2 mg once weekly (n=248), metformin 2000 mg/d (n=246), pioglitazone 45 mg/day (n=163), or sitagliptin 100 mg/d (n=163) for 26 weeks.
The mean age was 54, mean duration of diabetes 2.7 years, mean baseline HbA1c was 8.5% and mean BMI was 31 kg/m^2. It was not reported how many participants had had a previous myocardial

infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

Our confidence in the estimate of the between-group differences is limited by unclear blinding (dummy injection and dummy pills were utilised, but dosing of different oral therapy may give a clue as to the drug used).

In drug-naive patients, at 26 weeks, exenatide once weekly was non-inferior and superior, compared to sitagliptin.

GRADE: MODERATE quality of evidence

In drug-naive patients, at 26 weeks, there was a statistically significant difference in weight change with the addition of exenatide once weekly compared to the addition of sitagliptin.
There was more weight loss with exenatide once weekly than with sitagliptin.

GRADE: MODERATE quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 2% with exenatide once weekly and 1% with sitagliptin.
GRADE: not applicable

Rates of diarrhea were 11% with exenatide once weekly and 6% with sitagliptin.
Rates of nausea were 11% with exenatide once weekly and 4% with sitagliptin.
Rates of vomiting were 5% with exenatide once weekly and 2% with sitagliptin.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

7.2 Combination therapy with metformin

7.2.1 Exenatide once weekly + metformin versus pioglitazone + metformin

7.2.1.1 *Clinical evidence profile: exenatide once weekly versus sitagliptin, pioglitazone (all + metformin)*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Bergenstal 2010 DURATION-2(57) Design: RCT (DB) (PG) Duration of follow-up: 26 weeks	n: 514 Mean age: 52y Prior/current treatment: metformin +/- 1500 mg/d Mean DMII duration: 6y Mean baseline HbA1c: 8.5% Mean BMI: 32kg/m2 Previous CV event: NR Renal impairment:NR <u>Inclusion</u> aged 18 years or older, had type 2 diabetes and had been treated with a stable metformin regimen for at least 2 months	exenatide 2 mg once weekly vs sitagliptin 100 mg once daily vs pioglitazone 45 mg once daily in addition to this background treatment: Metformin mean dose +/- 1500mg <u>Stratification:</u> by country and by HbA1c at screening (<9·0% vs	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: <u>Discontinued treatment</u>: exe:21% sita:13% pio: 21% Reason described: yes <u>Hyperglycaemic rescue</u>: loss of glucose control 1 in each group <u>Statistical method for drop out/missing data</u>: LOCF
			Change in HbA1c from baseline at 26 weeks(PO)	exe: –1·5% (95% CI –1·7 to –1·4) sita: –0·9% (95% CI–1·1 to –0·7) pio: –1·2% (95% CI–1·4 to –1·0) treatment difference exe vs sita **–0·6% (95% CI –0·9 to –0·4)** **p<0·0001** exe vs pio **–0·3% (95% CI –0·6 to –0·1)** **p=0·0165)** 'Similar reductions were recorded for the evaluable patient group'	
			Body weight change from baseline	exe: –2·3 kg (95% CI–2·9 to –1·7) sita: ⁻0.8 kg (95% CI ⁻1.4 to⁻0.1) pio: 2·8 kg (95% CI 2·2 to 3·4). treatment difference exe vs sita **–1·5 kg, 95% CI –2·4 to –0·7,** **p=0·0002**	

	before screening; HbA1c of 7·1–11·0% and a body-mass index of 25–45 kg/m² Exclusion Clinically significant medical condition that could potentially affect study participation and/or personal well-being, as judged by the investigator, including but not limited to the following conditions: a. Hepatic disease or an alanine aminotransferase or aspartate aminotransferase value of >3 times the upper limit of normal b. Renal disease (corresponding to serum creatinine levels of >1.5 mg/dL in men and >1.4 mg/dL in women) c. Cardiovascular disease, including significant edema, congestive heart	≥9·0%).		exe vs pio **–5·1 kg, –5·9 to –4·3, p<0·0001**	Data handling for rescued patients: excluded from study, LOCF ITT: defined as all patients who received at least one dose of study drug (491 of 514) Evaluable population consisted of all intention-to-treat participants who completed study procedures up to week 22, in compliance with the protocol and received dequate exposure. SELECTIVE REPORTING: no Other important methodological remarks Multiplicity for the comparisons of exenatide versus sitagliptin or pioglitazone were adjusted by use of the Hochberg procedure15 to control the overall type 1 error rate at 5% for HbA1c, fasting plasma glucose, bodyweight, Analyses of change in HbA1c at each visit were based on a general linear model including
			Blood pressure change from baseline (SystBP/DiastBP)	SBP exe vs sita –4 mm Hg, 95% CI –6 to –1 exe vs pio NS DBP NS differences	
			Safety		
			Death	NR	
			Cardiovascular adverse events	cerebrovascular accident: sita n=1, pio n=1 coronary artery occlusion: pio n=2 unstable angina pio n= 1	
			Any adverse events	NR	
			Serious adverse events	exe:3% sita:3% pio:6%	
			Adverse event leading to withdrawal	exe:n=10 sita:n=5 pio:n=6	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	exe:18% sita:10% pio:7%	

	failure, or New York Heart Association Class III or Class IV cardiac status d. Gastroparesis e. Clinically significant malignant disease (with the exception of basal and squamous cell carcinoma of the skin) within 5 years of Visit 1 (Screening)			NT	treatment, country, and baseline HbA1c strata (<9·0% vs ≥9·0%). Sponsor: Amylin Pharmaceuticals and Eli Lilly
			Nausea	exe:24% sita:10% pio:5% NT	
			Vomiting	exe:11% sita:2% pio:3% 'more common with exenatide'	
			Severe hypoglycaemia	exe:0 sita:0 pio:0 NT	
			minor hypoglycaemia	exe:1% sita:3% pio:1% NT	
			Injection site reactions	exe:10% sita and pio 7% 'similar'	
			Thyroid cancer number of patients	exe:0 sita:1 pio:0	
			Pancreatitis number of patients	exe:0 sita:0 pio:2	

Table 116

Major hypoglycaemia was defined as loss of consciousness, seizure, or coma that resolved after treatment with glucagon or glucose, or severe impairment that required third-party assistance to resolve the episode and a blood glucose concentration of lower than 3 mmol/L.
Minor hypoglycaemia was defined as a report of symptoms consistent with hypoglycaemia and glucose of lower than 3 mmol/L before treatment of the episode.

Our study is limited by the fact that we did not study all classes of potential adjunctive drugs, particularly basal insulin and sulphonylureas. A direct comparison is also warranted with 1·8 mg liraglutide, which is a modified version of GLP-1 that is taken once daily. In combination with metformin in patients predominantly on metformin background, 26 weeks' treatment with 1·8 mg liraglutide resulted in a greater reduction in HbA1c (–1·3%) than did metformin alone (–0·4%), with similar weight loss and occurrence of nausea as we recorded with exenatide.30 Assessment of intermediate outcome markers (eg, HbA1c, bodyweight, blood pressure, fasting lipid profile) rather than long-term outcomes, such as mortality and cardiovascular disease, is also a limitation. Although long-term outcome studies of GLP-1-related therapies are needed, our study provides one of the most comprehensive direct comparisons of key intermediate outcome markers with adjunctive treatments to metformin

7.2.1.2 *Summary and conclusions*

Exenatide once weekly + MET versus pioglitazone + MET			
Bibliography: Bergenstal 2010 DURATION-2(57)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	342 (1) 26 weeks	Treatment difference Exe vs pio **–0·3% (95% CI –0·6 to –0·1)** **p=0·0165 => SS in favour of exenatide**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 >20% drop-out and LOCF Consistency: NA Directness: ok Imprecision: ok
Body weight change from baseline	342 (1) 26 weeks	Treatment difference Exe vs pio **–5·1 kg (95% CI –5·9 to –4·3)** **p<0·0001 => SS in favour of exenatide**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 >20% drop-out and LOCF Consistency: NA Directness: ok Imprecision: ok
Adverse events leading to withdrawal	342 (1) 26 weeks	exe: 6% pio: 3% NT	Not applicable
Diarrhea	342 (1) 26 weeks	exe:18% pio:7% NT	Not applicable
Nausea	342 (1) 26 weeks	exe:24% pio:5% NT	Not applicable:
Vomiting	342 (1) 26 weeks	exe:11% pio:3% NT	Not applicable
Severe hypoglycaemia	342 (1) 26 weeks	No events	Not applicable:

Table 117

In this double blind RCT, 514 patients with type 2 diabetes, inadequately controlled by metformin, were randomized to exenatide 2 mg once weekly (n=170), sitagliptin 100 mg once daily (n=172) or to pioglitazone 45 mg once daily (n=172) for 26 weeks. The mean age was 52, mean duration of diabetes 6 years., mean baseline HbA1c was 8.5%,. and mean BMI was 32 kg/m^2. It was not reported how many participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

There was a large drop-out throughout the study (21%) This limits our confidence in the estimate of the between-group differences.

In patients who were inadequately controlled on metformin, at 26 weeks, the addition of exenatide once weekly resulted in a statistically significant decrease of HbA1c compared to the addition of pioglitazone .

GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on metformin, at 26 weeks, there was a statistically significant difference in weight change with the addition of exenatide once weekly compared to the addition of pioglitazone.
The weight in the exenatide once weekly group was decreased compared to the pioglitazone group (in which the weight had increased from baseline).

GRADE: MODERATE quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 6% with exenatide once weekly and 3% with pioglitazone.
GRADE: not applicable

Rates of diarrhea were 18% with exenatide once weekly and 7% with pioglitazone.
Rates of nausea were 24% with exenatide once weekly and 5% with pioglitazone.
Rates of vomiting were 11% with exenatide once weekly and 3% with pioglitazone.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

7.2.2 Exenatide once weekly + metformin versus sitagliptin + metformin

7.2.2.1 *Clinical evidence profile*

See 7.2.1.1.

7.2.2.2 *Summary and conclusions*

Exenatide once weekly + MET versus sitagliptin + MET			
Bibliography: Bergenstal 2010 DURATION-2(57)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	342 (1) 26 weeks	treatment difference exe vs sita **–0·6% (95% CI –0·9 to –0·4)** **p<0·0001 => in favour of exenatide**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 ; unequal drop-out (21 vs 13%) and LOCF Consistency: NA Directness: ok Imprecision: ok
Body weight change from baseline	342 (1) 26 weeks	treatment difference exe vs sita **–1·5 kg (95% CI –2·4 to –0·7)** **p=0·0002 => SS in favour of exenatide**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 ; unequal drop-out (21 vs 13%) and LOCF Consistency: NA Directness: ok Imprecision: ok
Adverse events leading to withdrawal	342 (1) 26 weeks	exe: 6% sita: 3% NT	Not applicable
Diarrhea	342 (1) 26 weeks	exe:18% sita:10% NT	Not applicable
Nausea	342 (1) 26 weeks	exe:24% sita:10% NT	Not applicable:
Vomiting	342 (1) 26 weeks	exe:11% sita:2%	Not applicable
Severe hypoglycaemia	342 (1) 26 weeks	No events	Not applicable:

Table 118

In this double blind RCT, 514 patients with type 2 diabetes, inadequately controlled by metformin, were randomized to exenatide 2 mg once weekly (n=170), sitagliptin 100 mg once daily (n=172) or to pioglitazone 45 mg once daily (n=172) for 26 weeks. The mean age was 52, mean duration of diabetes 6 years., mean baseline HbA1c was 8.5%,. and mean BMI was 32 kg/m^2. It was not reported how many participants had had a previous myocardial infarction. Patients with mild renal

impairment were allowed in the study, but it is unclear how many of these patients were actually included.

The drop-out throughout the study was large in the exenatide group (21%) and unequal to the sitagliptin group (13%). This limits our confidence in the estimate of the between-group differences.

In patients who were inadequately controlled on metformin, at 26 weeks, the addition of exenatide once weekly resulted in a statistically significant decrease of HbA1c compared to the addition of sitagliptin .

GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on metformin, at 26 weeks, there was a statistically significant difference in weight change with the addition of exenatide once weekly compared to the addition of sitagliptin.
There was more weight loss with exenatide once weekly than with sitagliptin.

GRADE: MODERATE quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 6% with exenatide once weekly and 3% with sitagliptin.
GRADE: not applicable

Rates of diarrhea were 18% with exenatide once weekly and 10% with sitagliptin.
Rates of nausea were 24% with exenatide once weekly and 10% with sitagliptin.
Rates of vomiting were 11% with exenatide once weekly and 2% with sitagliptin.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

7.3 Combination therapy with OAD

7.3.1 Exenatide twice daily +/- OAD versus exenatide once weekly +/- OAD

See 6.7.1.1.

7.3.2 Exenatide once weekly + OAD versus liraglutide once daily + OAD

7.3.2.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref: Buse 2013(58) DURATION-6 Design: RCT (OL) (PG) Duration of follow-up: 26 weeks	n: 912 Mean age: 57 y Prior/current treatment: metformin, SU, metformin plus SU, or metformin plus pioglitazone Mean DMII duration: 8.5y Mean baseline HbA1c: 8.5% Mean BMI: 32.3 Previous CV event: NR Renal impairment: excluded	Exenatide 2 mg once weekly vs Liraglutide 1.8 mg/day in addition to this background treatment: +OAD (metformin, SU, metformin + SU, metformin + pio, metformin + SU + pio, pio) <u>Hyperglycaemia</u>	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: no FOLLOW-UP: <u>Study completers</u>: 87% <u>Discontinued treatment</u>: Exe: 13% Lira: 13% Reason described: yes <u>Uptitration of study medication</u>:
			Change in HbA1c from baseline (PO)	Exe: -1.28% (-1.38 to -1.18) Lira: -1.48% (-1.58 to -1.38) **Exe vs lira: 0.21% (0.08 to 0.33); p=0.02 => SS, more decrease with lira** *Exe not non-inferior to lira*	
			Body weight change from baseline	Exe: -2.68 (-3.03 to -2.32) Lira: -3.57 (-3.94 to -3.21) **Exe vs lira: 0.90 (0.39 to 1.40) => SS, more decrease with lira**	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP Exe: -2.48 (-3.58 to -1.37) Lira: -3.45 (-4.57 to -2.33) Exe vs lira: 0.97 (-0.53 to 2.47)=> NS DBP	

	Inclusion • ≥18 y • HbA1c 7.1%-11% • BMI ≤45 • Stable bodyweight for at least 3 months Exclusion • Active cardiac disease within 3 months • Inflammatory bowel disease or other severe gastrointestinal disease • Medullary carcinoma • Family history of MEN-2 syndrome • Liver or renal disease • Creatinine clearance of <60 mL/min • Active or untreated malignancy • Acute or chronic pancreatitis • Haemoglobinopathy	uptitration protocol: No protocol described Hyperglycaemia rescue protocol: No protocol described Stratification: • With or without SU • By screening HbA1c • By country		Exe: -0.49 (-1.21 to 0.22) Lira: -0.51 (-1.23 to 0.22) Exe vs lira: 0.01 (-0.96 to 0.98)=> NS	No applicable Hyperglycaemic rescue: *withdrawal* Exe: 2% Lira: <1% Statistical method for drop out/missing data: MMRM Data handling for rescued patients: MMRM ITT: defined as all randomised patients who received at least one dose of study drug. SELECTIVE REPORTING: yes, incomplete reporting of safety endpoints Other important methodological remarks : • Uptitration liraglutide from 0.6 mg to 1.2 mg to 1.8 mg in first three weeks of study; patients not tolerating 1.8 mg by week 4 were withdrawn
			Safety		
			Death	Exe: 2/461 (0.4%) Lira: 2/450 (0.4%) NT	
			Cardiovascular adverse events	NR	
			Any adverse events	Exe: 61% Lira: 68% NT	
			Serious adverse events	Exe: 3% Lira: 2% NT	
			Adverse event leading to withdrawal	Exe: 3% Lira: 6% NT	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	Exe: 6% Lira: 13% NT	
			Nausea	Exe: 9% Lira: 21% NT	

	• Haemolytic or chronic anaemia • ≥2 episodes of major hypoglycaemia within 6 months • Use of insulin, α-glucosidase inhibitors, meglinitides, DPP-4 inhibitors, GLP-1RA, or rosiglitazone.		**Vomiting**	Exe: 4% Lira: 11% NT	• Non-inferiority if upper limit of 95%CI was less than 0.25% • In this case we tested superiority, concluding superiority of exenatide if the upper limit of the 95% CI for the treatment difference (exenatide minus liraglutide) was less than zero. Sponsor: Eli Lilly and Company, Amylin Pharmaceuticals LLC
			Severe hypoglycaemia	No cases	
			Documented symptomatic hypoglycaemia *"minor hypoglycaemia"= signs or symptoms of hypoglycaemia accompanied by fingerstick blood glucose <3 mmol/L*	Exe: 11% Lira: 9% NT	
			Injection site reactions *injection-site nodule, pruritus, or erythema*	Exe: 16% Lira: 2% NT	
			Thyroid cancer	NR	
			Pancreatitis	Exe: 1/461 Lira: 0/450 NT	

Table 119

7.3.2.2 *Summary and conclusions*

Exenatide once weekly + OAD vs liraglutide once daily +OAD			
Bibliography: Buse 2013(58) DURATION-6			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	912 (1) 26 weeks	**Exe vs lira** **Treatment difference:** **0.21% (95%CI 0.08 to 0.33); p=0.02** **=> SS in favour of liraglutide** *Exenatide not non-inferior to liraglutide*	⊕⊕⊖⊖ **LOW** Study quality: 1 open label Consistency: NA Directness: -1 different background treatments Imprecision: ok
Body weight change from baseline	912 (1) 26 weeks	**Exe vs lira** **Treatment difference:** **0.90 (95%CI 0.39 to 1.40)** **=> SS in favour of liraglutide**	⊕⊕⊖⊖ **LOW** Study quality: -1 open label Consistency: NA Directness: -1 different background treatments Imprecision: ok
Adverse events leading to withdrawal	912 (1) 26 weeks	Exe: 3% Lira: 6% NT	Not applicable
Diarrhea	912 (1) 26 weeks	Exe: 6% Lira: 13% NT	Not applicable
Nausea	912 (1) 26 weeks	Exe: 9% Lira: 21% NT	Not applicable
Vomiting	912 (1) 26 weeks	Exe: 4% Lira: 11% NT	Not applicable
Severe hypoglycaemia	912 (1) 26 weeks	No events	Not applicable

Table 120

In this open-label RCT, 912 patients with type 2 diabetes, inadequately controlled by OAD (monotherapy or combinations of metformin, SU, pioglitazone) were randomized to exenatide 2 mg once weekly or liraglutide 1.8 mg/day for 26 weeks. The mean age was 57, mean duration of diabetes 8.5 years, mean baseline HbA1c was 8.5% and mean BMI was 32 kg/m^2. It was not reported how many participants had had a previous myocardial infarction. Patients with renal impairment were excluded from the study.

The interpretation of these results is limited by the inclusion of patients with any oral antidiabetic therapy. Based on these results, it is difficult to make statements about the combination of a glp-1 receptor agonist with a specific oral antidiabetic agent.

In patients who were inadequately controlled on oral antidiabetics, at 26 weeks, the addition of liraglutide 1.8 mg/day resulted in a statistically significant decrease of HbA1c compared to the addition of exenatide 2 mg once weekly.

GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on oral antidiabetics, at 26 weeks, there was a statistically significant difference in weight change with the addition of exenatide once weekly compared to the addition of liraglutide.
There was more weight loss with liraglutide than with exenatide once weekly.

GRADE: MODERATE quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 3% with exenatide once weekly and 6% with liraglutide.
GRADE: not applicable

Rates of diarrhea were 6% with exenatide once weekly and 13% with liraglutide.
Rates of nausea were 9% with exenatide once weekly and 21% with liraglutide.
Rates of vomiting were 4% with exenatide once weekly and 11% with liraglutide.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

7.3.3 Exenatide once weekly + metformin +/- SU versus insulin detemir + metformin +/- SU

7.3.3.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Davies 2013(59) Design: RCT (OL) (PG) Duration of follow-up: 26 weeks	n: 216 Mean age: 59 y Prior/current treatment: metformin +/- SU Mean DMII duration: 7.5y Mean baseline HbA1c: 8.4% Mean BMI: 34 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> • ≥18 y • Type 2 diabetes • HbA1c 7.1 to 10% • BMI 25-45 • Stable weight • Using a stable dose of metformin	Exenatide 2 mg once weekly vs insulin detemir (once or twice daily, titrated to FPG ≤5.5 mmol/L) in addition to this background treatment: metformin +/- SU <u>Hyperglycaemia uptitration protocol:</u> Not applicable <u>Hyperglycaemia rescue protocol</u>**:**	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: no FOLLOW-UP: <u>Study completers</u>: 88% <u>Discontinued treatment</u>: Exenatide: 17% Insulin: 6% Reason described: yes <u>Uptitration of study medication</u>: Not applicable <u>Hyperglycaemic rescue</u>: Exenatide: 1% Insulin: 1%
			Change in HbA1c from baseline	Exenatide: -1.3% Insulin: -0.9% Exenatide vs insulin: **LS mean: -0.4% (-0.6 to -0.2)** **P<0.0001 => SS**	
			Body weight change from baseline	Exenatide: -2.7 kg Insulin: +0.8 kg Exenatide vs insulin: **LS mean: -3.5 kg (-4.4 to -2.6)** **P<0.0001 => SS**	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP Exenatide: -6.8 mmHg Insulin: -2.4 mmHg **Exenatide vs insulin:** **LS mean: -4.4 mmHg (-7.9 to -1.0)** **P=0.013 => SS** DBP Exenatide: -0.4 mmHg Insulin: -0.3 mmHg Exenatide vs insulin: LS mean: -0.1 mmHg(-2.4 to 2.2)	
			Safety		

	≥1000 mg/day with or without SU <u>Exclusion</u> • Women of childbearing potential • Clinically significant condition that could preclude safe participation • More than three major hypoglycemic episodes in the past 6 months • Treated with a drug that promotes weight loss in last 3 months	exclusion <u>Stratification::</u>	**Death**	No events	<u>Statistical method for drop out/missing data</u>: LOCF <u>Data handling for rescued patients</u>: exclusion, LOCF <u>ITT</u>: defined as all randomized patients who received at least one dose of study drug SELECTIVE REPORTING: yes/no (describe if yes) Other important methodological remarks • Oral metformin therapy was continued unchanged • SU dosages were reduced by 50% at initiation Sponsor: Amylin Pharmaceuticals and Eli Lilly
			Cardiovascular adverse events	NR	
			Any adverse events	Exenatide: 93% Insulin:82% NT	
			Serious adverse events	Exenatide: 5% Insulin: 6% NT	
			Adverse event leading to withdrawal	Exenatide: 11% Insulin: 5% NT	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	Exenatide: 17% Insulin:11% NT	
			Nausea	Exenatide: 18% Insulin: 2% NT	
			Vomiting	Exenatide: 14% Insulin: 9% NT	
			Severe hypoglycaemia	No events	
			Documented symptomatic hypoglycaemia *Minor hypoglycemia: symptoms of hypoglycemia, self-*	Exenatide: 6% Insulin: 7% NT	

			treated or resolved on their own, with documented plasma glucose <3.0 mmol/L (<54 mg/dL)		
			Injection site reactions *Injection site nodule + injection site pruritus*	Exenatide: 31% Insulin: 1%	
			Thyroid cancer	NR	
			Death	No events	

Table 121

7.3.3.2 *Summary and conclusions*

Exenatide once weekly + MET +/- SU vs **insulin detemir** + MET +/- SU			
Bibliography: Davies 2013(59)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	216 (1) 26 weeks	Exenatide vs insulin: **LS mean: -0.4% (95%CI -0.6 to -0.2)** **P<0.0001 => SS in favour of exenatide**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label Consistency: NA Directness: ok Imprecision: ok
Body weight change from baseline	216 (1) 26 weeks	Exenatide vs insulin: **LS mean: -3.5 kg (95%CI -4.4 to -2.6)** **P<0.0001 => SS in favour of exenatide**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label,) Consistency: NA Directness: ok Imprecision: ok
Adverse events leading to withdrawal	216 (1) 26 weeks	Exenatide: 11% Insulin: 5% NT	Not applicable
Diarrhea	216 (1) 26 weeks	Exenatide: 17% Insulin:11% NT	Not applicable
Nausea	216 (1) 26 weeks	Exenatide: 18% Insulin: 2% NT	Not applicable
Vomiting	216 (1) 26 weeks	Exenatide: 14% Insulin: 9% NT	Not applicable
Severe hypoglycaemia	216 (1) 26 weeks	No events	Not applicable

Table 122

In this open label RCT, 216 patients with type 2 diabetes, inadequately controlled by metformin ≥1000mg with or without sulfonylurea, were randomized to exenatide 2 mg once weekly or insulin detemir (once or twice daily, titrated to fasting plasma glucose ≤5.5 mmol/L) for 26 weeks. The mean age was 59, mean duration of diabetes 7.5y, mean baseline HbA1c was 8.4% and mean BMI was 34 kg/m^2. It was not reported how many participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

Our confidence in the estimate of the between-group differences is limited by its open label design.

In patients who were inadequately controlled on metformine +/- SU, at 26 weeks, the addition of exenatide 2 mg once weekly resulted in a statistically significant decrease of HbA1c compared to the addition of insulin detemir.

GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on metformine +/- SU, at 26 weeks, there was a statistically significant difference in weight change with the addition of exenatide 2 mg once weekly compared to the addition of insulin detemir.
The weight in the exenatide 2 mg once weekly group was decreased compared to the insulin detemir group (in which the weight had increased from baseline).
or

GRADE: MODERATE quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 11% with exenatide once weekly and 5% with insulin detemir.
GRADE: not applicable

Rates of diarrhea were 17% with exenatide once weekly and 11% with insulin detemir.
Rates of nausea were 18% with exenatide once weekly and 2% with insulin detemir.
Rates of vomiting were 14% with exenatide once weekly and 9% with insulin detemir.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

7.3.4 Exenatide once weekly + metformin +/- SU versus insulin glargine + metformin +/- SU

7.3.4.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref : Diamant 2010(60, 61) (62)DURATION-3 Design: RCT (OL) (PG) Duration of follow-up: 26 week + Extension period: analysis at 84 weeks and at 3 years	n: 456 Mean age: 58y Prior/current treatment: MET or MET+SU Mean DMII duration: 8 years Mean baseline HbA1c: 8.3% Mean BMI: 32 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> • Type 2 diabetes • ≥18 years • Suboptimum glycaemic control despite maximum tolerated doses of MET or MET+SU for 3 months or	Exenatide 2mg, once weekly vs insulin glargine (once daily, target glucose 4.0-5.5 mmol/L) in addition to this background treatment: metformin +/- SU <u>Hyperglycaemia uptitration protocol:</u> No protocol <u>Hyperglycaemia rescue protocol</u>: No protocol	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: no FOLLOW-UP: <u>Study completers</u>: At 26 weeks: 92% At 84 weeks: 76% At 3 years: 66% <u>Discontinued treatment</u>: At 26 weeks: Exenatide: 10% Ins glargine: 6% P=0.13 NS Reason described: yes At 84 weeks: Exenatide: 26% Ins glargine: 27% Reason described: yes
			Change in HbA1c from baseline (PO) 26 weeks	Exenatide: -1.5% Ins glargine: -1.3% Exenatide vs ins glargine: **Mean difference: -0.16% (-0.29 to -0.03); p=0.017 => SS**	
			84 weeks	Exenatide: -1.2% Ins glargine: -1.0% Exenatide vs ins glargine: **Mean difference: -0.18 %(-0.33 to -0.02); p=0.029 => SS**	
			3 years	Exenatide: -1.0% Ins glargine: -0.8% Exenatide vs ins glargine: **Mean difference: -0.20 %(-0.39 to -0.02); p=0.03 => SS**	
			Body weight change from baseline 26 weeks	Exenatide:-2.6 kg Ins glargine:+1.4 kg Exenatide vs ins glargine: **Mean difference: -4.0 kg (-4.6 to -3.5); p<0.0001 => SS**	
			84 weeks	Exenatide:-2.1 kg Ins glargine:+2.4 kg Exenatide vs ins glargine: **Mean difference: -4.5 kg (-5.0 to -3.9) ; p<0.001 => SS**	

	longer. • HbA1c 7.1-11% • BMI 25 -45 • Stable bodyweight <u>Exclusion</u> • More than 3 episodes of major hypoglycaemia within 6 months of screening • treatment for more than 2 weeks with insulin, thiazolidinediones, α-glucosidase inhibitors, meglitinides, exenatide twice daily, DPP-4 inhibitors, or pramlintide acetate within 3 months of screening.	<u>Stratification:</u> • Country • Oral blood-glucose lowering treatment	3 years	Exenatide:-2.5 kg Ins glargine:+2.0 kg Exenatide vs ins glargine: **Mean difference: -4.5 kg (-5.2 to -3.8) ; p<0.001 => SS**	At 3 years: Exenatide: 37% Ins glargine: 31% Reason described: yes <u>Uptitration of study medication</u>: Not applicable <u>Hyperglycaemic rescue</u>: Not applicable <u>Statistical method for drop out/missing data</u>: MRMM <u>Data handling for rescued patients</u>: Exclusion and MRMM (after 48 weeks; see other important methodological remarks) <u>ITT</u>: defined as all randomized patients who received at least one dose of study drug and had both a baseline and at least one postbaseline measurement of HbA1c SELECTIVE REPORTING: no
			Blood pressure change from baseline (SystBP/DiastBP) 26 weeks	SBP Exenatide: 3 mmHg Ins glargine:-1 mmHg Exenatide vs ins glargine: -2 mmHg (-4 to 1) => NS DBP Exenatide: -1 mmHg Ins glargine: -1 mmHg Exenatide vs ins glargine: 0 mmHg (-2 to 1) => NS	
			84 weeks	SBP Exenatide: -4mmHg Ins glargine:-1 mmHg **Exenatide vs ins glargine: -3 mmHg (-6 to -0.4); p= 0.03=> SS** DBP Exenatide: -2 mmHg Ins glargine: -1 mmHg Exenatide vs ins glargine: -0.1 mmHg (-2 to 2) => NS	
			3 years	SBP Exenatide: -2mmHg Ins glargine:+2 mmHg NT	

				DBP Exenatide: -2 mmHg Ins glargine: -2 mmHg NT	<u>Other important methodological remarks:</u> Up to 48 weeks, investigators were required to keep patients on the metformin dose at which they entered the study. After 48 weeks investigators were allowed to increase the dose of the patients' current oral blood glucose-lowering medications to their treatment regimen. Data collected after any treatment regimen changes at 48 weeks or after (other than IG titration) were excluded from the analyses. Sponsor: Amylin Pharmaceuticals and Eli Lilly
			Safety		
			Death 26 weeks 84 weeks	No events	
			Cardiovascular adverse events 26 weeks	NR	
			Any adverse events 26 weeks	Exenatide: 70% Ins glargine: 61% NT	
			84 weeks	Exenatide: 82% Ins glargine: 78% NT	
			3 years	Exenatide: 79% Ins glargine: 74% NT	
			Serious adverse events 26 weeks	Exenatide: 5% Ins glargine: 4% NT	
			84 weeks	Exenatide: 9% Ins glargine: 10% NT	
			3 years	Exenatide: 16% Ins glargine: 15% NT	
			Adverse event leading to withdrawal	Exenatide: 5% Ins glargine: 1%	

			26 weeks	NT	
			84 weeks	Exenatide: 7% Ins glargine: 2% NT	
			3 years	Exenatide: 9% Ins glargine: 2% NT	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea 26 weeks	Exenatide: 9% Ins glargine: 4% NT	
			84 weeks	Exenatide: 12% Ins glargine: 6% **P<0.05 => SS**	
			3 years	Exenatide: 14% Ins glargine: 7% NT	
			Nausea 26 weeks	Exenatide: 13% Ins glargine: 1% NT	
			84 weeks	Exenatide: 15% Ins glargine: 1% **P<0.05 => SS**	
			3 years	Exenatide: 15% Ins glargine: 2% NT	
			Vomiting 26 weeks	Exenatide: 4% Ins glargine: 1% NT	

			3 years	Exenatide: 6% Ins glargine: 3% NT	
			Severe hypoglycaemia 26 weeks 84 weeks	Exenatide: 1/233 Ins glargine: 2/223 NT	
			Documented symptomatic hypoglycaemia *Minor hypoglaecemia: any time a patient felt that they had a sign or symptom, associated with concurrent blood glucose lower than 3.0 mmol/L, self-treated* 26 weeks	Exenatide: 8% Ins glargine: 26% NT	
			84 weeks	*Patients on metformin alone* Exenatide: 8% Ins glargine: 32% **P<0.001** *Patients on metformin + SU* Exenatide: 24% Ins glargine: 54% **P<0.001**	
			Injection site reactions 26 weeks	Exenatide: 13% Ins glargine: 2% NT	
			3 years	Exenatide: 13% Ins glargine: 2%	

				NT	
			Thyroid cancer	NR	
			Pancreatitis 26 weeks	Exenatide: 1/233 Ins glargine: 0/223 NT	
			3 years	Exenatide: 2/233 Ins glargine: 1/223 NT	

Table 123

7.3.4.2 *Summary and conclusions*

Exenatide once weekly + MET +/- SU vs **insulin glargine** + MET +/- SU			
Bibliography: Diamant 2010(60-62)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	456 (1) 26 weeks 84 weeks 3 years	Exenatide vs ins glargine: **<u>At 26 weeks</u>** **Mean difference: -0.16% (95%CI -0.29 to -0.03); p=0.017 => SS in favour of exenatide** **<u>At 84 weeks</u>** **Mean difference: -0.18 % (95%CI -0.33 to -0.02); p=0.029 => SS in favour of exenatide** **<u>At 3 years</u>** **Mean difference: -0.20 % (95%CI -0.39 to -0.02); p=0.03 => SS in favour of exenatide**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label Consistency: NA Directness: ok Imprecision: ok ⊕⊕⊖⊖ **LOW** Study quality: -2, open label, dropout 24% Consistency: NA Directness: ok Imprecision: ok ⊕⊕⊖⊖ **LOW** Study quality: -2, open label, dropout 34% Consistency: NA Directness: ok Imprecision: ok
Body weight change from baseline	456 (1) 26 weeks 84 weeks 3 years	Exenatide vs ins glargine: **<u>At 26 weeks</u>** **Mean difference: -4.0 kg (95%CI -4.6 to -3.5); p<0.0001 => SS in favour of exenatide** **<u>At 84 weeks</u>** **Mean difference: -4.5 kg (95%CI -5.0 to -3.9) ; p<0.001 => SS in favour of exenatide** **<u>At 3 years</u>** **Mean difference: -4.5 kg (95%CI -5.2 to -3.8) ;**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label Consistency: NA Directness: ok Imprecision: ok ⊕⊕⊖⊖ **LOW** Study quality: -2, open label, dropout 24% Consistency: NA Directness: ok Imprecision: ok ⊕⊕⊖⊖ **LOW** Study quality: -2, open label, dropout 34%

		p<0.001 => SS in favour of exenatide	Consistency: NA Directness: ok Imprecision: ok
Adverse events leading to withdrawal	456 (1) 26 weeks 84 weeks 3 years	<u>At 26 weeks</u> Exenatide: 5% Ins glargine: 1% NT	Not applicable
		<u>At 84 weeks</u> Exenatide: 7% Ins glargine: 2% NT	Not applicable
		<u>At 3 years</u> Exenatide: 9% Ins glargine: 2% NT	Not applicable
Diarrhea	456 (1) 26 weeks 84 weeks 3 years	<u>At 26 weeks</u> Exenatide: 9% Ins glargine: 4% NT	Not applicable
		<u>At 84 weeks</u> Exenatide: 12% Ins glargine: 6% **P<0.05 => SS in favour of insulin glargine**	⊕⊕⊖⊖ **LOW** Study quality: -2, open label, dropout 24% Consistency: NA Directness: ok Imprecision: ok
		<u>At 3 years</u> Exenatide: 14% Ins glargine: 7% NT	Not applicable
Nausea	456 (1) 26 weeks 84 weeks 3 years	<u>At 26 weeks</u> Exenatide: 13% Ins glargine: 1% NT	Not applicable
		<u>At 84 weeks</u> Exenatide: 15% Ins glargine: 1% **P<0.05 => SS in favour of insulin glargine**	⊕⊕⊖⊖ **LOW** Study quality: -2, open label, dropout 24% Consistency: NA Directness: ok Imprecision: ok
		<u>At 3 years</u> Exenatide: 15% Ins glargine: 2% NT	Not applicable
Vomiting	456 (1)	<u>At 26 weeks</u> Exenatide: 4%	Not applicable

	26 weeks 3 years	Ins glargine: 1% NT <u>At 3 years</u> Exenatide: 6% Ins glargine: 3% NT	Not applicable
Severe hypoglycaemia	456 (1) 26 weeks 84 weeks	<u>At 26 weeks</u> Exenatide: 1/233 Ins glargine: 2/223 NT <u>At 84 weeks</u> No new events	Not applicable Not applicable

Table 124

In this open label RCT, 456 patients with type 2 diabetes, inadequately controlled by maximum tolerated doses of metformin with or without sulfonylurea, were randomized to exenatide 2 mg once weekly or insulin glargine (once daily, target glucose 4.0-5.5 mmol/L) for 26 weeks. After 26 weeks, participants could enter an exension period with analysis at 84 weeks and 3 years.
The mean age was 58, mean duration of diabetes 8 years., mean baseline HbA1c was 8.3% and mean BMI was 32 kg/m^2. It was not reported how many participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

Our confidence in the estimate of the between-group differences is limited by its open-label design.

There was a large drop-out throughout the extension period (24% by week 84 and 34% at 3 years). This further limits our confidence in the estimate of the between-group differences.

In patients who were inadequately controlled on metformin with or without sulfonylurea, at 26 weeks, the addition of exenatide once weekly resulted in a statistically significant decrease of HbA1c compared to the addition of insulin glargine.

GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on metformin with or without sulfonylurea, at 84 weeks, the addition of exenatide once weekly resulted in a statistically significant decrease of HbA1c compared to the addition of insulin glargine.

GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin with or without sulfonylurea, at 3 years, the addition of exenatide once weekly resulted in a statistically significant decrease of HbA1c compared to the addition of insulin glargine.

GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin with or without sulfonylurea, at 26 weeks, there was a statistically significant difference in weight change with the addition of exenatide once weekly compared to the addition of insulin glargine.
The weight in the exenatide once weekly group was decreased compared to the insulin glargine group (in which the weight had increased from baseline).

GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on metformin with or without sulfonylurea, at 84 weeks, there was a statistically significant difference in weight change with the addition of exenatide once weekly compared to the addition of insulin glargine.
The weight in the exenatide once weekly group was decreased compared to the insulin glargine group (in which the weight had increased from baseline).

GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin with or without sulfonylurea, at 3 years, there was a statistically significant difference in weight change with the addition of exenatide once weekly compared to the addition of insulin glargine.
The weight in the exenatide once weekly group was decreased compared to the insulin glargine group (in which the weight had increased from baseline).

GRADE: LOW quality of evidence

Withdrawal from the study due to adverse events at 26 weeks was seen in 5% with exenatide once weekly and 1% with insulin glargine.
GRADE: not applicable

Withdrawal from the study due to adverse events at 84 weeks was seen in 7% with exenatide once weekly and 2% with insulin glargine.
GRADE: not applicable

Withdrawal from the study due to adverse events at 3 years was seen in 9% with exenatide once weekly and 2% with insulin glargine.
GRADE: not applicable

Rates of diarrhea at 26 weeks were 9% with exenatide once weekly and 4% with insulin glargine.
Rates of nausea at 26 weeks were 13% with exenatide once weekly and 1% with insulin glargine.

Rates of vomiting at 26 weeks were 4% with exenatide once weekly and 1% with insulin glargine.
GRADE: not applicable

Rates of diarrhea at 84 weeks were 12% with exenatide once weekly and 6% with insulin glargine. The difference was statistically significant.
Rates of nausea at 84 weeks were 15% with exenatide once weekly and 1% with insulin glargine. The difference was statistically significant.
GRADE: LOW quality of evidence

Rates of diarrhea at 3 years were 14% with exenatide once weekly and 7% with insulin glargine.
Rates of nausea at 3 years were 15% with exenatide once weekly and 2% with insulin glargine.
Rates of vomiting at 3 years were 6% with exenatide once weekly and 3% with insulin glargine.
GRADE: not applicable

Severe hypoglycemia at 26 weeks occurred in 1/233 with exenatide once weekly and 2/223 with insulin glargine. There were no new events at 84 weeks.
GRADE: not applicable

7.4 Exenatide once weekly: other endpoints from the RCTs

7.4.1 Blood pressure

Blood pressure change from baseline was reported in all of trials that were eligible for this review. Four of the trials performed statistical tests for this outcome. In 3 trials, there was a statistically significant decrease in systolic blood pressure from baseline with exenatide once weekly, compared to the comparator (sitagliptin (N=1), insulin glargine (N=1), and insulin detemir (N=1). Treatment differences were small (≤4.4 mmHg).

There was no statistically significant difference of diastolic blood pressure change from baseline between liraglutide and comparator in any trial.

The level of evidence is LOW because of incomplete reporting.

7.4.2 Injection site reactions

Injection site reactions (ISR) were reported in all of the trials that were eligible for this review. None performed statistical tests for this outcome:

Injection site reactions were reported in 5% to 31% of patients on liraglutide compared to 1% to 10% of patients on a comparator.

The definition of what was considered to be an injection site reaction was not always specified.

7.4.3 Cardiovascular adverse events (including heart failure)

To date, there are no results from trials that are designed to evaluate the cardiovascular safety of exenatide once weekly.

Cardiovascular adverse events were not reported in most of the trials that were eligible for this review. There was no independent adjudication for cardiovascular events in the two trials that did. Statistical tests were not performed and would be of little value due to the relatively short duration of the trials and the low event rate.

7.4.4 Pancreatitis and thyroid cancer

Because of the low event rate of pancreatitis and thyroid cancer, these outcomes will be discussed in the chapter ‘rare safety outcomes’.

8 Liraglutide– evidence tables and conclusions

8.1 Monotherapy

8.1.1 Liraglutide versus glimepiride

8.1.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Garber 2009 (63);(64)LEAD-3 Mono Design: RCT, DB, PG and open-label extension Duration of follow-up: 52 weeks + additional 52 weeks of open-label extension	n:746 Mean age: 53 y Prior/current treatment: diet and exercise and/or oral antidiabetic monotherapy, up to half the highest dose (incl.: sulphonylureas, meglitinides, aminoacids derivatives, biguanides, α-glucosidase inhibitors, thiazolidinediones)	Liraglutide (1.2 mg/day) vs liraglutide (1.8 mg/day) vs glimepiride (8 mg/day) Previous pharmacological treatment was discontinued at randomisation	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: unclear FOLLOW-UP: <u>Study completers at 52 weeks</u>: 65% <u>Discontinued treatment at week 52</u>: 35% lira 1.2: 89/251 (35%)
			Change in HbA1c from baseline at week 52 (PO)	Lira 1.2 mg: -0.84% (SD 1.23) Lira 1.8 mg: -1.14% (SD 1.24) Glim: -0.51% (SD 1.20) Lira 1.2 mg vs glim: -0.33% (-0.53 to -0.13, p=0.0014) **SS in favour of lira 1.2 mg** Lira 1.8 mg vs glim: -0.62%(-0.83 to -0.42 p<0.0001) **SS in favour of lira 1.8 mg** Lira 1.8 mg vs lira 1.2 mg: -0.29% (-0.50 to -0.09 p=0.0046) **SS in favour of lira 1.8 mg**	
			at week 104	*Lira 1.2 mg: -0.6%* *Lira 1.8 mg: -0.9%* *Glim: -0.3%*	

	Mean DMII duration: 5.4y Mean baseline HbA1c: 8.2% Mean BMI: 32.8- 33.2 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> Aged 18–80 years, had body-mass index of 45 kg/m² or less, and were diagnosed with type 2 diabetes mellitus. Eligible patients had been treated with diet and exercise or up to half the highest dose of oral antidiabetic drug monotherapy. Patients had a screening HbA1c value of 7–11% if treated with diet and exercise	<u>Hyperglycaemia uptitration protocol:</u> No protocol <u>Hyperglycaemia rescue protocol</u>**:** Participants with three consecutive FPG values >240 mg/dl after week 8 and 220 mg/dl after week 28, or who did not achieve adequate glycaemic control in the opinion of the investigator, were withdrawn for "ineffective therapy". <u>Stratification:</u>		*Lira 1.2 mg vs glim: -0.31% (-0.54 to -0.08, p=0.0076)* ***SS in favour of lira 1.2 mg*** *Lira 1.8 mg vs glim: -0.60%(-0.83 to -0.38 p<0.0001)* ***SS in favour of lira 1.8 mg***	Lira 1.8: 73/246 (30%) Glim: 96/248 (39%) Reason described: yes <u>Discontinued treatment during extension</u>: 16% lira 1.2: 39/251 (16%) Lira 1.8: 40/246 (16%) Glim: 40/248 (16%) Reason described: yes <u>Statistical method for drop out/missing data</u>: LOCF, no sensitivity analyses <u>Data handling for rescued patients</u>: excluded, LOCF <u>ITT</u>: defined as participants exposed to at least one dose. SELECTIVE REPORTING: yes, incomplete data reporting <u>Other important methodological</u>
			Body weight change from baseline at week 52	Participants who had nausea >7 days Lira 1.2 mg: -3.24 kg Lira 1.8 mg: -3.39 kg Glim: -1.43 kg Participants with nausea up to 7 days Lira 1.2 mg: -1.85 kg Lira 1.8 mg: -2.26 kg Glim: + 1.22 kg Figures for whole group not reported; **lira 1.2 vs glim: p=0.001=> SS** **Lira 1.8 vs glim: p= 0.001=>SS** Lira 1.2 vs lira 1.8: p=0.2584=> NS	
			at week 104	*Lira 1.2 mg: -1.89 kg* *Lira 1.8 mg: -2.70 kg* *Glim: +0.95 kg* *Lira 1.2 mg vs glim: -2.84% (-3.63 to -2.06, p=0.0001)* ***SS in favour of lira 1.2 mg*** *Lira 1.8 mg vs glim: -3.65%(-4.44 to -*	

	or 7–10% with oral antidiabetic monotherapy. <u>Exclusion</u> insulin treatment during the previous 3 months (except short-term treatment for intercurrent illness), treatment with systemic corticosteriods, hypoglycaemia unawareness or recurrent severe hypoglycaemia, and impaired liver function (aspartate aminotransferase or alanine aminotransferase concentrations ≥2·5 times upper normal range).	by baseline diabetes treatment (diet and exercise vs oral antidiabetic monotherapy)		*2.86; p<0.0001)* ***SS in favour of lira 1.8 mg***	<u>remarks</u> Hierarchical tests for non-inferiority and superiority were done but results of non-inferiority testing were not reported Sponsor: Novo Nordisk
			Blood pressure change from baseline at week 52 (SystBP/DiastBP)	SBP Lira 1.2 mg: -2.1 (SD 14.2) Lira 1.8 mg: -3.6 (SD 14.1) Glim -0.7 (SD 13.7) Lira 1.2 mg vs glim: p =0.2912 => NS **Lira 1.8 mg vs glim: p=0.0118 => SS in favour of lira 1.8** DBP "fell slightly but not significantly for all treatment groups"; exact figures not reported NT	
			at week 104	*SBP* *Lira 1.2 mg: -1.35 mmHg* *Lira 1.8 mg: -2.37 mmHg* *Glim -0.49 mmHg* *Lira 1.2 mg vs glim: -0.86 (-3.18 to 1.46, p=0.4657)=> NS* *Lira 1.8 mg vs glim: -1.88 (-4.21 to 0.45; p=0.1135)=> NS* *DBP* *Lira 1.2 mg: -0.58 mmHg*	

				Lira 1.8 mg: -0.81 mmHg *Glim -0.44 mmHg* *Lira 1.2 mg vs glim: -0.14 (-1.50 to 1.23, p=0.8429)=> NS* *Lira 1.8 mg vs glim: -0.37 (-1.74 to 1.00; p=0. 5965)=> NS*	
			Safety		
			Death at week 52	Lira 1.2 mg: 0 Lira 1.8 mg: 0 Glim: 1 (classified as not related to treatment) NT	
			at week 104	*Lira 1.2 mg: 0* *Lira 1.8 mg: 1* *Glim: 1 (classified as not related to treatment)* *NT*	
			Cardiovascular adverse events	NR	
			Any adverse events at 52 weeks	NR	
			at week 104	*Lira 1.2 mg: 213/251 (85%)* *Lira 1.8 mg: 207/246 (84%)* *Glim: 194/248 (78%)*	

				NT	
			Serious adverse events at week 52	Lira 1.2 mg: 18 Lira 1.8 mg: 9 Glim: 17 NT	
			at week 104	*Lira 1.2 mg: 28* *Lira 1.8 mg: 30* *Glim: 32* *NT*	
			Adverse event leading to withdrawal at week 52	Lira 1.2 mg: 25/251 (10%) Lira 1.8 mg: 18/246 (7.3%) Glim: 15/248 (6.0%) NT	
			at week 104	*NR*	
			Any gastro-intestinal adverse event at week 52	Lira 1.2 mg: 122/251 (49%) Lira 1.8 mg: 126/246 (51%) Glim: 64/248 (26%) NT	
			at week 104	*Lira 1.2 mg: 135/251 (54%)* *Lira 1.8 mg: 130/246 (53%)* *Glim: 70/248 (28%)* *NT*	
			Diarrhoea at week 52	Lira 1.2 mg: 39/251(15.5%) Lira 1.8 mg: 46/246 (18.7%) Glim:22/248 (8.9%)	

				Lira 1.2 mg vs glim; p =0.0283=> SS in favour of glim **Lira 1.8 mg vs glim; p =0.0017=> SS in favour of glim**	
			at week 104	*Lira 1.2 mg: 44/251 (18%)* *Lira 1.8 mg:48/246 (20%)* *Glim: 23/248 (9%)* *NT*	
			Nausea at week 52	Lira 1.2 mg: 69/251 (27.5%) Lira 1.8 mg: 72/246 (29.3%) Glim: 21/248 (8.5%) **Lira 1.2 mg vs glim; p <0.0001=> SS in favour of glim** **Lira 1.8 mg vs glim; p <0.0001=> SS in favour of glim**	
			at week 104	*Lira 1.2 mg: 72/251 (29%)* *Lira 1.8 mg: 75/246 (31%)* *Glim: 21/248 (9%)* *NT*	
			Vomiting at week 52	Lira 1.2 mg: 31/251 (9.3%) Lira 1.8 mg: 23/246 (12.4%) Glim: 9/248 (3.6%) **Lira 1.2 mg vs glim; p <0.0001=> SS in favour of glim** **Lira 1.8 mg vs glim; p <0.0001=> SS in**	

				favour of glim
			at week 104	*Lira 1.2 mg: 33/251 (10%)* *Lira 1.8 mg: 25/246 (13%)* *Glim: 10/248 (4%)* *NT*
			Severe hypoglycaemia at week 52	No events
			at week 104	*Lira 1.2 mg: 0/251* *Lira 1.8 mg: 1/246 ("occured after regular insulin was infused")* *Glim: 0/248* *NT*
			Minor hypoglycaemia at week 52 *(defined as measured plasma glucose <3.1 mmol/L, self-treated)*	Lira 1.2 mg: 12% Lira 1.8 mg: 8% Glim: 24% **Lira 1.2 mg vs glim; p <0.0001=> SS in favour of lira 1.2** **Lira 1.8 mg vs glim; p <0.0001 => SS in favour of lira 1.8**
			at week 104	*Lira 1.2 mg: 12%* *Lira 1.8 mg: 10%* *Glim: 26%* ***Lira 1.2 mg vs glim; p <0.0001=> SS in favour of lira 1.2*** ***Lira 1.8 mg vs glim; p <0.0001 => SS in favour of lira 1.8***

			Injection site reactions	NR	
			Thyroid cancer	NR	
			Pancreatitis at week 52	Lira 1.2 mg: 1 Lira 1.8 mg: 1 Glim: 0 NT	
			at week 104	*NR*	

Table 125

8.1.1.2 *Summary and conclusions*

Liraglutide versus glimepiride in monotherapy			
Bibliography: Garber 2009(63, 64)LEAD-3 Mono			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	746 (1) 52 weeks 104 weeks	52 weeks: Treatment difference: Lira 1.2 mg vs glim: -0.33% (95%CI -0.53 to -0.13, p=0.0014) **SS in favour of lira 1.2 mg** Lira 1.8 mg vs glim: -0.62%(95%CI -0.83 to -0.42 p<0.0001) **SS in favour of lira 1.8 mg** 104 weeks: Treatment difference: Lira 1.2 mg vs glim: -0.31% (95%CI -0.54 to -0.08, p=0.0076) **SS in favour of lira 1.2 mg** Lira 1.8 mg vs glim: -0.60%95%CI (-0.83 to -0.38 p<0.0001) **SS in favour of lira 1.8 mg**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 >20% discontinuation and LOCF Consistency: NA Directness: ok Imprecision: ok ⊕⊕⊖⊖ **LOW** Study quality: -2 >40% discontinuation and LOCF, open-label Consistency: NA Directness: ok Imprecision: ok
Body weight change from baseline	746 (1) 52 weeks 104 weeks	52 weeks: Treatment difference: **lira 1.2 vs glim: p=0.001=> SS infavour of lira 1.2 mg** **Lira 1.8 vs glim: p= 0.001=>SS in favour of lira 1.8 mg** 104 weeks: Treatment difference: Lira 1.2 mg vs glim: -2.84% (95%CI -3.63 to -2.06, p=0.0001) **SS in favour of lira 1.2 mg** Lira 1.8 mg vs glim: -3.65%(95%CI -4.44 to -2.86; p<0.0001)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 >20% discontinuation and LOCF Consistency: NA Directness: ok Imprecision: ok ⊕⊕⊖⊖ **LOW** Study quality: -2 >40% discontinuation and LOCF, open-label Consistency: NA Directness: ok Imprecision: ok

		SS in favour of lira 1.8 mg	
Adverse events leading to withdrawal	746 (1) 52 weeks 104 weeks	<u>52 weeks</u> Lira 1.2 mg: 25/251 (10%) Lira 1.8 mg: 18/246 (7.3%) Glim: 15/248 (6.0%) NT	Not applicable
Diarrhea	746 (1) 52 weeks 104 weeks	<u>52 weeks</u> Lira 1.2 mg: 39/251(15.5%) Lira 1.8 mg: 46/246 (18.7%) Glim:22/248 (8.9%) **Lira 1.2 mg vs glim; p =0.0283=> SS in favour of glim** **Lira 1.8 mg vs glim; p =0.0017=> SS in favour of glim** <u>104 weeks</u> Lira 1.2 mg: 44/251 (18%) Lira 1.8 mg:48/246 (20%) Glim: 23/248 (9%) NT	⊕⊕⊕⊖ **MODERATE** Study quality: -1 >20% discontinuation and LOCF Consistency: NA Directness: ok Imprecision: ok Not applicable
Nausea	746 (1) 52 weeks 104 weeks	<u>52 weeks</u> Lira 1.2 mg: 69/251 (27.5%) Lira 1.8 mg: 72/246 (29.3%) Glim: 21/248 (8.5%) **Lira 1.2 mg vs glim; p <0.0001=> SS in favour of glim** **Lira 1.8 mg vs glim; p <0.0001=> SS in favour of glim** <u>104 weeks</u> Lira 1.2 mg: 72/251 (29%) Lira 1.8 mg: 75/246 (31%) Glim: 21/248 (9%) NT	⊕⊕⊕⊖ **MODERATE** Study quality: -1 >20% discontinuation and LOCF Consistency: NA Directness: ok Imprecision: ok Not applicable
Vomiting	746 (1) 52 weeks 104 weeks	<u>52 weeks</u> Lira 1.2 mg: 31/251 (9.3%) Lira 1.8 mg: 23/246 (12.4%) Glim: 9/248 (3.6%) **Lira 1.2 mg vs glim; p**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 >20% discontinuation and LOCF Consistency: NA Directness: ok Imprecision: ok

		<0.0001=> SS in favour of glim **Lira 1.8 mg vs glim; p <0.0001=> SS in favour of glim** <u>104 weeks</u> Lira 1.2 mg: 33/251 (13%) Lira 1.8 mg: 25/246 (10%) Glim: 10/248 (4%) NT	Not applicable
Severe hypoglycaemia	746 (1) 52 weeks 104 weeks	<u>52 weeks</u> No events <u>104 weeks</u> Lira 1.2 mg: 0/251 Lira 1.8 mg: 1/246 Glim: 0/248 NT	Not applicable Not applicable

Table 126

In this double blind RCT with open-label extension, 746 patients with type 2 diabetes, inadequately controlled by diet and exercise and/or oral antidiabetic monotherapy, were randomized to liraglutide (1.2 mg or 1.8 mg/day) or glimepiride for 8 weeks. Previous oral antidiabetic medication was discontinued at randomization. The mean age was 53, mean duration of diabetes 5 years, mean baseline HbA1c was 8.2% and mean BMI was 33 kg/m^2. It was not reported how many participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

There was a large drop-out throughout the study (35 % by week 52, and 51% by week 104). This limits our confidence in the estimate of the between-group differences.

In patients who were inadequately controlled on diet and exercise and/or oral antidiabetic monotherapy, at 52 weeks, the addition of liraglutide (1.2 mg or 1.8 mg) resulted in a statistically significant decrease of HbA1c compared to the addition of glimepiride.

GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on diet and exercise and/or oral antidiabetic monotherapy, at 104 weeks, the addition of liraglutide (1.2 mg or 1.8 mg) resulted in a statistically significant decrease of HbA1c compared to the addition of glimepiride.

GRADE: LOW quality of evidence

In patients who were inadequately controlled on diet and exercise and/or oral antidiabetic monotherapy, at 52 weeks, there was a statistically significant difference in weight change with the addition of liraglutide (1.2 mg or 1.8 mg) compared to the addition of glimepiride.
The weight in the liraglutide group was decreased compared to the glimepiride group (in which the weight had increased from baseline).

GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on diet and exercise and/or oral antidiabetic monotherapy, at 104 weeks, there was a statistically significant difference in weight change with the addition of liraglutide (1.2 mg or 1.8 mg) compared to the addition of glimepiride.
The weight in the liraglutide group was decreased compared to the glimepiride group (in which the weight had increased from baseline).

GRADE: LOW quality of evidence

Withdrawal from the study due to adverse events at 52 weeks was seen in 10% with liraglutide 1.2 mg, in 7% with liraglutide 1.8 mg and in 6% with glimepiride.
GRADE: not applicable

At 52 weeks:
Rates of diarrhea were 16% with liraglutide 1.2 mg, 19% with liraglutide 1.8 mg , and 9%with glimepiride. The difference between liraglutide and glimepiride was statistically significant.

Rates of nausea were 28% with liraglutide 1.2 mg, 29% with liraglutide 1.8 mg , and 9%with glimepiride. The difference between liraglutide and glimepiride was statistically significant.

Rates of vomiting were 9% with liraglutide 1.2 mg, 12% with liraglutide 1.8 mg , and 4%with glimepiride. The difference between liraglutide and glimepiride was statistically significant.
GRADE: MODERATE quality of evidence

Adverse events at 104 weeks were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.
Rates of diarrhea were 18% with liraglutide 1.2 mg, 20% with liraglutide 1.8 mg , and 9%with glimepiride.
Rates of nausea were 29% with liraglutide 1.2 mg, 31% with liraglutide 1.8 mg , and 9%with glimepiride.
Rates of vomiting were 13% with liraglutide 1.2 mg, 10% with liraglutide 1.8 mg , and 4%with glimepiride.
GRADE: not applicable

There were no events of severe hypoglycemia at week 52.
There was one case of severe hypoglycemia in the liraglutide 1.8 mg group by week 104.
GRADE: not applicable

8.2 Combination therapy with metformin

8.2.1 Liraglutide + metformin versus placebo + metformin

8.2.1.1 *Clinical evidence profile: liraglutide versus glimepiride, placebo (all + metformin)*

Study details	n/Population	Comparison	Outcomes			Methodological
Ref Nauck 2009 LEAD-II study(65);(66) Design: RCT (DB) (PG) Duration of follow-up: 26 weeks + 18 months open-label extension	n: 1091 Mean age: 57y Prior/current treatment: Monotherapy: 36% Combination therapy 64% Mean DMII duration: 8y Mean baseline HbA1c: 8.4% Mean BMI: 31 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> 18-80y; DMII; AbH1c 7-	Liraglutide 0.6mg or 1.2mg or 1.8mg Vs Glimepiride 4mg Vs Placebo in addition to this background treatment: metformin 1g 2x/d <u>Hyperglycaemia</u>	Efficacy (ITT population unless specified)			RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: unclear FOLLOW-UP: <u>Study completers</u>: 80.7% <u>Discontinued treatment at 26 weeks</u>: 19.3% Lira 0.6mg: 14% Lira 1.2 mg: 18% Lira 1.8mg: 21% Glim: 14% Placebo: 39% Reason described: yes
			Change in HbA1c from baseline (PO) (at 26 weeks)	Liraglutide 0.6mg: Liraglutide 1.2mg: Liraglutide 1.8mg: Glimepiride 4mg: Placebo: **Lira 0.6 vs plac: -0.8% (-1.0, -0.6)=>SS** **Lira 1.2 vs plac: -1.1% (-1.3, -0.9) =>SS** **Lira 1.8 vs plac: -1.1% (-1.3, -0.9) =>SS** **(no p-values reported)** Lira 0.6 vs glim: NR Lira 1.2 vs glim: 0.0% (-0.2, 0.2) =>NS Lira 1.8 vs glim: -0.0% (-0.2, 0.2) =>NS Liraglutide is non-inferior to glim (no p-values reported)	-0.7 (SEM 0.1) -1.0 (SEM 0.1) -1.0 (SEM 0.1) -1.0 (SEM 0.1) +0.1 (SEM 0.1)	
			at 2 years; open label extension	*Liraglutide 0.6mg:* *Liraglutide 1.2mg:* *Liraglutide 1.8mg:* *Glimepiride 4mg:* *Placebo:*	*-0.4 (SE 0.1)* *-0.6 (SE 0.1)* *-0.6 (SE 0.1)* *-0.5 (SE 0.1)* *+0.3 (SE 0.1)*	

	11% (previous OAD monotherapy >= 3 months) or 7-10% (previous OAD combination therapy >= 3 months); BMI <=40 Exclusion Use of insuline during previous 3m (except short treatment)	rescue protocol: Withdrawal criteria: metformin dose <1500 mg or >2000 mg/ day; fasting plasma glucose >13.3 mmol/L after week 8; >12.2 mmol/L after week 26; >11.1 mmol/L after week 52 Stratification: Previous use of OAD monotherapy or combination therapy		***Lira 0.6 vs plac: -0.6% (-0.9, -0.4)=>SS*** ***Lira 1.2 vs plac: -0.8% (-1.1, -0.6) => SS*** ***Lira 1.8 vs plac: -0.8% (-1.1, -0.6) => SS*** ***P<0.0001 for superiority*** *Lira 0.6 vs glim: 0.1 (-0.1; 0.3) =>NS* *Lira 1.2 vs glim: -0.1% (-0.3, 0.1) =>NS* *Lira 1.8 vs glim: -0.1% (-0.3, 0.1) =>NS* *Liraglutide is non-inferior to glim* *Lira 0.6 mg vs glim: p=0.0052 for non-inferiority* *Lira 1.2 and 1.8 mg vs glim: p<0.0001 for non-inferiority* *Lira was also non-inferior in the group of study completers*	Discontinued treatment at 2 years: 52% Lira 0.6mg: 46% Lira 1.2 mg: 43% Lira 1.8mg: 51% Glim: 54% Placebo: 75% Reason described: yes Hyperglycaemic rescue at 26 weeks: 7%
			Body weight change from baseline	Liraglutide 0.6mg: -1.8kg (SD 0.2) Liraglutide 1.2mg: -2.6kg (SD 0.2) Liraglutide 1.8mg: -2.8kg (SD 0.2) Glimepiride 4mg: +1.0kg (SD 0.2) Placebo: -1.5kg (SD 0.3) **Lira 1.2mg and 1.8mg vs plac p<=0.01 =>SS** **Lira (all doses) vs glim p<0.0001 =>SS**	Liraglutide 0.6mg: 8% Liraglutide 1.2mg: 3% Liraglutide 1.8mg: 5% Glimepiride 4mg: 4% Placebo: 24% Hyperglycaemic rescue during extension: 19% Liraglutide 0.6mg: 15% Liraglutide 1.2mg: 13% Liraglutide 1.8mg: 18% Glimepiride 4mg: 25%
			at 2 years; open label extension	*Liraglutide 0.6mg: -2.1 kg* *Liraglutide 1.2mg: -3.0 kg* *Liraglutide 1.8mg: -2.9 kg*	

				Glimepiride 4mg: *+0.70 kg* *Placebo:* *-1.8 kg* ***Lira 1.2mg and 1.8mg vs plac: p=0.0185 and p=0.0378 respectively =>SS*** ***Lira (all doses) vs glim: p<0.0001 =>SS***	Placebo: 36% <u>Statistical method for drop out/missing data</u>: Missing data imputed as the last observation carried forward
			Blood pressure change from baseline (SystBP/DiastBP) (at 26 weeks)	SBP Liraglutide 0.6mg: -0.6 mmHg Liraglutide 1.2mg: -2.8 mmHg Liraglutide 1.8mg: -2.3 mmHg Glimepiride 4mg: +0.4 mmHg Placebo: -1.8 mmHg **Lira 1.2mg vs glim: -3.2 mmHg p=0.0128 => SS** **Lira 1.8 vs glim: -2.7 mmHg p=0.0467 =>SS** Other comparisons NR DBP "did not appear to change from baseline for any groups"	<u>Data handling for rescued patients</u>: excluded from study and LOCF <u>ITT</u>: defined as subjects who were exposed to at least one dose of trial product and had one post-baseline measurement of the parameter SELECTIVE REPORTING: yes, some endpoints were incompletely reported
			at 2 years; open label extension	*SBP* Liraglutide 0.6mg: +0.2 mmHg Liraglutide 1.2mg: -2.5 mmHg Liraglutide 1.8mg: -2.0 mmHg Glimepiride 4mg: +0.3 mmHg Placebo: -0.1 mmHg	<u>Other important methodological remarks:</u> Noninferiority testing: noninferiority was concluded if the upper limit of the two-sided

				All treatments vs placebo: NS *Lira (all doses) vs glim: NS* *DBP* Liraglutide 0.6mg: +0.4 mmHg Liraglutide 1.2mg: -0.8 mmHg Liraglutide 1.8mg: -0.5 mmHg Glimepiride 4mg: -0.0 mmHg Placebo: -0.3 mmHg *All treatments vs placebo: NS* *Lira (all doses) vs glim: NS*	95%CI for the treatment difference was <0.4% (<0% for superiority (no reason was described); noninferiority testing was not reported if superiority was achieved Sponsor: Novo Nordisk
			Safety		
			Death	No deaths after randomisation	
			at 2 years; open label extension	*2 deaths in 0.6 mg liraglutide group, considered "unlikely to be related to trial drug"*	
			Cardiovascular adverse events	NR	
			Any adverse events	NR	
			Serious adverse events	NR	
			at 2 years; open label extension	*"infrequent"* *6.6-14.9%*	
			Adverse event leading to withdrawal	Liraglutide 0.6mg: 5% Liraglutide 1.2mg: 10% Liraglutide 1.8mg: 12%	

				Glimepride 4mg: 3% Placebo: 2% NT	
			at 2 years; open label extension	*Liraglutide 0.6mg: 9.1%* *Liraglutide 1.2mg: 12.9%* *Liraglutide 1.8mg: 14.5%* *Glimepride 4mg: 5.7%* *Placebo: 2.5%* *NT*	
			Any gastro-intestinal adverse event	Liraglutide 0.6mg: 35% Liraglutide 1.2mg: 40% Liraglutide 1.8mg: 44% Glimepride 4mg: 17% Placebo: 17% NT	
			at 2 years; open label extension	Liraglutide 0.6mg: 43% Liraglutide 1.2mg: 47% Liraglutide 1.8mg: 49% Glimepride 4mg: 25% Placebo: 18% NT	
			Diarrhoea	Liraglutide 0.6mg: 10% Liraglutide 1.2mg: 8% Liraglutide 1.8mg: 15% Glimepride 4mg: 4% Placebo: 4% NT	
			at 2 years; open label extension	*Liraglutide 0.6mg: 12.8%* *Liraglutide 1.2mg: 11.3%*	

				Liraglutide 1.8mg:	*16.5%*
				Glimepride 4mg:	*5.8%*
				Placebo:	*4.1%*
				NT	
			Nausea	Liraglutide 0.6mg:	11
				Liraglutide 1.2mg:	16%
				Liraglutide 1.8mg:	19%
				Glimepride 4mg:	NR
				Placebo:	NR
				NT	
			at 2 years; open label extension	*Liraglutide 0.6mg:*	*12.4%*
				Liraglutide 1.2mg:	*17.5%*
				Liraglutide 1.8mg:	*21.5%*
				Glimepride 4mg:	*4.1%*
				Placebo:	*4.1%*
				NT	
			Vomiting	Liraglutide 0.6mg:	5-7%
				Liraglutide 1.2mg:	5-7%
				Liraglutide 1.8mg:	5-7%
				Glimepride 4mg:	1%
				Placebo:	1%
				NT	
			at 2 years; open label extension	*Liraglutide 0.6mg:*	*7.9%*
				Liraglutide 1.2mg:	*7.5%*
				Liraglutide 1.8mg:	*9.9%*
				Glimepride 4mg:	*0.4%*
				Placebo:	*0.0%*
				NT	
			Severe hypoglycaemia	None	

			at 2 years; open label extension	*1 event in liraglutide 1.2mg group*
			Documented symptomatic hypoglycaemia *(based on symptoms and plasma glucose <3.1 mmol/l); self-treated)*	Liraglutide 0.6mg: ±3% Liraglutide 1.2mg: ±3% Liraglutide 1.8mg: ±3% Glimepride 4mg: 17% Placebo: ±3% **Liraglutide vs glimepiride: p<0.001 =>SS**
			at 2 years; open label extension	*Liraglutide 0.6mg: 5%* *Liraglutide 1.2mg: 4.2%* *Liraglutide 1.8mg: 4.1%* *Glimepride 4mg: 24%* *Placebo: 2.5%* ***Liraglutide vs glimepiride: p<0.001 =>SS***
			Injection site reactions	NR
			Thyroid cancer	NR
			at 2 years; open label extension	*No cases*
			Pancreatitis	Lira 1.2 mg: n=1 Glim: n=1 NT

			at 2 years; open label extension	*Lira: n=1* *Glim: n=1* *(no new cases during extension)*	

Table 127

8.2.1.2 *Summary and conclusions*

Liraglutide (0.6 mg, 1.2 mg, 1.8 mg) + MET versus placebo + MET			
Bibliography: Nauck 2009; LEAD-II study(65);(66)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	846 (1) 26 weeks 2 years	<u>At 26 weeks</u> Treatment difference: **Lira 0.6 vs plac: -0.8% (95%CI -1.0, -0.6)=>SS in favour of lira** **Lira 1.2 vs plac: -1.1% (95%CI -1.3, -0.9) =>SS in favour of lira** **Lira 1.8 vs plac: -1.1% (95%CI -1.3, -0.9) => SS in favour of lira** <u>At 2 years:.</u> Treatment difference: **Lira 0.6 vs plac: -0.6% (95%CI -0.9, -0.4)=> SS in favour of lira** **Lira 1.2 vs plac: -0.8% (95%CI -1.1, -0.6) => SS in favour of lira** **Lira 1.8 vs plac: -0.8% (95%CI -1.1, -0.6) => SS in favour of lira** **P<0.0001 for superiority**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (19.3% discontinued, LOCF) Consistency: NA Directness: ok Imprecision: ok ⊕⊕⊖⊖ **LOW** Study quality: -2 (>20% discontinued, LOCF, open label) Consistency: NA Directness: ok Imprecision: ok
Body weight change from baseline	846 (1) 26 weeks 2 years	<u>At 26 weeks</u> Treatment difference: Liraglutide 0.6mg: -1.8kg Liraglutide 1.2mg:-2.6kg Liraglutide 1.8mg:-2.8kg Placebo: -1.5kg **Lira 1.2mg and 1.8mg vs plac p<=0.01** **=> SS in favour of liraglutide** <u>At 2 years:</u> Treatment difference: Liraglutide 0.6mg: -2.1 kg Liraglutide 1.2mg:-3.0 kg	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (19.3% discontinued, LOCF) Consistency: NA Directness: ok Imprecision: ok ⊕⊕⊖⊖ **LOW** Study quality: -2 (>20% discontinued, LOCF, open label Consistency: NA Directness: ok Imprecision: ok

		Liraglutide 1.8mg:-2.9 kg Placebo: -1.8 kg **Lira 1.2mg and 1.8mg vs plac: p=0.0185 and p=0.0378 respectively** **=> SS in favour of liraglutide**		
Adverse events leading to withdrawal	846 (1) 26 weeks 2 years	<u>At 26 weeks</u> Liraglutide 0.6mg: Liraglutide 1.2mg: Liraglutide 1.8mg: Placebo: NT <u>At 2 years:</u> Liraglutide 0.6mg: Liraglutide 1.2mg: Liraglutide 1.8mg: Placebo: NT	 5% 10% 12% 2% 9.1% 12.9% 14.5% 2.5%	Not applicable Not applicable
Diarrhea	846 (1) 26 weeks 2 years	<u>At 26 weeks</u> Liraglutide 0.6mg: Liraglutide 1.2mg: Liraglutide 1.8mg: Placebo: NT <u>At 2 years:</u> Liraglutide 0.6mg: Liraglutide 1.2mg: Liraglutide 1.8mg: Placebo: NT	 10% 8% 15% 4% 12.8% 11.3% 16.5% 4.1%	Not applicable Not applicable
Nausea	846 (1) 26 weeks 2 years	<u>At 26 weeks</u> Liraglutide 0.6mg: Liraglutide 1.2mg: Liraglutide 1.8mg: Placebo: NT <u>At 2 years:</u> Liraglutide 0.6mg: Liraglutide 1.2mg: Liraglutide 1.8mg: Placebo: NT	 11% 16% 19% NR 12.4% 17.5% 21.5% 4.1%	Not applicable Not applicable
Vomiting	846 (1) 26 weeks 2 years	<u>At 26 weeks</u> Liraglutide 0.6mg: Liraglutide 1.2mg: Liraglutide 1.8mg:	 5-7% 5-7% 5-7%	Not applicable

		Placebo: NT	1%	
		<u>At 2 years:</u> Liraglutide 0.6mg: Liraglutide 1.2mg: Liraglutide 1.8mg: Placebo: NT		Not applicable
Severe hypoglycaemia	846 (1) 26 weeks 2 years	<u>At 26 weeks</u> No events <u>At 2 years:</u> 1 event in liraglutide 1.2mg group		Not applicable Not applicable

Table 128

In this double blind RCT with open-label extension, 1091 patients with type 2 diabetes, inadequately controlled by oral antidiabetic medication, were randomized to liraglutide (0.6 mg (n=242), 1.2 mg (n=241) or 1.8 mg (n=242)), glimepiride 4 mg (n=244), or placebo (n=121) for 26 weeks. All participants had a background treatment with metformin 1g 2x/day. Patients could participate in an open-label extension of an additional 18 months. The mean age was 57, mean duration of diabetes 8 years., mean baseline HbA1c was 8.4%. and mean BMI was 31 kg/m^2. It was not reported how many participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

There was a large drop-out throughout the study (19% by week 26 and 52% by year 2). This limits our confidence in the estimate of the between-group differences.

In patients who were inadequately controlled on oral antidiabetic medication at 26 weeks, the addition of liraglutide (0.6 mg, 1.2 mg, or 1.8 mg) to metformin 2000 mg/day ,resulted in a statistically significant decrease of HbA1c compared to the addition of placebo (which was increased from baseline).

GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on oral antidiabetic medication at 2 years, the addition of liraglutide (0.6 mg, 1.2 mg, or 1.8 mg) to metformin 2000 mg/day resulted in a statistically significant decrease of HbA1c compared to the addition of placebo (which was increased from baseline).

GRADE: LOW quality of evidence

In patients who were inadequately controlled on oral antidiabetic medication, at 26 weeks, there was a statistically significant difference in weight change with the addition of liraglutide (1.2 mg, or 1.8 mg) to metformin 2000 mg/day, compared to the addition of placebo.
There was more weight loss with liraglutide than with placebo.

GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on oral antidiabetic medication, at 2 years, there was a statistically significant difference in weight change with the addition of liraglutide (1.2 mg, or 1.8 mg) to metformin 2000 mg/day, compared to the addition of placebo.
There was more weight loss with liraglutide than with placebo.

GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events at 26 weeks was seen in 5% with liraglutide 0.6 mg, in 10% with liraglutide 1.2 mg, in 12% with liraglutide 1.8 mg and in 2% with placebo.
GRADE: not applicable

Withdrawal from the study due to adverse events at 2 years was seen in 9% with liraglutide 0.6 mg, in 13% with liraglutide 1.2 mg, in 15% with liraglutide 1.8 mg and in 3% with placebo.
GRADE: not applicable

Rates of diarrhea at week 26 were 10% with liraglutide 0.6 mg, 8% with liraglutide 1.2 mg, 15% with liraglutide 1.8 mg and 4% with placebo
Rates of nausea at week 26 were 11% with liraglutide 0.6 mg, 16% with liraglutide 1.2 mg, 19% with liraglutide 1.8 mg. Rates were not reported for placebo.
Rates of vomiting at week 26 were 5-7% with liraglutide 0.6 mg, 1.2 mg, and 1.8 mg and 1% with placebo
GRADE: not applicable

Rates of diarrhea at 2 years were 13% with liraglutide 0.6 mg, 11% with liraglutide 1.2 mg, 17% with liraglutide 1.8 mg and 4% with placebo
Rates of nausea at 2 years were 12% with liraglutide 0.6 mg, 18% with liraglutide 1.2 mg, 22% with liraglutide 1.8 mg and 4% with placebo.
Rates of vomiting at 2 years were 8% with liraglutide 0.6 mg, 8% with liraglutide 1.2 mg, 10% with liraglutide 1.8 mg and 0% with placebo.
GRADE: not applicable

There were no events of severe hypoglycemia at week 26.

There was one event of severe hypoglycemia in the liraglutide 1.2 mg group at 2 years.
GRADE: not applicable

8.2.2 Liraglutide + metformin versus glimepiride + metformin

8.2.2.1 *Clinical evidence profile*

See 8.2.1.1.

8.2.2.2 *Summary and conclusions*

Liraglutide (0.6 mg, 1.2 mg, 1.8 mg) + MET versus placebo + MET			
Bibliography: Nauck 2009; LEAD-II study(65);(66)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	969 (1) 26 weeks 2 years	<u>At 26 weeks</u> Treatment difference: Lira 0.6 vs glim: NR Lira 1.2 vs glim: 0.0% (95%CI -0.2, 0.2) Lira 1.8 vs glim: -0.0% (95%CI -0.2, 0.2) Liraglutide is non-inferior to glimepiride (no p-values reported) <u>At 2 years:</u> Treatment difference: Lira 0.6 vs glim: 0.1 (95%CI -0.1; 0.3); p= 0.0052 for non-inferiority Lira 1.2 vs glim: -0.1% (95%CI -0.3, 0.1); p<0.0001 for non-inferiority Lira 1.8 vs glim: -0.1% (95%CI -0.3, 0.1) ; p<0.0001 for non-inferiority *Lira was also non-inferior in the group of study completers*	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (19.3% discontinued, LOCF) Consistency: NA Directness: ok Imprecision: ok ⨁⨁⊖⊖ **LOW** Study quality: -2 (>20% discontinued, LOCF, open label) Consistency: NA Directness: ok Imprecision: ok
Body weight change from baseline	969 (1) 26 weeks 2 years	<u>At 26 weeks</u> Treatment difference: Liraglutide 0.6mg: -1.8kg (SD 0.2) Liraglutide 1.2mg:-2.6kg (SD 0.2) Liraglutide 1.8mg:-2.8kg (SD 0.2) Glimepiride 4mg:+1.0kg (SD 0.2)	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (19.3% discontinued, LOCF) Consistency: NA Directness: ok Imprecision: ok

		Lira (all doses) vs glim **p<0.0001** **=>SS in favour of liraglutide** At 2 years: Treatment difference: Liraglutide 0.6mg: -2.1 kg Liraglutide 1.2mg:-3.0 kg Liraglutide 1.8mg:-2.9 kg Glimepiride 4mg:+0.70 kg **Lira (all doses) vs glim:** **p<0.0001 =>SS in favour of liraglutide**	⊕⊕⊖⊖ **LOW** Study quality: -2 (>20% discontinued, LOCF, open label) Consistency: NA Directness: ok Imprecision: ok
Adverse events leading to withdrawal	969 (1) 26 weeks 2 years	At 26 weeks Liraglutide 0.6mg: 5% Liraglutide 1.2mg: 10% Liraglutide 1.8mg: 12% Glimepride 4mg: 3% NT At 2 years: Liraglutide 0.6mg: 9.1% Liraglutide 1.2mg: 12.9% Liraglutide 1.8mg: 14.5% Glimepride 4mg: 5.7% NT	Not applicable Not applicable
Diarrhea	969 (1) 26 weeks 2 years	At 26 weeks Liraglutide 0.6mg: 10% Liraglutide 1.2mg: 8% Liraglutide 1.8mg: 15% Glimepride 4mg: 4% NT At 2 years: Liraglutide 0.6mg: 12.8% Liraglutide 1.2mg: 11.3% Liraglutide 1.8mg: 16.5% Glimepride 4mg: 5.8% NT	Not applicable Not applicable
Nausea	969 (1) 26 weeks 2 years	At 26 weeks Liraglutide 0.6mg: 11 Liraglutide 1.2mg: 16% Liraglutide 1.8mg: 19% Glimepride 4mg: NR NT At 2 years: Liraglutide 0.6mg: 12.4%	Not applicable Not applicable

		Liraglutide 1.2mg: 17.5% Liraglutide 1.8mg: 21.5% Glimepride 4mg: 4.1% NT	
Vomiting	969 (1) 26 weeks 2 years	<u>At 26 weeks</u> Liraglutide 0.6mg: 5-7% Liraglutide 1.2mg: 5-7% Liraglutide 1.8mg: 5-7% Glimepride 4mg: 1% NT <u>At 2 years:</u> Liraglutide 0.6mg: 7.9% Liraglutide 1.2mg: 7.5% Liraglutide 1.8mg: 9.9% Glimepride 4mg: 0.4% NT	Not applicable Not applicable
Severe hypoglycaemia	969 (1) 26 weeks 2 years	<u>At 26 weeks</u> No events <u>At 2 years:</u> 1 event in liraglutide 1.2mg group	Not applicable Not applicable

Table 129

In this double blind RCT with open-label extension, 1091 patients with type 2 diabetes, inadequately controlled by oral antidiabetic medication, were randomized to liraglutide (0.6 mg (n=242), 1.2 mg (n=241) or 1.8 mg (n=242)), glimepiride 4 mg (n=244), or placebo (n=121) for 26 weeks. All participants had a background treatment with metformin 1g 2x/day. Patients could participate in an open-label extension of an additional 18 months. The mean age was 57, mean duration of diabetes 8 years., mean baseline HbA1c was 8.4%. and mean BMI was 31 kg/m^2. It was not reported how many participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

There was a large drop-out throughout the study (19% by week 26 and 52% by year 2). This limits our confidence in the estimate of the between-group differences.

In patients who were inadequately controlled on oral antidiabetic medication at 26 weeks, the addition of liraglutide (1.2 mg, or 1.8 mg) to metformin 2000 mg/day , was non-inferior compared to the addition of glimepiride 4 mg for the lowering of HbA1c.

GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on oral antidiabetic medication at 2 years, the addition of liraglutide (0.6 mg, 1.2 mg, or 1.8 mg) to metformin 2000 mg/day , was non-inferior compared to the addition of glimepiride 4 mg for the lowering of HbA1c.

GRADE: LOW quality of evidence

In patients who were inadequately controlled on oral antidiabetic medication, at 26 weeks, there was a statistically significant difference in weight change with the addition of liraglutide (0.6 mg, 1.2 mg, or 1.8 mg) to metformin 2000 mg/day, compared to the addition of glimepiride 4 mg.
The weight in the liraglutide group was decreased compared to the glimepiride group (in which the weight had increased from baseline).

GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on oral antidiabetic medication, at 2 years, there was a statistically significant difference in weight change with the addition of liraglutide (0.6 mg, 1.2 mg, or 1.8 mg) to metformin 2000 mg/day, compared to the addition of placebo.
The weight in the liraglutide group was decreased compared to the glimepiride group (in which the weight had increased from baseline).

GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events at 26 weeks was seen in 5% with liraglutide 0.6 mg, in 10% with liraglutide 1.2 mg, in 12% with liraglutide 1.8 mg and in 3% with glimepiride 4mg.
GRADE: not applicable

Withdrawal from the study due to adverse events at 2 years was seen in 9% with liraglutide 0.6 mg, in 13% with liraglutide 1.2 mg, in 15% with liraglutide 1.8 mg and in 6% with glimepiride 4mg.
GRADE: not applicable

Rates of diarrhea at week 26 were 10% with liraglutide 0.6 mg, 8% with liraglutide 1.2 mg, 15% with liraglutide 1.8 mg and 4% with glimepiride 4mg.
Rates of nausea at week 26 were 11% with liraglutide 0.6 mg, 16% with liraglutide 1.2 mg, 19% with liraglutide 1.8 mg. Rates were not reported for glimepiride 4mg.
Rates of vomiting at week 26 were 5-7% with liraglutide 0.6 mg, 1.2 mg, and 1.8 mg and 1% with glimepiride 4mg.
GRADE: not applicable

Rates of diarrhea at 2 years were 13% with liraglutide 0.6 mg, 11% with liraglutide 1.2 mg, 17% with liraglutide 1.8 mg and 6% with glimepiride 4mg.
Rates of nausea at 2 years were 12% with liraglutide 0.6 mg, 18% with liraglutide 1.2 mg, 22% with liraglutide 1.8 mg and 4% with glimepiride 4mg.
Rates of vomiting at 2 years were 8% with liraglutide 0.6 mg, 8% with liraglutide 1.2 mg, 10% with liraglutide 1.8 mg and 0% with glimepiride 4mg.
GRADE: not applicable

There were no events of severe hypoglycemia at week 26.
There was one event of severe hypoglycemia in the liraglutide 1.2 mg group at 2 years.
GRADE: not applicable

8.2.3 Liraglutide + metformin versus sitagliptin + metformin (+/- glimepiride intensification)

8.2.3.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref: Charbonnel 2013(67) Design: RCT (OL) (PG) Non-inferiority study Duration of follow-up: 26 weeks	n: 653 Mean age: 57y Prior/current treatment: metformin monotherapy ≥1,500 mg/day Mean DMII duration: 6y Mean baseline HbA1c: 8.2% Mean BMI: 32-33 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> age 18–79 years, on a stable dose of metformin monotherapy ≥1,500	"Oral strategy": sitagliptin 100 mg/day vs "injectable strategy": liraglutide 1.2 mg/day in addition to this background treatment: metformin ≥1500 mg/day <u>Hyperglycaemia uptitration protocol:</u> After 12 weeks, patients in the oral strategy group with	Efficacy (per protocol population)		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: no Remarks on blinding method: Open-label FOLLOW-UP: <u>Study completers</u>: 81.5% <u>Discontinued treatment</u>: OS: 51/326 (15.6%) IS: 70/327 (21.4%) Reason described: yes <u>Uptitration of study medication</u>: OS: 47.2%
			Change in HbA1c from baseline (PO)	*Per protocol analysis* OS: -1.3% (-1.4 to -1.2) IS: -1.4%(-1.5 to -1.3) OS vs IS: 0.1% (-0.1 to 0.2) Oral strategy is non-inferior to injectable strategy (no p-value reported) *"Glycemic efficacy results in the full analysis set population were consistent with those in the PP population (data not shown))"*	
			Body weight change from baseline (post hoc)	OS: -0.4 kg (-0.8 to 0.0) IS= -2.8 kg (-3.2 to -2.3) **OS vs IS: +2.3 kg(1.8 to 2.9)=> SS** **More weight loss with injectable strategy**	
			Blood pressure change from baseline (SystBP/DiastBP) (post hoc)	SBP OS: 0.8 mmHg (-0.5 to 2.2) IS: -1.9 mmHg (-3.3 to -0.5) **OS vs IS +2.8 mmHg(0.8 to 4.8)=> SS**	

	mg/day for ≥12 weeks, with an HbA1c ≥7.0% (53 mmol/mol) and ≤11.0% (97 mmol/mol) and a fasting fingerstick glucose (FFG) <15 mmol/l (<270 mg/dl), deemed capable by the investigator of using a Victoza pen injection device <u>Exclusion</u> type 1 diabetes mellitus, a history of ketoacidosis, uncontrolled hypertension, new or worsening signs/symptoms (within past 3 months) of cardiovascular disease, presence of severe active peripheral vascular disease, a history of	anHbA1c ≥7.0% (53mmol/mol) and FFG >6.1 mmol/l (110 mg/dl) had glimepiride added to their treatment regimen for an additional 14 weeks. After 12 weeks, patients in the injectable strategy group with an HbA1c ≥7.0% (53 mmol/mol) had the liraglutide dose, as per label, uptitrated to 1.8 mg/day <u>Hyperglycaemia rescue protocol</u>: Patients were to		**More lowering of SBP with injectable strategy** DBP OS: 0.8 mmHg (-0.1 to 1.6) IS: 0.4 mmHg (-0.5 to 1.3) OS vs IS +0.4 mmHg(-0.9 to 1.7)	IS: 25.0% <u>Hyperglycaemic rescue</u>: OS: 1/326 IS: 0/327 <u>Statistical method for drop out/missing data</u>: Excluded from analysis; per protocol analysis <u>Data handling for rescued patients</u>: excluded <u>ITT</u>: no ITT SELECTIVE REPORTING: yes No reporting of efficacy in full analysis set <u>Other important methodological remarks</u> Non-inferiority was to be declared if the upper bound of the two-sided 95% CI for the between-group difference in least squares (LS) mean change from
			Safety (full analysis set)		
			Death	OS: 1/326 IS: 0/324 NT	
			Cardiovascular adverse events	NR	
			Any adverse events	OS: 156/326 (47.9%) IS: 171/324 (52.8%) -4.9% (-12.6 to 2.8)=> NS	
			Serious adverse events	OS: 17/326 (5.2%) IS: 12/324 (3.7%) +1.5(-1.8 to 4.9)	
			Adverse event leading to withdrawal	OS: 8/326 (2%) IS: 29/324 (9%) NT	

	hypersensitivity or any contraindication to the antihyperglycaemic agents used in the present study or been treated with any antihyperglycaemic therapy other than metformin monotherapy within the 12 weeks before the screening visit. Additional exclusion criteria were a history of malignancy or clinically important haematological disorder that required disease-specific treatment, a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, an elevated serumcreatinine value (≥124 µmol/l	be discontinued because of hyperglycaemia if the following criteria were met: (1) FPG (with value repeated and confirmed within 7 days) >15mmol/l (270 mg/dl) from randomisation through to week 6; (2) FPG >13.33 mmol/l (240 mg/dl) after week 6 through to week 18; FPG >11.11 mmol/l (200 mg/dl) after week 18 through to week 26.	**Any gastro-intestinal adverse event**	OS: 10.7% IS: 32.7% NT	baseline in HbA1c (oral strategy minus injectable strategy) was less than 0.4% (non-inferiority margin).; no reason reported Sponsor: Merck Sharp & Dohme Corp.
			Diarrhoea	OS: 7/326(2.1%) IS: 35/324 (10.8%) **-8.7 (-12.7 to -5.1); p<0.001=>SS**	
			Nausea	OS: 10/326(3.1%) IS: 63/324 (19.4%) **-16.4(-21.3 to 11.8) p<0.001=>SS**	
			Vomiting	OS: 6/326(1.8%) IS: 21/324 (6.5%) **-4.6 (-8.1 to -1.7) p<0.05=>SS**	
			Severe hypoglycaemia	OS: 1/326 IS: 1/324 NT	
			Documented symptomatic hypoglycaemia *(Any episode considered likely to be represent symptomatic hypoglycaemia by the investigator; diagnosis did not require blood glucose results)*	OS: 39/326(12%) IS: 13/324 (4.0%) **8.0 (3.9 to 12.3) p<0.001=>SS**	

	[1.4mg/dl] for men and ≥115 µmol/l [1.3mg/dl] for women), an estimated glomerular filtration rate (eGFR) <60 ml min−1 (1.73 m)−2 or an alanine or aspartate aminotransferase level >2 times the upper limit of the normal range.		**Injection site reactions**	NR	
			Thyroid cancer	NR	
			Pancreatitis	NR	

Table 130

Study details	n/Population	Comparison	Outcomes		Methodological
Ref: Pratley 2010(68, 69) Design: RCT (OL) (PG) Duration of follow-up:	n: 665 Mean age: 55y Prior/current treatment: metformin ≥1500 mg/day Mean DMII duration: 6.4y Mean baseline HbA1c: 8.5% Mean BMI: 32-33	Liraglutide 1.2mg Vs Liraglutide 1.8mg Vs Sitagliptine 100 mg in addition to	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: no FOLLOW-UP: <u>Study completers at 26w</u>: 83% <u>Study completers at 52w</u>: 75%
			Change in HbA1c from baseline (PO) at 26 weeks	ITT population Lira 1.2mg: –1.24% (-1.37 to -1.11) Lira 1.8mg: –1.50% (-1.63 to -1.73) Sita 100mg: –0.90% (-1.03 to -0.77) **Lira 1.2 vs sita mean diff= -0.34%(-0.51, -0.16), p<0.0001 ; SS** **Lira 1.8 vs sita mean diff= -0.60% (-0.77, -0.43), p<0.0001 ; SS** Similar results in per protocol set	
			at 52 weeks	*Lira 1.2mg: -1.29%(-1.43 to -1.15)* *Lira 1.8mg: -1.51% (-1.65 to -1.37)* *Sita 100mg: -0.88% (-1.02 to -0.74)*	

26 w + 26 w extension trial	Previous CV event: NR Renal impairment: NR <u>Inclusion</u> 18-80y; HbA1c 7.5-10%; BMI <=45; treated with metformin (>=1500 mg) for at least 3m <u>Exclusion</u> Recurrent mayor hypglycaemia or hypoglycaemic unawareness; use of any drug except metformin that could affect glucose; CI to trial drug; impaired renal or hepatic function; cardiovascular disease; cancer	this background treatment: metformin≥1500 mg/day <u>Hyperglycaemia uptitration protocol:</u> No protocol <u>Hyperglycaemia rescue protocol</u>**:** Not described for initial 26 weeks; During extension period: Elevated FPG>11.1 mmol/L (200 mg/dl) with no treatable intercurrent cause =>		***Mean diff lira 1.2mg vs sita:-0.40% (-0.59, -.022), SS, p<0.0001*** ***Mean diff lira 1.8mg vs sita:-0.63% (-0.81, -0.44), SS, p<0.0001*** *Results of per protocol set not reported*	<u>Discontinued treatment at 26w</u>: Lira 1.2mg: 52/225 (23.1%) Lira 1.8mg: 27/221 (12.2%) Sita 100mg.: 25/219 (11.4%) Reason described: yes <u>Discontinued treatment at 52w</u>: Lira 1.2mg: 20/225 (8.9%) Lira 1.8mg:26/221 (11.8%) Sita 100mg.: 15/219 (6.8%) Reason described: yes <u>Hyperglycaemic rescue at 52 w</u>: Lira 1.2mg: 2/225 (0.9%) Lira 1.8mg:3/221 (1.4%) Sita 100mg.: 7/219 (3.2%) <u>Statistical method for drop out/missing data</u>: LOCF <u>Data handling for rescued patients</u>: excluded, LOCF
			Body weight change from baseline at 26 weeks	Lira 1.2mg: -2.86kg(-3.39 to -2.32) Lira 1.8mg: -3.38kg (-3.91 to -2.84) Sita 100mg: -0.96kg(-1.50 to -0.42) **Lira 1.2 vs sita mean diff= -1.9 (-2.61,-1.18) , SS** **Lira 1.8 vs sita mean diff= -2.42 (-3.14, -1.70), SS**	
			at 52 weeks	*Lira 1.2mg: -2.78kg (-3.39 to -2.17)* *Lira 1.8mg: -3.68kg (-4.29 to -3.07)* *Sita 100mg: -1.16kg (-1.77 to -0.55)* ***Mean diff lira 1.2mg vs sita: -1.62kg (-2.43,-0.82), SS, p<0.0001*** ***Mean diff lira 1.8mg vs sita: -2.53kg (-3.33, -1.72), SS, p<0.0001***	
			Blood pressure change from baseline at 26 weeks (SystBP/DiastBP)	SBP Lira 1.2mg: -0.55 mmHg(-2.30 to 1.19) Lira 1.8mg: -0.72 mmHg (-2.47 to 1.03) Sita 100mg: -0.94 mmHg (-2.69 to 0.81) Lira 1.2 vs sita mean diff 0.39 mmHg (-1.96 to 2.73); p=0.7464 => NS Lira 1.8 vs sita mean diff 0.22 mmHg (-	

		withdrawal from study <u>Stratification:</u> none		2.12 to 2.57); p=0.8528 => NS DBP Lira 1.2mg: -0.71 mmHg (-1.88 to 0.46) Lira 1.8mg: -0.07 mmHg (-1.10 to 1.23) Sita 100mg: -1.78 mmHg (-2.95 to -0.61) Lira 1.2 vs sita mean diff 1.07 mmHg (-0.50 to 2.64); p=0.1826 => NS **Lira 1.8 vs sita mean diff 1.85 mmHg (0.28 to 3.41); p=0.0210=> SS, more BP lowering with sitagliptin**	<u>ITT</u>: "full analysis set"= randomised participants who were exposed to at least one dose of trial drug and with at least one HbA1c measurement taken after baseline" SELECTIVE REPORTING: no <u>Other important methodological remarks:</u> assessed hierarchically by a non-inferiority comparison, with a margin of 0·4%, and then by a superiority comparison. "Non-inferiority and superiority were tested as two-sided hypotheses, with p values of less than 0·05 judged to be signifi cant. Primary effi cacy analyses were done on the full analysis set (randomised participants who were exposed to at least one dose of trial drug and with at least one HbA1c measurement taken after baseline) with missing values
			at 52 weeks)	*SBP* *Lira 1.2mg: -0.37 mmHg(-2.19 to 1.45)* *Lira 1.8mg: -2.55 mmHg (-4.37 to -0.72)* *Sita 100mg: -1.03 mmHg (-2.85 to 0.79)* *Lira 1.2 vs sita mean diff 0.66 mmHg (-1.79 to 3.10); p=0.60 => NS* *Lira 1.8 vs sita mean diff -1.53 mmHg (-3.97 to 0.92); p=0.22 => NS* *DBP* *Lira 1.2mg: -0.53 mmHg (-1.65 to 0.59)* *Lira 1.8mg: -0.87 mmHg (-1.99 to 0.25)* *Sita 100mg: -1.47 mmHg (-2.59 to -0.35)*	

				Lira 1.2 vs sita mean diff 0.94 mmHg (-0.57 to 2.45); p=0.22 => NS *Lira 1.8 vs sita mean diff 0.60 mmHg (-0.90 to 2.11); p=0.43=> NS*	imputed by last observation carried forward, and on the per-protocol set. For non-inferiority, we expected similar outcomes to be recorded with the full analysis and per-protocol sets, but for superiority, we judged the full analysis set to be primary. We present data for the full analysis set." Sponsor: Novo Nordisk
			Safety		
			Death at 26 weeks	Lira 1.2mg: 0/221 (0%) Lira 1.8mg: 1/218 (<1%) Sita 100mg: 1/219 (<1%) NT	
			at 52 weeks	*Lira 1.2mg: 0/221 (0%)* *Lira 1.8mg: 1/218 (0.5%)* *Sita 100mg: 2/219 (0.9%)* *NT*	
			Cardiovascular adverse events at 26 weeks	Lira 1.2mg: 0/221 (0%) Lira 1.8mg: 1/218 (<1%) Sita 100mg: 1/219 (<1%) NT	
			at 52 weeks	Lira 1.2mg: 2/221 (0.9%) Lira 1.8mg: 1/218 (0.5%) Sita 100mg: 1/219 (0.5%) NT	
			Any adverse events at 26 weeks	Lira 1.2mg: 146/221 (66%) Lira 1.8mg: 159/218 (73%) Sita 100mg: 127/219 (58%) NT	
			at 52 weeks	Lira 1.2mg: 158/221 (71.5%) Lira 1.8mg: 167/218 (76.6%) Sita 100mg: 139/219 (63.5%) NT	

			Serious adverse events at 26 weeks	"Serious adverse events" (no definition given) Lira 1.2mg: 6/221 (3%) Lira 1.8mg: 6/218 (3%) Sita 100mg: 4/219 (2%) NT "Severe adverse events" (no definition given) Lira 1.2mg: 7/221 (3%) Lira 1.8mg: 7/218 (3%) Sita 100mg: 8/219 (4%) NT	
			at 52 weeks	*"Serious adverse events" (no definition given)* *Lira 1.2mg: 10/221 (4.5%)* *Lira 1.8mg: 13/218 (6.0%)* *Sita 100mg: 12/219 (5.5%)* *NT* *"Severe adverse events" (no definition given)* *Lira 1.2mg: 12/221 (5.4%)* *Lira 1.8mg: 15/218 (6.9%)* *Sita 100mg: 13/219 (5.9%)* *NT*	
			Adverse event leading to withdrawal at 26 weeks	Lira 1.2mg: 14/221 (6.3%) Lira 1.8mg: 15/218 (6.8%) Sita 100mg: 4/219 (1.8%) NT	

			at 52 weeks	*Lira 1.2mg: 19/221 (8.6%)* *Lira 1.8mg: 25/218 (11.5%)* *Sita 100mg: 7/219 (3.2%)* *NT*	
			Any gastro-intestinal adverse event at 26 weeks	Lira 1.2mg: 73/221 (33%) Lira 1.8mg: 88/218 (40%) Sita 100mg: 46/219 (21%) NT	
			at 52 weeks	*Lira 1.2mg: 80/221 (36.2%)* *Lira 1.8mg: 94/218 (43.1%)* *Sita 100mg: 52/219 (23.7%)* *NT*	
			Diarrhoea at 26 weeks	Lira 1.2mg: 16/221 (7%) Lira 1.8mg: 25/218 (11%) Sita 100mg: 10/219 (5%) NT	
			at 52 weeks	*Lira 1.2mg:20/221 (9.0%)* *Lira 1.8mg: 27/218 (12.4%)* *Sita 100mg: 14/219 (6.4%)* *NT*	
			Nausea at 26 weeks	Lira 1.2mg: 46/221 (21%) Lira 1.8mg: 59/218 (27%) Sita 100mg: 10/219 (5%) NT	
			at 52 weeks	*Lira 1.2mg: 48/221 (21.7%)* *Lira 1.8mg: 60/218 (27.5%)* *Sita 100mg: 12/219 (5.5%)* *NT*	
			Vomiting at 26 weeks	Lira 1.2mg: 17/221 (8%) Lira 1.8mg: 21/218 (10%)	

				Sita 100mg: 9/219 (4%) NT	
			at 52 weeks	*Lira 1.2mg: 18/221 (8.1%)* *Lira 1.8mg: 23/218 (10.6%)* *Sita 100mg: 11/219 (5.0%)* *NT*	
			Severe hypoglycaemia at 26 weeks	Lira 1.2 n=1/221 NT	
			at 52 weeks	*Lira 1.2 n=1/221* *NT* *No new events*	
			Documented symptomatic hypoglycaemia at 26 weeks *("minor hypoglycemia= plasma glucose <3.1 mmol/L, self-treated)*	Lira 1.2mg: 12/221 (5%) Lira 1.8mg: 11/218 (5%) Sita 100mg: 10/219 (5%) NT	
			at 52 weeks	*Lira 1.2mg: 0.143 episodes/patient/year* *Lira 1.8mg: 0.154 episodes/patient/year* *Sita 100mg: 0.137 episodes/patient/year* *NT*	
			Injection site reactions at 26 weeks	NR	
			at 52 weeks	*NR*	
			Thyroid cancer at 26 weeks	No events	
			at 52 weeks	*No events*	

			Pancreatitis at 26 weeks	No events	
			at 52 weeks	No events of acute pancreatitis 1 case of “non-acute pancreatitis” in lira 1.8mg group	

Table 131

8.2.3.2 *Summary and conclusions*

Liraglutide + MET vs sitagliptin + MET (+/- glimepiride intensification)			
Bibliography: Charbonnel 2013{Charbonnel, 2013 #429			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	653 (1) 26 weeks	*Per protocol analysis* sitagliptin vs liraglutide treatment difference: 0.1% (95%CI -0.1 to 0.2) Oral strategy is non-inferior to injectable strategy *No p-value reported* *"Glycemic efficacy results in the full analysis set population were consistent with those in the PP population (data not shown)"*	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 open label, incomplete reporting of non-inferiority analysis Consistency: NA Directness: -1 exclusion of eGFR <60 mL/min Imprecision: ok
Body weight change from baseline	653 (1) 26 weeks	treatment difference: **sitagliptin vs liraglutide: +2.3 kg (95%CI 1.8 to 2.9)** **=> SS in favour of liraglutide**	⊕⊕⊖⊖ **LOW** Study quality: -1 open label Consistency: ok Directness: -1 exclusion of eGFR <60 mL/min Imprecision: ok
Adverse events leading to withdrawal	653 (1) 26 weeks	sitagliptin: 8/326 (2%) liraglutide: 29/324 (9%) NT	Not applicable
Diarrhea	653 (1) 26 weeks	sitagliptin: 7/326(2%) liraglutide: 35/324 (11%) **-8.7 %(95%CI -12.7 to -5.1); p<0.001=> SS in favour of sitagliptin**	⊕⊕⊖⊖ **LOW** Study quality: -1 open label Consistency: ok Directness: -1 exclusion of eGFR <60 mL/min Imprecision: ok
Nausea	653 (1) 26 weeks	sitagliptin: 10/326(3%) liraglutide: 63/324 (19%) **-16.4% (95%CI -21.3 to 11.8) p<0.001=>SS in favour of sitagliptin**	⊕⊕⊖⊖ **LOW** Study quality: -1 open label Consistency: ok Directness: -1 exclusion of eGFR <60 mL/min Imprecision: ok

Vomiting	653 (1) 26 weeks	sitagliptin: 6/326(2%) liraglutide: 21/324 (7%) **-4.6% (95%CI -8.1 to -1.7) p<0.05=> SS in favour of sitagliptin**	⊕⊕⊖⊖ **LOW** Study quality: -1 open label Consistency: ok Directness: -1 exclusion of eGFR <60 mL/min Imprecision: ok
Severe hypoglycaemia	653 (1) 26 weeks	sitagliptin: 1/326 liraglutide: 1/324 NT	Not applicable

Table 132

Table 133

In this open-label RCT, 653 patients with type 2 diabetes, inadequately controlled by metformin monotherapy, were randomized to sitagliptin 100 mg or liraglutide 1.2 mg for 26 weeks. After 12 weeks, medication could be intensified by adding glimepiride in the sitagliptin group, or by uptitrating liraglutide to 1.8 mg. The mean age was 57, mean duration of diabetes 6 years, mean baseline HbA1c was 8.2%, and mean BMI was 33 kg/m^2. It is not reported how many participants had had a previous myocardial infarction. Patients with an eGFR < 60 mL/min/m^2 were excluded from the trial.

Our confidence in the results of this trial is limited by its open-label design.

In patients who were inadequately controlled on metformin, at 26 weeks, the addition of sitagliptin was non-inferior compared to the addition of liraglutide for the lowering of HbA1c.

GRADE: VERY LOW quality of evidence

In patients who were inadequately controlled on metformin, at 26 weeks, there was a statistically significant difference in weight change with the addition of liraglutide compared to the addition of sitagliptin.
There was more weight loss with liraglutide than with sitagliptin.

GRADE: LOW quality of evidence

Withdrawal from the study due to adverse events at 26 weeks was seen in 9% with liraglutide and 2% with sitagliptin.
GRADE: not applicable

Rates of diarrhea at 26 weeks were 11% with liraglutide and 2% with sitagliptin. The difference was statistically significant.
Rates of nausea at 26 weeks were 19% with liraglutide and 3% with sitagliptin. The difference was statistically significant.

Rates of vomiting at 26 weeks were 7% with liraglutide and 2% with sitagliptin. The difference was statistically significant.
GRADE: LOW quality of evidence

Severe hypoglycemia at 26 weeks occurred in 1/324 with liraglutide and in1/326 with sitagliptin.
GRADE: not applicable

Liraglutide + MET vs sitagliptin + MET			
Bibliography: Pratley 2010(68, 69)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	665 (1) 26 weeks	**Lira 1.2 vs sita mean diff= -0.34%(95%CI -0.51, -0.16), SS** **Lira 1.8 vs sita mean diff= -0.60% (95%CI -0.77, -0.43), SS**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label Consistency: NA Directness: ok Imprecision: ok
	665 (1) 52 weeks	**Mean diff lira 1.2mg vs sita:-0.40% (95%CI -0.59, -.022), SS, p<0.0001** **Mean diff lira 1.8mg vs sita:-0.63 95%CI (-0.81, -0.44), SS, p<0.0001**	⊕⊕⊖⊖ **LOW** Study quality: -2 open label, >20% drop-out + LOCF Consistency: NA Directness: ok Imprecision: ok
Body weight change from baseline	665 (1) 26 weeks	**Lira 1.2 vs sita mean diff= -1.9 (95%CI -2.61,-1.18); SS** **Lira 1.8 vs sita mean diff= -2.42 (95%CI -3.14, -1.70), SS**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label Consistency: NA Directness: ok Imprecision: ok
	665 (1) 52 weeks	**Mean diff lira 1.2mg vs sita: -1.62kg (95%CI -2.43,-0.82), SS, p<0.0001** **Mean diff lira 1.8mg vs sita: -2.53kg (95%CI -3.33, -1.72), SS, p<0.0001**	⊕⊕⊖⊖ **LOW** Study quality: -2 open label, >20% drop-out + LOCF Consistency: NA Directness: ok Imprecision: ok
Adverse events leading to withdrawal	665 (1) 26 weeks	Lira 1.2mg: 14/221 (6%) Lira 1.8mg: 15/218 (7%) Sita 100mg: 4/219 (2%) NT	Not applicable
	665 (1) 52 weeks	Lira 1.2mg: 5/221 (9%) Lira 1.8mg: 10/218 (12%) Sita 100mg: 3/219 (3%) NT	Not applicable
Diarrhea	665 (1) 26 weeks	Lira 1.2mg: 16/221 (7%) Lira 1.8mg: 25/218 (11%) Sita 100mg: 10/219 (5%) NT	Not applicable
	665 (1) 52 weeks	Lira 1.2mg:20/221 (9%) Lira 1.8mg: 27/218 (12%) Sita 100mg: 14/219 (6%) NT	Not applicable
Nausea	665 (1) 26 weeks	Lira 1.2mg: 46/221 (21%) Lira 1.8mg: 59/218 (27%) Sita 100mg: 10/219 (5%) NT	Not applicable
	665 (1) 52 weeks	Lira 1.2mg: 48/221 (22%) Lira 1.8mg: 60/218 (28%) Sita 100mg: 12/219 (6%) NT	Not applicable

Vomiting	665 (1) 26 weeks	Lira 1.2mg: 17/221 (8%) Lira 1.8mg: 21/218 (10%) Sita 100mg: 9/219 (4%) NT	Not applicable
	665 (1) 52 weeks	Lira 1.2mg: 18/221 (8%) Lira 1.8mg: 23/218 (11%) Sita 100mg: 11/219 (5%) NT	Not applicable
Severe hypoglycaemia	665 (1) 26 weeks	Lira 1.2 n=1/221 NT	Not applicable
	665 (1) 52 weeks	Lira 1.2 n=1/221 NT No new events	Not applicable

Table 134

Pratley:
In this open-label RCT, 665 patients with type 2 diabetes, inadequately controlled by metformin monotherapy, were randomized to sitagliptin 100 mg or liraglutide 1.2 mg or 1.8 mg for 26 weeks, followed by a 26-week extension trial. The mean age was 55, mean duration of diabetes 6 years, mean baseline HbA1c was 8.5%, and mean BMI was 32-33 kg/m^2. It is not reported how many participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

Our confidence in the results of this trial is limited by its open-label design. By 52 weeks, there was a large drop-out throughout the study (25%).

In patients who were inadequately controlled on metformin, at 26 weeks, the addition of liraglutide 1.2 mg or 1.8 mg resulted in a statistically significant decrease of HbA1c compared to the addition of sitagliptin .

GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on metformin, at 52 weeks, the addition of liraglutide 1.2 mg or 1.8 mg resulted in a statistically significant decrease of HbA1c compared to the addition of sitagliptin .

GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin, at 26 weeks, there was a statistically significant difference in weight change with the addition of liraglutide 1.2 mg or 1.8 mg compared to the addition of sitagliptin.
There was more weight loss with liraglutide than with sitagliptin.

GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on metformin, at 52 weeks, there was a statistically significant difference in weight change with the addition of liraglutide 1.2 mg or 1.8 mg compared to the addition of sitagliptin.
There was more weight loss with liraglutide than with sitagliptin.

GRADE: LOW quality of evidence

Withdrawal from the study due to adverse events at 26 weeks was seen in 6% with liraglutide 1.2 mg, 7% with liraglutide 1.8 mg and 2% with sitagliptin.
GRADE: not applicable

Withdrawal from the study due to adverse events at 52 weeks was seen in 9% with liraglutide 1.2 mg, 12% with liraglutide 1.8 mg and 3% with sitagliptin.
GRADE: not applicable

Rates of diarrhea at 26 weeks were 7% with liraglutide 1.2 mg, 11% with liraglutide 1.8 mg and 5% with sitagliptin.
Rates of nausea at 26 weeks were 21% with liraglutide 1.2 mg, 27% with liraglutide 1.8 mg and 5% with sitagliptin.
Rates of vomiting at 26 weeks were 8% with liraglutide 1.2 mg, 10% with liraglutide 1.8 mg and 4% with sitagliptin.
GRADE: not applicable

Rates of diarrhea at 52 weeks were 9% with liraglutide 1.2 mg, 12% with liraglutide 1.8 mg and 6% with sitagliptin.
Rates of nausea at 52 weeks were 22% with liraglutide 1.2 mg, 28% with liraglutide 1.8 mg and 6% with sitagliptin.
Rates of vomiting at 52 weeks were 8% with liraglutide 1.2 mg, 11% with liraglutide 1.8 mg and 5% with sitagliptin.
GRADE: not applicable

Severe hypoglycemia at 26 weeks occurred in 1/221 with liraglutide 1.2 mg. No new events had occurred by week 52.
GRADE: not applicable

8.2.4 Lixisenatide + metformin versus liraglutide + metformin

8.2.4.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Nauck 2016(70) Design: RCT OL PG Duration of follow-up: 26 weeks	n: 404 Mean age: 56.2 ± 10.3 y Prior/current treatment: metformin Mean DMII duration: 6.4 (±5.1) Mean baseline HbA1c: 8.4 (±0.8) Mean BMI: 34.7 (6.7%) Previous CV event: unknown Renal impairment: patients with renal impairment excluded <u>Inclusion</u> males and females with type 2 diabetes, age ≥18 years, HbA1c 7.52 - 10.5% BMI ≥20 kg/m2	Liraglutide 1.8 mg (n = 202) vs Lixisenatide 20 µg (n = 202) (morning or evening) in addition to this background treatment: Metformin (at least 1g/day) <u>Hyperglycaemia uptitration protocol:</u> / <u>Hyperglycaemia rescue protocol</u>**:** Patients meeting predefined hyperglycemia	Efficacy		RANDO: adequate (interactive voice/web response system) ALLOCATION CONC: adequate BLINDING : Participants: open label study Personnel: open label study Assessors: open label study FOLLOW-UP: <u>Study completers*</u>: Liraglutide: 88.1% Lixisenatide: 80.2% Reason described: yes <u>Discontinued treatment*</u>: Lira: 11.9% n = 24 (13 for AE) Lixi: 19.8% n = 40 (15 for AE) <u>Uptitration of study medication</u>: Starting dose of 10µg, escalated to 20µg from day 15
			Change in HbA1c from baseline (PO)	Liraglutide: -1.8% Lixisenatide: -1.2% Treatment difference: -0.6% (95% CI: -0.8; -0.4) p<0.0001 SS in favour of liraglutide	
			Body weight change from baseline	Liraglutide: -4.3 kg Lixisenatide: -3.7 kg Difference: -0.6 kg (95% CI: -1.6 ; 0.4) p = 0.23 NS	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP Liraglutide: -4.7 mmHg Lixisenatide: -3.5 mmHg Difference: -1.2 mmHg (95% CI: -3.9; 1.5) NS DBP Liraglutide: -2.62mmHg Lixisenatide:-2.69mmHg NS	
			Safety		
			Death	unknown	
			Cardiovascular adverse	unknown	

	on unchanged metformin treatment at the maximum tolerated dose (1,000 to 3,000 mg/day) for at least 90 days prior to screening. Exclusion - female patients of child-bearing potential who was pregnant, breast-feeding, or intending to become pregnant or not using adequate contraception - patients who were previously treated with a GLP-1 RA -who were treated with glucose-lowering agents other than metformin within 90 days of screening - who had a history of chronic pancreatitis or idiopathic acute pancreatitis, a screening calcitonin	criteria were offered rescue treatment (suitable marketed products or attempt to further increase metformin dose) at the discretion of the investigator as add-on to the trial product during the remainder of the trial. Stratification: none reported	**events**		Hyperglycaemic rescue: at discretion of investigator Statistical method for drop out/missing data: MMRM (mixed model for repeated measurements) Data handling for rescued patients: kept in study and included in safety analyses ITT: defined as "FAS": full analysis set, all randomized patients Also works with SAS for safety (safety analysis set): all patients receiving at least one dose of any of the trial products SELECTIVE REPORTING: no Other important methodological remarks / Sponsor: Novo Nordisk (produces liraglutide)
			Any adverse events	Lira: 71.8% Lixi:63.9%	
			Serious adverse events	Lira:5.9% (n of SAE = 13) Lixi: 3.5% (n of SAE = 7)	
			Adverse event leading to withdrawal	Lira: 6.4% (13 patients) Lixi: 7.4% (15 patients)	
			Any gastro-intestinal adverse event	unknown	
			Diarrhoea	Lira: 12.4% Lixi: 9.9%	
			Nausea	Lira: 21.8% Lixi: 21.8%	
			Vomiting	Lira: 6.9% Lixi: 8.9%	
			Severe hypoglycaemia	Lira: 0 Lixi: 0	
			Documented symptomatic hypoglycaemia	Lira: 3 patients (1.5%) with 4 events Lixi: 5 patients (2.5%) and 8 events p = 0.5	
			Injection site reactions	unknown	
			Thyroid cancer	unknown	

	value ≥50 ng/L, - personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, impaired liver function (alanine aminotransferase ≥2.5 times the upper normal limit [UNL]), - impaired renal function (estimated glomerular filtration rate 60 mL/min/1.73 m2 per MDRD formula) - any chronic disorder or severe disease that in the opinion of the investigator might jeopardize the patient's safety or compliance with the protocol		**Pancreatitis**	Lira: 0 Lixi: 0	

Table 135

* Statistically significant (p<0.05) difference (less drop-outs with liraglutide) as calculated by literature group with http://vassarstats.net/odds2x2.html

8.2.4.2 *Summary and conclusions*

Lixisenatide + metformin vs liraglutide + metformin for patients with type II diabetes not achieving adequate glycemic control			
Bibliography: Nauck 2016 (70)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	404 (1) 26 weeks	Liraglutide: -1.8% Lixisenatide: -1.2% Mean difference: -0.6% (95% CI: -0.8; -0.4) **p<0.0001** **SS in favour of liraglutide**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label Consistency: N/A Directness: ok Imprecision: ok
Body weight change from baseline	404 (1) 26 weeks	Liraglutide: -4.3 kg Lixisenatide: -3.7 kg Difference: -0.6 kg (95% CI: -1.6 ; 0.4) p = 0.23 NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label Consistency: N/A Directness: ok Imprecision: ok
Adverse events leading to withdrawal	404 (1) 26 weeks	Lira: 6.4% (13 patients) Lixi: 7.4% (15 patients)	NA
Diarrhea	404 (1) 26 weeks	Lira: 12.4% Lixi: 9.9%	NA
Nausea	404 (1) 26 weeks	Lira: 21.8% Lixi: 21.8%	NA
Vomiting	404 (1) 26 weeks	Lira: 6.9% Lixi: 8.9%	NA
Severe hypoglycaemia	404 (1) 26 weeks	Lira: 0 Lixi: 0	NA:

Table 136

In this open label RCT, 404 patients with type 2 diabetes, inadequately controlled by metformin (at least 1g/day), were randomized to lixisenatide or liraglutide for 26 weeks. The mean age was 56, mean duration of diabetes 6.4 years, mean baseline HbA1c was 8.4 and mean BMI was 34.7 kg/m^2.

It is unclear how many participants had had a previous myocardial infarction. Patients with renal impairment were excluded from the study.

The interpretation of these results is further limited because of the inclusion of patients with any oral antidiabetic therapy. Based on these results, it is difficult to make statements about the combination of a glp-1 receptor agonist with a specific oral antidiabetic agent.

In patients who were inadequately controlled on at least 1 gram of metformin/day, at 26 weeks, the addition of liraglutide **resulted** in a statistically significant **stronger** decrease of HbA1c compared to the addition of lixisenatide.
GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on at least 1 gram of metformin/day, at 26 weeks, there was **no** statistically significant difference in weight change with the addition of liraglutide compared to the addition of lixisenatide.
GRADE: MODERATE quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 11.9% with liraglutide and 19.8% with lixisenatide.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

8.2.5 Dulaglutide + metformin versus liraglutide + metformin

See 5.2.3.1.

8.3 Combination therapy with SU

8.3.1 Liraglutide + SU versus placebo + SU

8.3.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Marre 2009(71) LEAD-1 SU Design: RCT (DB) (PG) Duration of follow-up: 26 weeks	n: 809 (rosiglitazone arm excluded for this table) Mean age: 56.1y Prior/current treatment: OAD monotherapy: 30% Combination therapy: 70% Mean DMII duration: 6.6y Mean baseline HbA1c: 8.5% Mean BMI: 30 Previous CV event: NR Renal impairment: NR	Liraglutide (0.6 mg, 1.2 mg, 1.8 mg) vs placebo (vs. rosiglitazone 4 mg/day :will not be reported in this table) in addition to this background treatment: glimepiride (2-4 mg/day)	Efficacy		RANDO: Unclear (method of randomization not explained) ALLOCATION CONC: unclear(method of allocation concealment not explained) BLINDING : Participants: yes Personnel: yes Assessors: unclear FOLLOW-UP: <u>Study completers</u>: 87% <u>Discontinued treatment</u>: Lira 0.6 mg: 11% Lira 1.2 mg: 14% Lira 1.8 mg: 9% Placebo: 27%
			Change in HbA1c from baseline (PO)	Lira 0.6 mg: -0.6 % Lira 1.2 mg: -1.1% Lira 1.8 mg: -1.1% Placebo: +0.2% **Lira 0.6 mg vs pla: -0.8% (-1.1 to -0.6)** **Lira 1.2 mg vs pla: -1.3% (-1.5 to -1.1)** **Lira 1.8 mg vs pla: -1.4% (-1.6 to -1.1)** **Lira (all doses) vs pla p<0.0001=> SS**	
			Body weight change from baseline	Lira 0.6 mg: +0.7 kg Lira 1.2 mg: +0.3 kg Lira 1.8 mg: -0.2 kg Placebo:-0.1 kg Unclear/discrepant reporting of results of statistical testing (in text: “no significant differences compared with placebo”; in figure 6: all were p<0.05 compared with placebo)	

	Inclusion • TD2 treated with OAD for ≥3 months • 18-80y • HbA1c 7-11% (monotherapy); 7-10% (combination therapy) • BMI ≤45 Exclusion • Used insulin within 3 months • Impaired liver or renal function • Uncontrolled hypertension (≥180/100 mmHg) • Cancer • Used any drugs apart from OAD likely to affect glucose concentrations	Hyperglycaemia uptitration protocol: No protocol Hyperglycaemia rescue protocol: No protocol Stratification: According to previous treatment (mono- or combination therapy)	**Blood pressure change from baseline (SystBP/DiastBP)**	SBP No significant reduction compared to placebo DBP No significant reduction compared to placebo	Reason described: yes Uptitration of study medication: Not applicable Hyperglycaemic rescue: not applicable Statistical method for drop out/missing data: LOCF Data handling for rescued patients: not applicable ITT: defined as subjects exposed to ≥ 1 dose of trial products. SELECTIVE REPORTING: yes, incomplete reporting of secondary endpoints Other important methodological remarks: the non-inferiority/ superiority margin vs. active control was set to 0.4% and the difference to detect (superiority vs. placebo) was set to 0.5%.
			Safety		
			Death	none	
			Cardiovascular adverse events	NR	
			Any adverse events	NR	
			Serious adverse events	Lira 0.6 mg: 3% Lira 1.2 mg: 4% Lira 1.8 mg: 5% Placebo:3% NT	
			Adverse event leading to withdrawal	Lira 0.6 mg: 2% Lira 1.2 mg: 5% Lira 1.8 mg: 4% Placebo: 5% NT	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	Lira 0.6 mg: NR Lira 1.2 mg: 7.9% Lira 1.8 mg: NR Placebo: NR	

				NT	Sponsor: Novo Nordisk
			Nausea	Lira 0.6 mg: 10.5% Lira 1.2 mg: NR Lira 1.8 mg: NR Placebo: 1.8% NT	
			Vomiting	Lira 0.6 mg: NR Lira 1.2 mg: 4.4% Lira 1.8 mg: NR Placebo: NR NT	
			Severe hypoglycaemia	Lira 0.6 mg: 0 Lira 1.2 mg: 0 Lira 1.8 mg: 1 Placebo: 0 NT	
			Documented symptomatic hypoglycaemia *"Minor hypoglycaemia" (=PG levels (<3.1 mmol/l), self-treated*)	Lira 0.6 mg: 5.2% Lira 1.2 mg: 9.2% Lira 1.8 mg: 8.1% Placebo: 2.6% **Lira 1.2 mg vs pla: p=0.048 => SS** Lira 0.6 mg and 1.8 mg vs pla=> NS	
			Injection site reactions	NR	
			Thyroid cancer	NR	

			Pancreatitis	Lira 0.6 mg: 1 patient developed chronic pancreatitis Lira 1.2 mg: 0 Lira 1.8 mg: 0 Placebo: 0 NT	

Table 137

8.3.1.2 *Summary and conclusions*

Liraglutide + SU vs. placebo + SU			
Bibliography: Marre 2009(71)LEAD-1 SU			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	809 (1) 26 weeks	**Treatment difference:** **Lira 0.6 mg vs pla: -0.8% (95%CI -1.1 to -0.6)** **Lira 1.2 mg vs pla: -1.3% (95%CI -1.5 to -1.1)** **Lira 1.8 mg vs pla: -1.4% (95%CI -1.6 to -1.1)** **Lira (all doses) vs pla p<0.0001=> SS**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 unclear rando, unclear allocation concealment Consistency: NA Directness: ok Imprecision: ok
Body weight change from baseline	809 (1) 26 weeks	Lira 0.6 mg: +0.7 kg Lira 1.2 mg: +0.3 kg Lira 1.8 mg: -0.2 kg Placebo:-0.1 kg Unclear/discrepant reporting of results of statistical testing (in text: "no significant differences compared with placebo"; in figure 6: all were p<0.05 compared with placebo)	Not applicable
Adverse events leading to withdrawal	809 (1) 26 weeks	Lira 0.6 mg: 2% Lira 1.2 mg: 5% Lira 1.8 mg: 4% Placebo: 5% NT	Not applicable
Diarrhea	809 (1) 26 weeks	Lira 0.6 mg: NR Lira 1.2 mg: 7.9% Lira 1.8 mg: NR Placebo: NR NT	Not applicable
Nausea	809 (1) 26 weeks	Lira 0.6 mg: 10.5% Lira 1.2 mg: NR Lira 1.8 mg: NR Placebo: 1.8% NT	Not applicable
Vomiting	809 (1) 26 weeks	Lira 0.6 mg: NR Lira 1.2 mg: 4.4% Lira 1.8 mg: NR Placebo: NR NT	Not applicable
Severe hypoglycaemia	809 (1) 26 weeks	Lira 0.6 mg: 0/233 Lira 1.2 mg: 0/228 Lira 1.8 mg: 1/234 Placebo: 0/114	Not applicable

	NT

Table 138

In this double blind RCT, 809 patients with type 2 diabetes, inadequately controlled by glimepiride 2-4 mg/day were randomized to liraglutide (0.6 mg, 1.2 mg, 1.8 mg) or placebo for 26 weeks. The mean age was 56, mean duration of diabetes 7 years, mean baseline HbA1c was 8.5% and mean BMI was 30 kg/m^2. It was not reported how many participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

In patients who were inadequately controlled on glimepiride 2-4 mg at 26 weeks, the addition of liraglutide (0.6 mg, 1.2 mg, 1.8 mg) resulted in a statistically significant decrease of HbA1c compared to the addition of placebo (which was increased from baseline).
GRADE: MODERATE quality of evidence

Body weight change from baseline was reported, but the reporting of the statistical testing was unclear. Therefore, GRADE cannot be applied.

In patients who were inadequately controlled on glimepiride 2-4 mg at 26 weeks, the body weight change from baseline was -0.2 kg to +0.7 kg with the addition of liraglutide, compared to -0.1 kg with the addition of placebo.
GRADE: Not applicable

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 2 to 5% with liraglutide and 5% with placebo.
GRADE: not applicable

Rates of diarrhea were 8% with liraglutide 1.2 mg. Rates of diarrhea with placebo or other doses of liraglutide were not reported.
Rates of nausea were 11% with liraglutide 0.6 mg and 2% with placebo. Rates of nausea with other doses of liraglutide were not reported.
Rates of vomiting were 4% with liraglutide 1.2 mg. Rates of vomiting with placebo or other doses of liraglutide were not reported.
GRADE: not applicable

Severe hypoglycemia occurred in 1/234 with liraglutide 1.8 mg. There were no events in the other groups.
GRADE: not applicable

8.4 Combination therapy with metformin +/- SU

8.4.1 Liraglutide + metformin + glimepiride versus placebo + metformin + glimepiride

8.4.1.1 *Clinical evidence profile: liraglutide versus insulin glargine, placebo (all + metformin and glimepiride)*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Russell-Jones 2009(72) LEAD-5 Design: RCT (DB/OL) (PG) Duration of follow-up: 26 w	n: 581 Mean age: 57 Prior/current treatment: oral glucose-lowering drugs (94-95% combination therapy) Mean DMII duration: 9.4y Mean baseline HbA1c: 8.3% Mean BMI: 30.4 Previous CV event: NR Renal impairment: NR <u>Inclusion</u> - Adults with type 2 diabetes - HbA1c 7-10% - BMI≤45kg/m2	Liraglutide 1.8mg/d Vs insulin glargine (dose titration: FPG< 100mg/dl) *(average dose at 26 w was 24 IU/day, 20% of the group reached FPG< 100 mg/dl)* vs placebo in addition to this background treatment: metformin 2000mg/d + glimepiride	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING (placebo arm) Participants: yes Personnel: yes Assessors: yes BLINDING (insulin arm) Participants: no Personnel: no Assessors: no Remarks on blinding method: Liraglutide and placebo were blinded, insulin was open-label. Metformin and glimepiride were open-label. FOLLOW-UP: <u>Study completers</u>: 90.6%
			Change in HbA1c from baseline (PO)	Liraglutide: -1.33% (SEM 0.09) Insulin: -1.09% (SEM 0.09) Pla: -0.24% (SEM 0.11) **Liraglutide vs pla: -1.09% (95%CI -1.28 to -0.9) p<0.0001; SS** **Liraglutide vs insulin: -0.24% (95%CI -0.39 to -0.08) ; p =0.0015; SS** *"Similar results were achieved using the per protocol analysis population (data not shown)"*	
			Body weight change from baseline	Liraglutide: -1.8kg (SEM 0.33) Insulin: +1.6kg (SEM 0.33) Pla: -0.4kg (SEM 0.39) **Liraglutide vs pla: -1.39kg (95%CI -2.10 to -0.69) ; p=0.0001; SS** **Liraglutide vs insulin: -3.43kg (95%CI -4.00 to -2.86); p<0.0001; SS**	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP Liraglutide: -4.0 mmHg Insulin: +0.54 mmHg Pla: -1.4 mmHg	

	Exclusion - Insulin treatment 3 months prior - Impaired renal or hepatic function - Significant cardiovascular disease - Proliferative retinopathy or maculopathy - Hypertension (≥180/100) - cancer	4mg/d Hyperglycaemia uptitration protocol: No protocol Hyperglycaemia rescue protocol: Participants with a confirmed FPG reading >13.3 mmol/l at week 8 and no intercurrent treatable illness were withdrawn Stratification: Monotherapy or combination therapy at baseline		Liraglutide vs pla: -2.53 mmHg (95%CI –5.36 to 0.29) ; p=0.08; NS **Liraglutide vs insulin: -4.51 mmHg (95%CI -6.82 to -2.20); p<0.0001; SS** DBP "no significant difference in the reduction in DBP was observed relative to either comparator."	Discontinued treatment: Lira: 23/230 (10%) Insulin: 13/232 (6%) Pla: : 18/114 (16%) Reason described: yes Hyperglycaemic rescue: Lira: 2/230 (<1%) Insulin: 1/232 (<1%) Pla: : 13/114 (11%) Statistical method for drop out/missing data: LOCF Data handling for rescued patients: LOCF ITT: defined as randomized participants that received at least one dose of the study drug SELECTIVE REPORTING: yes; incomplete reporting of some endpoints Other important methodological remarks - 2 week screening period, 3 week dose-escalation period, 3
			Safety		
			Death	NR	
			Cardiovascular adverse events *"cardiac disorders"(not defined)*	Liraglutide: 4.3% Insulin:3.9 % Pla: 3.5% NT	
			Any adverse events	Liraglutide: 65.7% Insulin:54.7 % Pla: 56.1% NT	
			Serious adverse events	Liraglutide: 4% Insulin: 7% Pla: 7% NT	
			Adverse event leading to withdrawal	Liraglutide: 4% Insulin: 2.2% Pla: 0.8% NT	
			Any gastro-intestinal adverse event	Liraglutide: 37.8% Insulin: 7.8% Pla: 15.8% NT	

			Diarrhoea	Liraglutide: 10% Insulin: 1.3% Pla: 5.3% **(p < 0.0001 for difference between 3 treatments)**	week maintenance period, 26 week treatment period - The non-inferiority margin against glargine was set to 0.4% and the difference to detect superiority against placebo was set to 0.5%. - For superiority and non-inferiority of liraglutide vs comparators, hierarchical tests were conducted. A sequential testing procedure was employed to protect the overall type 1 error rate. First, superiority of liraglutide to that of placebo had to be declared, then non-inferiority against glargine was tested and, if declared, superiority was tested. Finally, a test for superiority of insulin glargine vs placebo was performed. - Insulin glargine was titrated by patients Sponsor: Novo Nordisk
			Nausea	Liraglutide: 13.9% Insulin: 1.3% Pla: 3.5% **(p < 0.0001 for difference between 3 treatments)**	
			Vomiting	Liraglutide: 6.5% Insulin: 0.4% Pla: 3.5% **(p = 0.0005 for difference between 3 treatments)**	
			Severe hypoglycaemia	Liraglutide: 2.2% Insulin: 0 events Pla: 0 events NT	
			Documented symptomatic hypoglycaemia *(minor hypoglycaemia: FGP <3.1 mmol/l and symptoms)*	Liraglutide: 27.4% Insulin: 28.9% Pla: 16.7% NT	
			Injection site reactions	NR	
			Thyroid cancer	NR	

			Pancreatitis	No events	

Table 139

8.4.1.2 *Summary and conclusions*

Liraglutide + metformin + glimepiride vs **placebo**+ metformin + glimepiride			
Bibliography: Russell-Jones 2009(72)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	344 (1) 26 weeks	**Treatment difference: Liraglutide vs pla: -1.09% (95%CI -1.28 to -0.9) p<0.0001; SS in favour of liraglutide**	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: NA Directness: ok Imprecision: ok
Body weight change from baseline	344 (1) 26 weeks	**Treatment difference: Liraglutide vs pla: -1.39kg (95%CI -2.10 to -0.69) ; p=0.0001; SS in favour of liraglutide**	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: NA Directness: ok Imprecision: ok
Adverse events leading to withdrawal	344 (1) 26 weeks	Liraglutide: 4% Pla: 0.8% NT	Not applicable
Diarrhea	344 (1) 26 weeks	Liraglutide: 10% Pla: 5% **p < 0.0001 => SS in favour of placebo**	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: NA Directness: ok Imprecision: ok
Nausea	344 (1) 26 weeks	Liraglutide: 14% Pla: 4% **p < 0.0001 => SS in favour of placebo**	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: NA Directness: ok Imprecision: ok
Vomiting	344 (1) 26 weeks	Liraglutide: 7% Pla: 4% **p = 0.0005 => SS in favour of placebo**	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: NA Directness: ok Imprecision: ok
Severe hypoglycaemia	344 (1) 26 weeks	Liraglutide: 2% Pla: 0 events NT	Not applicable:

Table 140

In this open-label RCT, 581 patients with type 2 diabetes, inadequately controlled by metformin 2000mg/day + glimepiride 4 mg/day were randomized to liraglutide 1.8 mg (n=230), insulin glargine (dose titration: fasting plasma glucose <100 mg/dL) (n=232), or placebo (n=114) for 26 weeks. The mean age was 57, mean duration of diabetes 9 years, mean baseline HbA1c was 8.3%. and mean BMI was 30 kg/m^2. It was not reported how many participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

In patients who were inadequately controlled on metformin 2000mg/day + glimepiride 4 mg/day, at 26 weeks, the addition of liraglutide 1.8 mg resulted in a statistically significant decrease of HbA1c compared to the addition of placebo.

GRADE: HIGH quality of evidence

In patients who were inadequately controlled on metformin 2000mg/day + glimepiride 4 mg/day, at 26 weeks, there was a statistically significant difference in weight change with the addition of liraglutide 1.8 mg compared to the addition of placebo.
There was more weight loss with liraglutide than with placebo.

GRADE: HIGH quality of evidence

Withdrawal from the study due to adverse events was seen in 4% with liraglutide and <1% with placebo.
GRADE: not applicable

Rates of diarrhea were 10% with liraglutide and 5% with placebo. The difference was statistically significant.
Rates of nausea were 14% with liraglutide and 4% with placebo. The difference was statistically significant.
Rates of vomiting were 7% with liraglutide and 4% with placebo. The difference was statistically significant.
GRADE: HIGH quality of evidence

Severe hypoglycemia occurred in 2% with liraglutide; there were no events with placebo.
GRADE: not applicable

8.4.2 Liraglutide + metformin + glimepiride versus insulin glargine + metformin + glimepiride

8.4.2.1 *Clinical evidence profile*

See 8.4.1.1

8.4.2.2 *Summary and conclusions*

Liraglutide + metformin + glimepiride vs **insulin glargine** + metformin + glimepiride			
Bibliography: Russell-Jones 2009(72) LEAD-5			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	462 (1) 26 weeks	**Treatment difference: Liraglutide vs insulin: -0.24% (95%CI -0.39 to -0.08) p =0.0015; SS in favour of liraglutide**	⊕⊕⊖⊖ **LOW** Study quality: -1 (open label) Consistency: -1; other study (see 8.4.3) shows SS effect in favour of insulin glargine, possibly due to difference in titration protocol Directness: ok Imprecision: ok
Body weight change from baseline	462 (1) 26 weeks	**Treatment difference: Liraglutide vs insulin: -3.43kg (95%CI -4.00 to -2.86); p<0.0001; SS in favour of liraglutide**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (open label) Consistency: NA Directness: ok Imprecision: ok
Adverse events leading to withdrawal	462 (1) 26 weeks	Liraglutide: 4% Insulin: 2% NT	Not applicable
Diarrhea	462 (1) 26 weeks	Liraglutide: 10% Insulin: 1% **p < 0.0001 for difference between treatments = > SS in favour of insulin**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (open label) Consistency: NA Directness: ok Imprecision: ok
Nausea	462 (1) 26 weeks	Liraglutide: 14% Insulin: 1% **p < 0.0001 for difference between treatments = > SS in favour of insulin**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (open label) Consistency: NA Directness: ok Imprecision: ok
Vomiting	462 (1) 26 weeks	Liraglutide: 7% Insulin: 0.4% **p = 0.0005 for difference between treatments = > SS in favour of insulin**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (open label) Consistency: NA Directness: ok Imprecision: ok
Severe hypoglycaemia	462 (1) 26 weeks	Liraglutide: 2% Insulin: 0 events NT	Not applicable:

Table 141

In this open-label RCT, 581 patients with type 2 diabetes, inadequately controlled by metformin 2000mg/day + glimepiride 4 mg/day were randomized to liraglutide 1.8 mg (n=230), insulin glargine (dose titration: fasting plasma glucose <100 mg/dL) (n=232), or placebo (n=114) for 26 weeks. The mean age was 57, mean duration of diabetes 9 years, mean baseline HbA1c was 8.3%. and mean BMI was 30 kg/m^2. It was not reported how many participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

Our confidence in the estimate of the between-group differences is limited by the open-label design of the trial.

In patients who were inadequately controlled on metformin 2000mg/day + glimepiride 4 mg/day, at 26 weeks, the addition of liraglutide 1.8 mg resulted in a statistically significant decrease of HbA1c compared to the addition of insulin glargine.

GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin 2000mg/day + glimepiride 4 mg/day, at 26 weeks, there was a statistically significant difference in weight change with the addition of liraglutide 1.8 mg compared to the addition of insulin glargine.
The weight in the liraglutide group was decreased compared to the insulin glargine group (in which the weight had increased from baseline).

GRADE: MODERATE quality of evidence

Withdrawal from the study due to adverse events was seen in 4% with liraglutide and 2% with insulin glargine.
GRADE: not applicable

Rates of diarrhea were 10% with liraglutide and 1% with insulin glargine. The difference was statistically significant.
Rates of nausea were 14% with liraglutide and 1% with insulin glargine. The difference was statistically significant.
Rates of vomiting were 7% with liraglutide and <1% with insulin glargine. The difference was statistically significant.
GRADE: not applicable
GRADE: MODERATE quality of evidence

Severe hypoglycemia occurred in 2% with liraglutide and 0% with insulin glargine.
GRADE: not applicable

8.4.3 Liraglutide + MET+/-SU versus insulin glargine + MET+/-SU

8.4.3.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref: D'Alessio 2015 (73) EAGLE Design: RCT (OL) (PG) Duration of follow-up: 24 weeks	n: 978 Mean age: 57y • Prior/current treatment: >3 months of metformin, alone or in combination with SU, glinides or a DPP4-i Mean DMII duration: 9 y Mean baseline HbA1c: 9.0% Mean BMI: 32 Previous CV event: • Myocardial infarction: 4% • Angina pectoris: 5% • Coronary artery disease: 11% • Heart failure: 1%	Insulin glargine (titrated to target fasting plasma glucose of 4.0-5.5 mmol/L) vs liraglutide 1.8 mg in addition to this background treatment: metformin +/- SU <u>Hyperglycaemia uptitration protocol:</u> No protocol <u>Hyperglycaemia rescue protocol</u>**:**	Efficacy		RANDO: unclear ALLOCATION CONC: unclear BLINDING : Participants: no Personnel: no Assessors: no FOLLOW-UP: <u>Study completers</u>: 89% <u>Discontinued treatment</u>: Insulin: 7.6% liraglutide: 13.7% **p<0.001** Reason described: yes, in supplementary materials <u>Uptitration of study medication</u>: Not applicable <u>Hyperglycaemic rescue</u>: not
			Change in HbA1c from baseline	Insulin: -1.94% Liraglutide: -1.79% **Mean difference: -0.15 %(-0.28 to -0.02)** **P=0.019 => SS**	
			Body weight change from baseline	Insulin: +2.0 kg Liraglutide: -3.0 kg **Mean difference: 4.9kg (4.41 to 5.37)** **P<0.001**	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP Insulin: -0.1 mmHg Liraglutide: -3.1 mmHg **Mean difference 3.1 mmHg (1.56 to 4.69)** **P<0.001** DBP Insulin: -0.3 mmHg Liraglutide: -0.9 mmHg Mean difference 1.0mmHg (-0.04 to 2.06) P=0.059	

	• Stroke:2 % • TIA: 2% • PAD: 8% Renal impairment: NR <u>Inclusion</u> • Age 35-75y • DM2 for ≥1 year • HbA1c 7.5-12% • BMI 25-40 • >3 months of metformin, alone or in combination with SU, glinides or a DPP4-i <u>Exclusion</u> • Treated with GLP-1, insulin in previous year • Treated with thiazolidinediones or α-glucosidase inhibitors in previous 3 months • Impaired renal or hepatic function • Any condition that investigators felt	No protocol	Safety		applicable <u>Statistical method for drop out/missing data</u>: LOCF <u>Data handling for rescued patients</u>: not applicable <u>ITT</u>: defined as all participants randomly assigned to treatment groups who had received at least one dose of the study drug and had at least one on-treatment assessment of any primary or secondary efficacy variable. SELECTIVE REPORTING: yes, incomplete reporting of secondary and safety endpoints Sponsor: Sanofi
			Death	NR	
			Cardiovascular adverse events	NR	
			Any adverse events	Insulin: 50.2% Liraglutide: 65.9% **P<0.001**	
			Serious adverse events	Insulin: 2.3% Liraglutide: 3.1% NT	
			Adverse event leading to withdrawal	Insulin: 1.2% Liraglutide: 7.1% **P<0.0001**	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea	Insulin: 3.7% Liraglutide: 12.9% **P<0.0001**	
			Nausea	Insulin: 2.7% Liraglutide: 30.4% **P<0.0001**	
			Vomiting	Insulin: 1.7% Liraglutide: 9.6% **P<0.0001**	
			Severe hypoglycaemia	Insulin: 0/484 Liraglutide: 2/481	
			Documented symptomatic	Insulin: 45% Liraglutide:18%	

	would compromise the patient's safety or participation in the study		**hypoglycaemia** *=event with typical symptoms, with or without an associated plasma glucose level <4.0 mmol/L*		
			Injection site reactions	NR	
			Thyroid cancer	NR	
			Pancreatitis	Insulin: 0/484 Liraglutide: 1/481	

Table 142

8.4.3.2 *Summary and conclusions*

Liraglutide + MET +/- SU vs insuline glargine + MET +/- SU			
Bibliography: D'Alessio 2015(73) EAGLE			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	978 (1) 24 w	**Mean difference:** **MD -0.15 %(95%CI -0.28 to -0.02)** **p=0.019** **SS in favour of insulin glargine**	⊕⊕⊖⊖ **LOW** Study quality: -1 open label, unclear randomization and allocation concealment Consistency: -1; other study SS in favour of liraglutide (see 8.4.2), possibly due to differences in titration protocol Directness: ok Imprecision: ok
Body weight change from baseline	978 (1) 24 w	**MD 4.9kg (95%CI 4.41 to 5.37)** **p<0.001** **SS in favour of liraglutide**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label, unclear randomization and allocation concealment Consistency: NA Directness: ok Imprecision: ok
Adverse events leading to withdrawal	978 (1) 24 w	**Insulin: 1.2%** **Liraglutide: 7.1%** **P<0.0001** **SS in favour of insulin glargine**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label, unclear randomization and allocation concealment Consistency: NA Directness: ok Imprecision: ok
Diarrhea	978 (1) 24 w	Insulin: 3.7% Liraglutide: 12.9% **P<0.0001** **SS in favour of insulin glargine**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label, unclear randomization and allocation concealment Consistency: NA Directness: ok Imprecision: ok
Nausea	978 (1) 24 w	Insulin: 2.7% Liraglutide: 30.4% **P<0.0001** **SS in favour of insulin glargine**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label, unclear randomization and allocation concealment Consistency: NA Directness: ok Imprecision: ok
Vomiting	978 (1) 24 w	Insulin: 1.7% Liraglutide: 9.6% **P<0.0001** **SS in favour of insulin glargine**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label, unclear randomization and allocation concealment Consistency: NA Directness: ok Imprecision: ok
Severe hypoglycaemia	978 (1) 24 w	Insulin: 0/484 Liraglutide: 2/481 (0.4%) NT	Not applicable

Table 143

In this open-label RCT, 978 patients with type 2 diabetes, inadequately controlled by metformin +/- sulfonylurea, were randomized to insulin glargine (titrated to a fasting plasma glucose of 4.0-5.5 mmol/L) or liraglutide 1.8 mg for 24 weeks. The mean age was 57, mean duration of diabetes 9 years, mean baseline HbA1c was 9.0% and mean BMI was 32 kg/m^2. Only 4% of participants had had a previous myocardial infarction. Patients with renal impairment excluded from the trial.

In patients who were inadequately controlled on metformin +/- sulfonylurea, at 24 weeks, the addition of insulin glargine resulted in a statistically significant decrease of HbA1c compared to the addition of liraglutide.

GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin +/- sulfonylurea, at 24 weeks, there was a statistically significant difference in weight change with the addition of insulin glargine compared to the addition of liraglutide.
The weight in the liraglutide group was decreased compared to the insulin glargine group (in which the weight had increased from baseline).

GRADE: MODERATE quality of evidence

Withdrawal from the study due to adverse events was seen in 7.2% with liraglutide and 1.2% with insulin glargine. The difference was statistically significant.
GRADE: MODERATE quality of evidence

Rates of diarrhea were 12.9% with liraglutide and 3.7% with insulin glargine. The difference was statistically significant.
Rates of nausea were 30.4% with liraglutide and 2.7% with insulin glargine. The difference was statistically significant.
Rates of vomiting were 9.6% with liraglutide and 1.7% with insulin glargine. The difference was statistically significant.
GRADE: not applicable
GRADE: MODERATE quality of evidence

Severe hypoglycemia occurred in 0% with liraglutide and 0.4% with insulin glargine.
GRADE: not applicable

8.4.4 Exenatide twice daily + metformin +/- SU versus liraglutide + metformin +/- SU

See 6.4.2.1.

8.5 Combination therapy with OAD

8.5.1 Liraglutide +/- OAD versus placebo +/- OAD (aim = weight loss)

8.5.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref: Davies 2015(74) SCALE Design: RCT (DB) (PG) Duration of follow-up: 56 weeks	n: 846 Mean age: 55y Prior/current treatment: diet and exercise only, metformin, SU, metformin + glitazone, metformin + SU, metformin+SU+glitazone, SU+glitazone Mean DMII duration: 7.3y Mean baseline HbA1c: 7.9% Mean BMI: 37.2 Previous CV event: NR Renal impairment: NR	Liraglutide 3.0 mg/day Vs Liraglutide 1.8 mg/day Vs placebo in addition to this background treatment: diet with 500 kcal/d deficit+ exercise program (≥150 min/week brisk walking) +/- OAD (=metformin, SU, metformin + glitazone, metformin + SU, metformin+SU+glitazone,	Efficacy		RANDO: Unclear (method not described) ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: unclear FOLLOW-UP: <u>Study completers</u>: 74% <u>Discontinued treatment</u>: Lira 3.0 mg: 23% Lira 1.8 mg: 22% Placebo: 34%
			Change in HbA1c from baseline	Lira 3.0 mg: -1.3% Lira 1.8 mg: -1.1% Placebo:-0.3% **Lira 3.0 mg vs pla: -0.93 (-1.08 to -0.78); p<0.001 => SS** **Lira 1.8 mg vs pla: -0.74 (-0.91 to -0.57); p<0.001 => SS**	
			Body weight change from baseline (PO)	Lira 3.0 mg: -6.0 kg Lira 1.8 mg: -4.6 kg Placebo: -2.0 kg **Lira 3.0 mg vs pla: -4.0 kg (-5.1 to -2.9); p<0.001 => SS** **Lira 1.8 mg vs pla: -2.7 kg (-4.0 to -1.4); p<0.001=> SS**	
			Blood pressure change from	SBP Lira 3.0 mg: -2.8 mmHg	

	Inclusion • BMI ≥27 • Age ≥18 y • Stable body weight • Type II diabetes • HbA1c 7-10% • Treated with diet, exercise +/- 1 to 3 OAD (metformin, thiazolidinedione, SU) Exclusion • Treatment with any hypoglycemic agent other than metformin, SU and glitazone in the 3 months prior to screening • Recent major hypoglycemia or hypoglycemic awareness • History of chronic or	SU+glitazone) Hyperglycaemia uptitration protocol: No protocol Hyperglycaemia rescue protocol**:** No protocol Stratification: Background treatment Baseline HbA1c	**baseline (SystBP/DiastBP)**	Lira 1.8 mg: -3.5 mmHg Placebo:-0.4 mmHg **Lira 3.0 mg vs pla: -2.59 mmHg (-4.56 to -0.62); p=0.01 => SS** **Lira 1.8 mg vs pla: -2.68 mmHg (-4.98 to -0.38); p=0.02=> SS** DBP Lira 3.0 mg: -0.9 mmHg Lira 1.8 mg: -1.1 mmHg Placebo:-0.5 mmHg Lira 3.0 mg vs pla: -0.36 (-1.69 to 0.96); p=0.59 => NS Lira 1.8 mg vs pla: -0.19 (-1.74 to 1.36); p=0.81=> NS	Reason described: yes Uptitration of study medication: Not applicable Hyperglycaemic rescue: Not applicable Statistical method for drop out/missing data: Weight endpoints: multiple imputation All other endpoints: LOCF Data handling for rescued patients: not applicable ITT: defined as “modified intention to treat” Full analysis set described as: participants exposed to ≥1 treatment dose with ≥1 postbaseline efficacy assessment SELECTIVE REPORTING: no Sponsor: Novo Nordisk
			Safety		
			Death	Lira 3.0 mg: 0/422 Lira 1.8 mg: 1/210 Placebo: 0/212 NT	
			Cardiovascular adverse events *Adjucation-confirmed*	Lira 3.0 mg: 0.5% Lira 1.8 mg: 1.4% Placebo: 1.4% NT	
			Any adverse events	Lira 3.0 mg: 92.9% Lira 1.8 mg: 90.5% Placebo: 85.8% NT	

	idiopathic acute pancreatitis • Personal history of non-familial medullary thyroid carcinoma • Cancer (past or present) which in the investigator's opinion could interfere with the results of the trial		**Serious adverse events**	Lira 3.0 mg: 8.8% Lira 1.8 mg: 8.6% Placebo: 6.1% NT	
			Adverse event leading to withdrawal	Lira 3.0 mg: 9.2% Lira 1.8 mg: 8.6% Placebo: 3.3% NT	
			Any gastro-intestinal adverse event	Lira 3.0 mg: 62.5% Lira 1.8 mg: 56.2% Placebo: 39.2% NT	
			Diarrhoea	Lira 3.0 mg: 25.6% Lira 1.8 mg: 17.6% Placebo:12.7 % NT	
			Nausea	Lira 3.0 mg: 32.7% Lira 1.8 mg: 31.4% Placebo: 13.7% NT	
			Vomiting	Lira 3.0 mg: 15.6% Lira 1.8 mg: 10.0% Placebo: 5.7% NT	
			Severe hypoglycaemia	Lira 3.0 mg: 5/423 Lira 1.8 mg: 3/211 Placebo: 0/212 NT	
			Documented symptomatic hypoglycaemia *"minor hypoglycaemia":*	Lira 3.0 mg: 87 events per 100 patient-years Lira 1.8 mg: 95 events per 100 patient-years Placebo: 31 events per 100 patient-	

			confirmed plasma glucose <56 mg/dl (3.1 mmol/l) , symptomatic and self-treatable, or asymptomatic	years NT	
			Injection site reactions	NR	
			Thyroid cancer	Lira 3.0 mg: 0/423 Lira 1.8 mg: 0/211 Placebo: 1/212 NT	
			Pancreatitis	No cases	

Table 144

8.5.1.2 *Summary and conclusions*

Liraglutide +/- OAD vs placebo +/- OAD (aim= weight loss)			
Bibliography: Davies 2015(74) SCALE			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline	422 (1) 56 weeks	**Lira 1.8 mg vs pla** **Treatment difference:** **-0.74 (95%CI -0.91 to -0.57)** **p<0.001 => SS in favour of liraglutide**	⊕⊕⊖⊖ **LOW** Study quality: -1 (unclear randomization, >20% drop-out and LOCF) Consistency: NA Directness: -1 different background treatments Imprecision: ok
Body weight change from baseline (PO)	422 (1) 56 weeks	**Lira 1.8 mg vs pla** **Treatment difference:** **-2.7 kg (95%CI -4.0 to -1.4)** **p<0.001=> SS in favour of liraglutide**	⊕⊕⊖⊖ **LOW** Study quality: -1 (unclear randomization, >20% drop-out) Consistency: NA Directness: -1 different background treatments Imprecision: ok
Adverse events leading to withdrawal	422 (1) 56 weeks	Lira 1.8 mg: 9% Placebo: 3% NT	Not applicable
Diarrhea	422 (1) 56 weeks	Lira 1.8 mg: 18% Placebo: 13 % NT	Not applicable
Nausea	422 (1) 56 weeks	Lira 1.8 mg: 31% Placebo: 14% NT	Not applicable
Vomiting	422 (1) 56 weeks	Lira 1.8 mg: 10% Placebo: 6% NT	Not applicable
Severe hypoglycaemia	422 (1) 56 weeks	Lira 1.8 mg: 3/211 (1%) Placebo: 0/212 (0%) NT	Not applicable

Table 145

In this double blind RCT, 846 patients with type 2 diabetes, inadequately controlled by oral diabetic medication (metformin, SU, pioglitazon mono-, duo- or tritherapy) were randomized to liraglutide 3.0 mg/day (n=422), 1.8 mg/day (n=210), or placebo (n=212). for 56 weeks. The primary endpoint in this trial was weight loss.
The mean age was 55, mean duration of diabetes 7 years, mean baseline HbA1c was 7.9%. and mean BMI was 37 kg/m^2. It is not reported how many participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

There was a large drop-out throughout the study (26%). This limits our confidence in the estimate of the between-group differences.

The interpretation of these results is further limited because of the inclusion of patients with any oral antidiabetic therapy. Based on these results, it is difficult to make statements about the combination of a glp-1 receptor agonist with a specific oral antidiabetic agent.

In patients who were inadequately controlled on OAD, at 56 weeks, the addition of liraglutide 1.8 mg resulted in a statistically significant decrease of HbA1c compared to the addition of placebo

GRADE: LOW quality of evidence

In patients who were inadequately controlled on OAD,; at 56 weeks, there was a statistically significant difference in weight change with the addition of liraglutide 1.8 mg compared to the addition of placebo.
There was more weight loss with liraglutide than with placebo.

GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 9% with liraglutide and 3% with placebo.
GRADE: not applicable

Rates of diarrhea were 18% with liraglutide and 13% with placebo.
Rates of nausea were 31% with liraglutide and 14% with placebo.
Rates of vomiting were 10% with liraglutide and 6% with placebo.
GRADE: not applicable

There were no events of severe hypoglycemia.
Severe hypoglycemia occurred in 1% with liraglutide and 0% with placebo. The difference was **not** statistically significant.
GRADE: not applicable

8.5.2 Liraglutide + OAD versus placebo + OAD in patients with moderate renal impairment

8.5.2.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref: Davies 2016 (75)LIRA-RENAL Design: RCT (DB) (PG) Duration of follow-up: 26 week	n: 279 Mean age: 67 y Prior/current treatment: metformin, SU, pioglitazone (mono or dual therapy), insulin in monotherapy or combination with metformin and/or pioglitazone Mean DMII duration: 15 y Mean baseline HbA1c: 8% Mean BMI: 34 Previous CV event: NR Renal impairment: 100%; 43% had stage 3B CKD (eGFR 30-<45	Liraglutide 1.8 mg vs placebo in addition to this background treatment: antidiabetic medication: metformin, SU, prioglitazon (mono or dual therapy), insulin monotherapy, combination with metformin and/or pioglitazone)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: <u>Study completers</u>: 75% <u>Discontinued treatment</u>: "approximately 25% of patients in each group withdrew from the trial" Reason described: no <u>Uptitration of study medication</u>: Not applicable
			Change in HbA1c from baseline (PO)	Lira: -1.05% Pla: -0.38% **Lira vs pla: -0.66% (-0.90 to -0.43); p<0.0001 => SS**	
			Body weight change from baseline	Lira: -2.41 kg Pla: -1.09 kg **Lira vs pla: -1.32 kg (-2.24 to -0.40) P=0.0052 => SS**	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP Lira: -2.45 Pla: -0.33 Lira vs pla: p=0.25 => NS DBP "there was no difference between treaments in BDP" Lira vs pla: p=0.89 => NS	
			Safety		
			Death	Lira: 4/140	

	mL/min/1.73 m^2) Inclusion • Age 18-80y • Type 2 diabetes • Stable diabetes treatment for >90 days • OAD: metformin, SU, prioglitazon (mono or dual therapy), insulin monotherapy, combination with metformin and/or pioglitazone) • Moderate renal impairment >90 days before screening • BMI 25-45 Exclusion • Recurrent hypoglycemic unawareness and/or recurrent severe hypoglycemia	Hyperglycaemia uptitration protocol: No protocol Hyperglycaemia rescue protocol: No protocol Stratification: eGFR < or ≥45 mL/min/1.73 m^2		Pla: 1/137 NT	Hyperglycaemic rescue: not applicable Statistical method for drop out/missing data: MMRM Data handling for rescued patients: not applicable ITT: defined as patients who received at least one dose of trial medication SELECTIVE REPORTING: yes, incomplete and unclear reporting of secondary endpoints and safety endpoints Other important methodological remarks For patients using insulin with an HbA1c ≤8% at screening, the pretrial insulin dose was reduced by 20% at day 0 and kept fixed until the liraglutide dose
			Cardiovascular adverse events *"cardiac disorders", not defined*	Lira: 3.6% Pla: 2.9% NT	
			Any adverse events	Lira: 76.4% Pla: 68.6% NT	
			Serious adverse events	Lira: 10.0% Pla: 10.9% NT	
			Adverse event leading to withdrawal	Lira: 13.6% Pla: 2.9% NT	
			Any gastro-intestinal adverse event	Lira: 35.7% Pla: 17.5% NT	
			Diarrhoea	Lira: 7.1% Pla: 2.9% NT	
			Nausea	Lira: 21.4% Pla: 4.4% NT	
			Vomiting	Lira: 12.1% Pla: 2.2%	

	• Impaired liver function • History of chronic pancreatitis or idiopathic acute pancreatitis • NYHA IV heart failure • Episode of unstable angina, acute coronary event, cerebral stroke/transient ischemic attack, or other significant cardiovascular event within the past 180 days • SBP ≥180 mmHg or DBP ≥100 mmHg • Screening calcitonin value ≥50 ng/L • Personal history of medullary thyroid carcinoma or MEN type 2			NT	escalation was complete. Titration to the pretrial insulin dose was allowed at the discretion of the investigator. Sponsor: Novo Nordisk
			Severe hypoglycaemia	Lira: 1/140 Pla: 0/137 NT	
			Documented symptomatic hypoglycaemia	Lira: 20.7% Pla: 26.3% NT	
			Injection site reactions	NR	
			Thyroid cancer	NR	
			Pancreatitis	No events of acute pancreatitis 1 case of chronic asymptomatic pancreatitis in liraglutide group	

Table 146

8.5.2.2 *Summary and conclusions*

Liraglutide + antidiabetic medication vs placebo + antidiabetic medication in patients with moderate renal impairment			
Bibliography: Davies 2016 (75)LIRA-RENAL			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	279 (1) 26 weeks	**Lira vs pla** **Treatment difference:** **-0.66% (95%CI -0.90 to -0.43)** **p<0.0001 => SS in favour of liraglutide**	⊕⊕⊖⊖ **LOW** Study quality: -1 drop-out 25%, reasons not described Consistency: NA Directness: -1 different background medications Imprecision: ok
Body weight change from baseline	279 (1) 26 weeks	**Lira vs pla** **Treatment difference:** **-1.32 kg (95%CI -2.24 to -0.40)** **P=0.0052 => SS in favour of liraglutide**	⊕⊕⊖⊖ **LOW** Study quality: -1 drop-out 25%, reasons not described Consistency: NA Directness: -1 different background medications Imprecision: ok
Adverse events leading to withdrawal	279 (1) 26 weeks	Lira: 14% Pla: 3% NT	Not applicable
Diarrhea	279 (1) 26 weeks	Lira: 7% Pla: 3% NT	Not applicable
Nausea	279 (1) 26 weeks	Lira: 21% Pla: 4% NT	Not applicable
Vomiting	279 (1) 26 weeks	Lira: 12% Pla: 2% NT	Not applicable
Severe hypoglycaemia	279 (1) 26 weeks	Lira: 1/140 (1%) Pla: 0/137 (0%) NT	Not applicable

Table 147

In this double blind RCT, 279 patients with type 2 diabetes, inadequately controlled by antidiabetic medication (monotherapy or combinations of metformin, SU, pioglitazone and insulin), were randomized to liraglutide 1.8 mg or placebo for 26 weeks. The mean age was 67, mean duration of diabetes 15 years, mean baseline HbA1c was 8% and mean BMI was 34 kg/m^2. It was not reported how many of the participants had had a previous myocardial infarction. 100% of included patients had renal impairment ; 43% had stage 3B chronic kidney disease (eGFR 30-45 mL/min/7.73m^2).

There was a large drop-out throughout the study (25%). Although drop-out was similar in both groups, the reasons for withdrawal was not reported. This limits our confidence in the estimate of the between-group differences.
The interpretation of these results is further limited because of the inclusion of patients with any antidiabetic therapy. Based on these results, it is difficult to make statements about the combination of a glp-1 receptor agonist with a specific antidiabetic agent.

In patients with moderate renal impairment who were inadequately controlled on antidiabetic medication, at 26 weeks, the addition of liraglutide 1.8 mg resulted in a statistically significant decrease of HbA1c compared to the addition of placebo.

GRADE: LOW quality of evidence

In patients with moderate renal impairment who were inadequately controlled on antidiabetic medication, at 26 weeks, there was a statistically significant difference in weight change with the addition of liraglutide compared to the addition of y.
There was more weight loss with liraglutide than with placebo.

GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 14% with liraglutide and 3% with placebo.
GRADE: not applicable
GRADE: HIGH MODERATE LOW VERY LOW quality of evidence

Rates of diarrhea were 7% with liraglutide and 3% with placebo.
Rates of nausea were 21% with liraglutide and 4% with placebo.
Rates of vomiting were 12% with liraglutide and 2% with placebo.
GRADE: not applicable

There were no events of severe hypoglycemia.
Severe hypoglycemia occurred in 1% with liraglutide and 0% with placebo.
GRADE: not applicable

8.5.3 Exenatide once weekly + OAD versus liraglutide once daily + OAD

See 7.3.2.1.

8.6 Combination therapy with insulin

8.6.1 Liraglutide + basal insulin analogues +/- metformin versus placebo + basal insulin analogues +/- metformin

8.6.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Ahmann 2015 (76) Design: RCT (DB) (PG) Duration of follow-up: 26 weeks	n: 451 Mean age: 58y Prior/current treatment: stable doses of basal insulin analogue (glargine or detemir, ≥20U/day) +/- metformin (≥1500 mg/day) Mean DMII duration: 12y Mean baseline HbA1c: 8.3% Mean BMI: 32	Liraglutide 1.8 mg (1x/day) vs placebo in addition to this background treatment: basal insulin analogue (≥20 U/day) +/- metformin (≥1500 mg/day)	Efficacy		RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Study completers: 81% Discontinued treatment: Liraglutide: 15.5% Placebo: 22.7% Reason described: no
			Change in HbA1c from baseline (PO)	Liraglutide: -1.3 % Placebo: -0.1 % **Treatment difference: -1.2 %(-1.4 to -1.0); P<0.0001 => SS**	
			Body weight change from baseline	Liraglutide: -3.5 kg Placebo: -0.4 kg **Treatment difference: -3.1 kg(-3.9 to -2.4); P<0.0001 => SS**	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP Liraglutide: -5.8 mmHg Placebo:-0.8 mmHg **Treatment difference: -5.0 mmHg (-7.5 to -2.6) p<0.0001=>SS** DBP	

	Previous CV event: NR Renal impairment: NR <u>Inclusion</u> • Age 18-80y • HbA1c 7-10% • BMI 20-45 • Treated with stable doses of basal insulin analogue (glargine or detemir, ≥20U/day) +/- metformin (≥1500 mg/day) for at least 8 weeks before enrolment <u>Exclusion</u> • Hypoglycaemic unawareness and/or recurrent severe hypoglycaemic episodes • Treatment with glucose-lowering	<u>Hyperglycaemia uptitration protocol:</u> No protocol <u>Hyperglycaemia rescue protocol</u>**:** No protocol <u>Stratification:</u> • Screening HbA1c ≤8% vs >8% • Insulin glargine vs detemir • Metformin/no metformin		Liraglutide: -1.2 mmHg Placebo:-0.52 mmHg Treatment difference: -0.7 mmHg (-2.3 to -0.9) p=0.41=> NS	<u>Uptitration of study medication</u>: Not applicable <u>Hyperglycaemic rescue</u>: not applicable <u>Statistical method for drop out/missing data</u>: MMRM <u>Data handling for rescued patients</u>: not applicable <u>ITT</u>: "full analysis set" defined as all randomized subjects who received ≥1 dose of trial product and who provided at least one baseline and one post-baseline efficacy value SELECTIVE REPORTING: yes, incomplete reporting of safety endpoints Other important methodological remarks
			Safety		
			Death	2 deaths due to neoplasm (1 in lira group, 1 in placebo) described but unclear whether these were total figures	
			Cardiovascular adverse events	NR	
			Any adverse events	Liraglutide: 69% Placebo: 58% NT	
			Serious adverse events	Liraglutide: 5% Placebo: 3% NT	
			Adverse event leading to withdrawal	NR	
			Any gastro-intestinal adverse event	Liraglutide: 41% Placebo: 17% NT	
			Diarrhoea	Liraglutide: 11% Placebo: 5% NT	
			Nausea	Liraglutide: 22% Placebo: 3%	

	agents other than stated in the inclusion critera (3 months prior to screening) • Impaired renal function (GFR <60 mL/min/1.73m^2) • History of chronic or idiopathic acute pancreatitis • Within past 6 months: unstable angina, acute coronary event, or other significant cardiovascular event			NT	For subjects with baseline HbA1c ≤8.0%, insulin dose was reduced by 20% at randomization. Up-titration of insulin to no higher than the pre-study dose was allowed during weeks 3-8. After randomization, insulin adjustments above the pre-study dose were not allowed. Sponsor: Novo Nordisk
			Vomiting	Liraglutide: 9% Placebo: 1% NT	
			Severe hypoglycaemia	No events	
			Documented symptomatic hypoglycaemia *Confirmed hypoglycaemia: minor and/or severe hypoglycaemia*	Liraglutide: 126 events per 100 patient years Placebo: 83 events per 100 patient **Treatment ratio for rate:** **2.0 (1.03 to 3.89) p=0.04 => SS**	
			Injection site reactions	NR	
			Thyroid cancer	No cases	
			Pancreatitis	No events	

Tabel 1

8.6.1.2 *Summary and conclusions*

Liraglutide + basal insulin analogues +/- metformin vs placebo + basal insulin analogues +/- metformin			
Bibliography: Ahmann 2015(76)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	451 (1) 26 w	**Treatment difference:** **-1.2 %(95%CI -1.4 to -1.0)** **p<0.0001** **SS in favour of liraglutide**	⨁⨁⨁⊖ **MODERATE** Study quality: -1 unclear randomization and allocation concealment Consistency: NA Directness: ok Imprecision: ok
Body weight change from baseline	451 (1) 26 w	**Treatment difference:** **-3.1 kg(95%CI -3.9 to -2.4)** **p<0.0001** **SS in favour of liraglutide**	⨁⨁⨁⊖ **MODERATE** Study quality: -1 unclear randomization and allocation concealment Consistency: NA Directness: ok Imprecision: ok
Adverse events leading to withdrawal	/	NR	Not applicable
Diarrhea	451 (1) 26 w	Liraglutide: 11% Placebo: 5% NT	Not applicable
Nausea	451 (1) 26 w	Liraglutide: 22% Placebo: 3% NT	Not applicable
Vomiting	451 (1) 26 w	Liraglutide: 9% Placebo: 1% NT	Not applicable
Severe hypoglycaemia		No events	Not applicable

Table 148

In this double blind RCT, 451 patients with type 2 diabetes, inadequately controlled by a basal insulin analogue (insulin glargine or detemir ≥20U/day), with or without metformin ≥1500 mg/day, were randomized to liraglutide 1.8 mg or placebo for 26 weeks. The mean age was 58, mean duration of diabetes 12 years, mean baseline HbA1c was 8.3% and mean BMI was 32 kg/m^2. It was not reported how many of the participants had had a previous myocardial infarction. Patients with a glomerular filtration rate <60 mL/min/1.73m^2 were excluded from the trial.

In patients who were inadequately controlled on a basal insulin analogue, with or without metformin, at 26 weeks, the addition of liraglutide 1.8 mg resulted in a statistically significant decrease of HbA1c compared to the addition of placebo.

GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on a basal insulin analogue, with or without metformin, at 26 weeks, there was a statistically significant difference in weight change with the addition of liraglutide 1.8 mg compared to the addition of placebo.
There was more weight loss with liraglutide than with placebo.

GRADE: MODERATE quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was not reported.
GRADE: not applicable

Rates of diarrhea were 11% with liraglutide and 5% with placebo.
Rates of nausea were 22% with liraglutide and 3% with placebo.
Rates of vomiting were 9% with liraglutide and 1% with placebo.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

8.6.2 Liraglutide + multiple daily insulin versus placebo + multiple daily insulin

8.6.2.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref: Lind 2015 (77) MDI Liraglutide trial Design: RCT (DB) (PG) Duration of follow-up: 24 weeks	n: 124 Mean age: 64 y Prior/current treatment: metformin/insulin Mean DMII duration: 17y Mean baseline HbA1c: 9% Mean BMI: 34 Previous CV event: • Previous MI: 13% • Previous stroke: 1% • Previous PCI: 11% • Previous coronary bypass surgery: 10% Renal impairment: NR	Liraglutide 1.8 mg Vs Placebo in addition to this background treatment: Multiple daily insulin injections (separate basal and mealtime injections, at least 2 mealtime insulin doses/day) (unclear whether or not metformin was discontinued)).	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: unclear FOLLOW-UP: <u>Study completers</u>: 96% <u>Discontinued treatment</u>: Lira: 5% Placebo: 3% Reason described: yes <u>Uptitration of study medication</u>: Not applicable <u>Hyperglycaemic rescue</u>:
			Change in HbA1c from baseline (PO)	Lira: -1.5% Placebo: -0.4% **Lira vs placebo: -1.1% (-1.5 to -0.8); p<0.001=> SS**	
			Body weight change from baseline	Lira: -3.8 kg Placebo: -0.0 kg **Lira vs placebo: -3.8 kg(-4.9 to -2.8); p<0.001=> SS**	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP Lira: -4.6 mmHg Placebo: +0.9 mmHg **Lira vs placebo: -5.5 mmHg (-9.9 to -1.1)** **P=0.015 => SS** DBP Lira: +0.6 mmHg Placebo: +0.3 mmHg Lira vs placebo: +0.3 mmHg(-3.0 to 3.6); p=0.88 =>NS	

	Inclusion • Type 2 diabetes • Multiple daily insulin injections (seperate basal and mealtime injections, at least 2 mealtime insulin doses/day) • HbA1c ≥7.5-11.5% • BMI 27.5- 45 Exclusion • Patients using premixed insulin • Use of any OAD apart from metformin during previous 3 months	*At 24 weeks, in the liraglutide group the total daily basal insulin dose was reduced by 6.8 units and total daily mealtime insulin dose by 11.2 units. In the placebo group the corresponding reductions were 0.5 units and 1.9 units* Hyperglycaemia uptitration protocol: No protocol Hyperglycaemia rescue protocol**:** self-measured blood glucose on 3 seperate			Lira: 1.6% Placebo: 5% Statistical method for drop out/missing data: LOCF; sensitivity analysis performed on all predefined endpoints including all randomized patients Data handling for rescued patients: exclusion, LOCF ITT: "full analysis set" defined as all randomised participants who received at least one dose of study drug and had at least one follow-up measurement. SELECTIVE REPORTING: yes; incomplete and unclear reporting of safety endpoints Other important methodological remarks No general reduction in insulin doses were recommended when initiating or titrating liraglutide or
			Safety		
			Death	NR	
			Cardiovascular adverse events	NR	
			Any adverse events	NR	
			Serious adverse events	Lira: 5% Placebo: 7% NT	
			Adverse event leading to withdrawal	NR	
			Any gastro-intestinal adverse event	Lira: 47% Placebo: 13% NT	
			Diarrhoea	Lira: 8% Placebo: 5% NT	
			Nausea	Lira: 33% Placebo: 2% NT	
			Vomiting	NR	
			Severe hypoglycaemia	No events	

		days or any analysed by laboratory >279 mg/dL (baseline to week 12) or >245 mg/dL (week 12-24); if no intercurrent cause for hyperglycaemia: investigator-assisted increase of insulin dose <u>Stratification:</u> No stratification	**Documented symptomatic hypoglycaemia** *"Non-severe symptomatic <4.0 mmol/L":*	Lira: 1.3 events Placebo: 1.2 events P=0.96 => NS	placebo. Sponsor: "investigator initiated trial, supported in part by Novo Nordisk and InfuCare"
			Injection site reactions	NR	
			Thyroid cancer	No events	
			Pancreatitis	No events	

Table 149

8.6.2.2 *Summary and conclusions*

Liraglutide + multiple daily insulin vs **placebo** + multiple daily insulin			
Bibliography: Lind 2015(77) MDI Liraglutide trial			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	124 (1) 24 w	Treatment difference: **-1.1% (95%CI -1.5 to -0.8);** **p<0.001** **SS in favour of liraglutide**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1; small, specific population, short duration Imprecision: ok
Body weight change from baseline	124 (1) 24 w	Treatment difference: **-3.8 kg(95%CI -4.9 to -2.8)** **p<0.001** **SS in favour of liraglutide**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1; small, specific population, short duration Imprecision: ok
Adverse events leading to withdrawal	/	NR	Not applicable
Diarrhea	124 (1) 24 w	Lira: 8% Placebo: 5% NT	Not applicable
Nausea	124 (1) 24 w	Lira: 33% Placebo: 2% NT	Not applicable
Vomiting	/	NR	Not applicable
Severe hypoglycaemia	124 (1) 24 w	No events	Not applicable

Table 150

In this double blind RCT, 124 patients with type 2 diabetes, inadequately controlled by multiple daily insulin injections, were randomized to liraglutide 1.8 mg or placebo for 24 weeks. The mean age was 64, mean duration of diabetes 17 years, mean baseline HbA1c was 9% and mean BMI was 34 kg/m^2. 13% of participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

In patients who were inadequately controlled on multiple daily insulin injections, at 24 weeks, the addition of liraglutide resulted in a statistically significant decrease of HbA1c compared to the addition of placebo .

GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on multiple daily insulin injections, at 24 weeks, there was a statistically significant difference in weight change with the addition of liraglutide compared to the addition of placebo.
There was more weight loss with liraglutide than with placebo.

GRADE: MODERATE quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Rates of withdrawal from the study due to adverse events were not reported
GRADE: not applicable

Rates of diarrhea were 8% with liraglutide and 5% with placebo.
Rates of nausea were 33% with liraglutide and 2% with placebo.
Rates of vomiting were not reported.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

8.7 Liraglutide versus placebo (in addition to standard care): hard endpoints

8.7.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
RefMarso 2016 LEADER Design: RCT (DB) (PG) non-inferiority trial Duration of follow-up: median 3.8y (min. 42m, max 60m)	n:9340 Race/Ethnicity: 35% Europe, 30% north America, 7.7% asia Mean age: 64y Prior/current treatment: see below DMII duration:12.8y Baseline HbA1c:8.7% Mean BMI: 32.5% Previous CV disease: 81.3% Previous MI: 31% Renal impairment: CKD stage 3 or higher 24.7% <u>Inclusion</u> type 2 diabetes, HbA1c ≥ 7.0%, treatment-naieve or on (1 or more) OAD or insulin	liraglutide 1.8mg (or max tolerated dose-median 1.78mg) vs placebo in addition to this background treatment: standard care (no drugs, OAD and/or insulin, see below) Hyperglycaemia protocol**:** **For patients who did not meet the recommended target (HbA1c ≤7% or**	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: <u>Study completers</u>: 96.8% Reason described: yes <u>Uptitration of medication</u>: see below: SS more insulin and other OAD in placebo group SELECTIVE REPORTING: no <u>Other important methodological remarks</u>
			Composite (death from cardiovascular causes, nonfatal myocardial infarction (including silent MI), nonfatal stroke) (PO) time to (first) event External Event Adjudication Committee	lira: 13.0% pla: 14.9% HR 0.87 (95%CI 0.78 to 0.97) p<0.001 or noninferiority p=0.01 for superiority The number of patients who would need to be treated to prevent one event in 3 years was 66 'sensitivity analyses confirmed the robustness of the results' subgroup analyses show significant interactions for eGFR of ≥60 ml/min/1.73 m2 versus an eGFR <60 ml/min/1.73 m2, with a benefit favoring the lower eGFR and for the presence versus absence of established cardiovascular disease at baseline, with benefit for those with cardiovascular disease at baseline

	or a combination. - ≥50 y with at least one CV condition (CHD, CVD, peripheral vascular disease, CKD of stage 3 or greater, or CHF NYHA class II-III) or - ≥60 years with at least 1 CV risk factor, as determined by the investigator (microalbuminuria or proteinuria, hypertension and LVH, LV systolic or diastolic dysfunction, or ankle–brachial index < 0.9) <u>Exclusion</u> - type 1 diabetes; the use of GLP-1–receptor agonists, DPP-4 inhibitors, pramlintide, or rapid-acting insulin; a familial or personal history of multiple endocrine neoplasia	**individualized target at the investigator's discretion) after randomization, the addition of any AD except for GLP-1–RA, DPP-4 inhibitors, or pramlintide was permitted.** <u>Stratification:</u> according to the estimated glomerular filtration rate (eGFR) at screening (<30 or ≥30 ml per minute per 1.73 m2 MDRD equation.	**expanded composite (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or hospitalization for heart failure)**	lira: 20.3% pla: 22.7% HR 0.88 (95%CI 0.81 to 0.96) p= 0.005	2 week placebo run-in before randomization No adjustments for multiplicity were performed for the prespecified exploratory outcomes. follow-up 1-3-6 m and every 6 months thereafter The mean percentage of time that patients received the trial regimen was 84% for liraglutide and 83% for placebo. The median follow-up was 3.8 years in each group. Sponsor: Novo Nordisk
			death from cardiovascular causes	lira:4.7% pla:6.0% HR: 0.78 (95% CI, 0.66 to 0.93) P = 0.007	
			death from any cause	lira:8.2% pla:9.6% HR: 0.85 (95% CI, 0.74 to 0.97) P = 0.02 The number of patients who would need to be treated to prevent one death from any cause in 3 years is 98	
			Total myocardial infarction	lira : 6.3% pla : 7.3% HR : 0.86 (95% CI 0.73–1.00) p= 0.046	
			nonfatal myocardial infarction	lira:6.0% pla:6.8% HR: 0.88 (95% CI 0.75–1.03)	
			total stroke	lira : 3.7%	

	type 2 or medullary thyroid cancer; and the occurrence of an acute coronary or cerebrovascular event within 14 days before screening and randomization.			pla : 4.3% HR : 0.86 (95% CI 0.71–1.06) p= 0.16	
			nonfatal stroke	lira:3.4% pla:3.8% HR: 0.89 (95% CI 0.72–1.11)	
			hospitalization for heart failure	lira : 4.7% pla : 5.3% HR : 0.87 (95% CI 0.73–1.05)	
			microvascular events (composite of retinal and renal), see below for definition	lira : 7.6% pla : 8.9% HR : 0.84 (95% CI 0.73–0.97) p = 0.02	
			nephropathy	lira : 5.7% pla : 7.2% HR : 0.78 (95% CI0.67–0.92) p= 0.003	
			Change in HbA1c from baseline at 36 months MMRM	mean difference -0.40% (95%CI -0.45 to -0.34) SS in favour of liraglutide	
			Body weight change from baseline	mean difference 2.3 kg (95% CI 1.9 to 0.5) lower with liraglutide	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP 0.6mmHg (95%CI 0.2 to 1.0) lower with liraglutide	
			Safety		
			Any adverse events	lira:62.3% pla:60.8% p: 0.12	

			Serious adverse events	lira:49.7% pla:50.4% p:0.51	
			Adverse event leading to withdrawal	lira:9.5% pla:7.3% p<0.001	
			Any gastro-intestinal adverse event	NR	
			Diarrhoea leading to discontinuation of trial	lira:0.6% pla:0.1% p<0.001	
			Nausea leading to discontinuation of trial	lira:1.6% pla:0.4% p<0.001	
			Vomiting leading to discontinuation of trial	lira:0.7% pla<0.1% p<0.001	
			Severe hypoglycaemia defined as hypoglycemia for which the patient required assistance from a third party.	lira:2.4% pla:3.3% p:0.02	
			Confirmed hypoglycemia defined a plasma glucose level of less than 56 mg per deciliter (3.1 mmol per liter).	lira:43.7% pla:45.6% p:0.06	
			Injection site reactions	lira:0.7% pla:0.3% p:0.002	

			Thyroid cancer External Event Adjudication Committee	lira:0 pla:1 p:0.32	
			Pancreatitis External Event Adjudication Committee	lira:0.4% pla:0.5% p:0.44	
			Pancreatic carcinoma External Event Adjudication Committee	lira:0.3% pla:0.1% p: 0.06	
			total neoplasms External Event Adjudication Committee	lira:10.1% pla: 9.0% HR 1.12 (95%CI 0.98-1.28) p:	

Table 151

Antihyperglycemic medication at baseline:
LIRA: metformin 75.8%, SU 50.6%, TZD 6.3%, insulin 43.6%
PLA: metformin 77.0%, SU 50.5%, TZD 6.0%, insulin 45.5%

Antihyperglycemic medication introduced during trial :
LIRA: metformin 5.4%, SU 7.6%, TZD 2.1%, insulin 28.6%
PLA: metformin 6.4%, SU 10.8%, TZD 3.4%, insulin 43.2%
(p= 0.026 for metformin and < 0.001 for all other comparisons

Not on insulin at end of trial:
LIRA 39.2%
PLA: 28.7%
P<0.001

composite renal and retinal microvascular outcome: (nephropathy [defined as the new onset of macroalbuminuria or a doubling of the

serum creatinine level and an eGFR of ≤45 ml per minute per 1.73 m2, the need for continuous renal-replacement therapy, or death from renal disease] and retinopathy [defined as the need for retinal photocoagulation or treatment with intravitreal agents, vitreous hemorrhage, or the onset of diabetes-related blindness])

Subgroup analyses for the primary outcome
'Significant interactions were observed for an eGFR of 60 ml or more per minute per 1.73 m2 versus an eGFR of less than 60 ml per minute per 1.73 m2, with a benefit favoring the lower Egfr and for the presence versus absence of established cardiovascular disease at baseline, with benefit for those with cardiovascular disease at baseline'

≥50y of age and established CVD (n= 7598) HR= 0.83 (95%CI 0.74-0.93)
≥60y and risk factors for CVD (n=1742) HR= 1.20 (95%CI 0.86 – 1.67)
P for interaction 0.04

Renal function < 60ml/min/1.73m2 (n= 2158) HR= 0.69 (95%CI 0.57 – 0.85)
Renal function ≥ 60ml/min/1.73m2 (n= 7182) HR = 0.94 (95%CI 0.83 to 1.07)
P for interaction 0.01
But
Renal function < 30ml/min/1.73m2 (n= 224) HR= 0.89 (95%CI 0.51 – 1.54)
Renal function ≥ 30ml/min/1.73m2 (n= 9116) HR= 0.87 (95%CI 0.77 to 0.97)
P for interaction 0.93

Table S1. LEADER standard of care guidelines.

	Treatment / Guideline
Blood glucose	HbA1c ≤7.0% (individualized depending on patient) If >7.0%, additional HbA1c measurement after 3m. If HbA1c still >7.0%, treatment should be intensified to achieve target if appropriate
Therapy	Lifestyle modifications and metformin are considered foundational therapy in most countries Add-on therapy: thiazolidinediones, sulfonylureas, alpha glucosidase inhibitors for intensification according to local labels (DPP-IV and other incretin-based therapies are not allowed) Insulin therapy: should be based on local practice, including basal, basal/bolus, premix, and mealtime bolus
Blood pressure	Target: 130/80 mm Hg
Antihypertensive therapy	First line: ACE inhibitors or ARBs Based on individual patient needs: Ca2+ blockers, diuretics, others
Lipids	Target LDL: <100 mg/dL (<70 mg/dL in patients with previous cardiovascular events) Statins: recommended for all patients Second-line therapy: investigator discretion
Antiplatelet therapy	Aspirin or clopidogrel (if aspirin intolerant) for patients with prior cardiovascular events (MI, CVA, or revascularization)

HbA1c: glycated hemoglobin; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blockers; MI: myocardial infarction; CVA: cerebrovascular accident

8.7.1.2 *Summary and conclusions*

Liraglutide 1.8mg/d + standard antidiabetic treatment versus placebo + standard antidiabetic treatment in patients with cardiovascular disease or high cardiovascular risk			
Bibliography: Marso 2016 LEADER(78)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Composite (death from cardiovascular causes, nonfatal myocardial infarction (including silent MI), nonfatal stroke) (PO)	9340 (1) median 3.8y	lira: 13.0% pla: 14.9% **HR 0.87 (95%CI 0.78 to 0.97)** **p<0.001 for non-inferiority** **p=0.01 for superiority** *'The number of patients who would need to be treated to prevent one event in 3 years was 66'* *NNT/3 years=67 (95% CI 39 to 285)**	⊕⊕⊕⊖ **MODERATE** Study quality:ok Consistency:NA Directness:-1 very specific population, HbA1c and AD treatment differed between groups Imprecision: ok, but see note
Death from any cause	9340 (1) median 3.8y	lira:8.2% pla:9.6% **HR: 0.85 (95% CI 0.74 to 0.97)** **P = 0.02** *'The number of patients who would need to be treated to prevent one death from any cause in 3 years is 98'* *NNT/3 years = 89 (95%CI 51 to 444)*	⊕⊕⊕⊖ **MODERATE** Study quality:ok Consistency:NA Directness:-1 very specific population, HbA1c and treatment differed between groups Imprecision: ok but upper boundry of CI includes no effect.
Death from cardiovascular causes	9340 (1) median 3.8y	lira:4.7% pla:6.0% HR: 0.78 (95% CI, 0.66 to 0.93) P = 0.007 *NNT/3 years = 95* *(95%CI 61 to 298)**	⊕⊕⊕⊖ **MODERATE** Study quality:ok Consistency:NA Directness:-1 very specific population, HbA1c and treatment differed between groups Imprecision: ok but upper boundry of CI includes no effect.
Total myocardial infarction	9340 (1) median 3.8y	lira : 6.3% pla : 7.3% HR : 0.86 (95% CI 0.73–1.00) p= 0.046 *NNT/3 years = 125 (95%CI 65 to ∞)**	⊕⊕⊕⊖ **MODERATE** Study quality:ok Consistency: NA Directness:-1 very specific population, HbA1c and treatment differed between groups Imprecision: ok but upper boundry of CI includes no effect.
Hospitalization for heart failure	9340 (1) median 3.8y	lira : 4.7% pla : 5.3% HR : 0.87 (95% CI 0.73–1.05) NS	⊕⊕⊕⊖ **MODERATE** Study quality:ok Consistency:NA Directness:-1 very specific population, HbA1c and treatment differed between groups Imprecision: ok but upper boundry of CI includes no effect.

Microvascular events (composite of retinal and renal)	9340 (1) median 3.8y	lira : 7.6% pla : 8.9% HR : 0.84 (95% CI 0.73–0.97) p = 0.02 *NNT/3 years = 91 (95%CI 54 to 483)**	⨁⨁⨀⨀ **LOW** Study quality: -1 definition of outcome Consistency:NA Directness:-1 very specific population, HbA1c and additional treatment differed between groups Imprecision: ok but upper boundry of CI includes no effect.
HbA1c change from baseline (PO)	9340 (1) median 3.8y	mean difference -0.40% (95%CI -0.45 to -0.34) SS in favour of liraglutide	not applied, see below
Body weight change from baseline	9340 (1) median 3.8y	mean difference -2.3 kg (95% CI 1.9 to 0.5) SS lower with liraglutide	⨁⨁⨁⨀ **MODERATE** Study quality:ok Consistency: NA Directness:-1 additional antidiabetic treatment different between groups Imprecision: ok
Adverse events leading to withdrawal	9340 (1) median 3.8y	lira:9.5% pla:7.3% p<0.001	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness:-1 additional treatment different between groups Imprecision: ok
Diarrhea leading to discontinuation of trial	9340 (1) median 3.8y	lira:0.6% pla:0.1% p<0.001	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness:-1 additional treatment different between groups Imprecision:ok
Nausea leading to discontinuation of trial	9340 (1) median 3.8y	lira:1.6% pla:0.4% p<0.001	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness:-1 additional antidiabetic treatment different between groups Imprecision: ok
Vomiting leading to discontinuation of trial	9340 (1) median 3.8y	lira:0.7% pla<0.1% p<0.001	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness:-1 additional antidiabetic treatment different between groups Imprecision: ok
Severe hypoglycaemia	9340 (1) median 3.8y	lira:2.4% pla:3.3% p:0.02	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness:-1 additional antidiabetic treatment different between groups Imprecision: ok

Table 152

** NNT calculations by the literature group, based on hazard ratio and event rate per 100 person-years. This is an approximation, because we have insufficient data to perform a correct NNT assessment based on actual survival at any given timepoint.*

In this double blind, non-inferiority RCT, 9,340 patients with type 2 diabetes, inadequately controlled by OAD and/or insulin, were randomized to liraglutide or placebo for a median of 3.8 years. These patients had high cardiovascular (CV) risk (established CV condition if ≥50y or ≥1 CV risk factor if ≥60y).
The mean age was 64y, mean duration of diabetes 12.8 y, mean baseline HbA1c was 8.7% and mean BMI was 32.5 kg/m^2. 31% of participants had had a previous myocardial infarction, 81% a history of CV disease and 25% had chronic kidney disease stage 3 or higher.
76% of patients were taking metformin at baseline (+/- other antidiabetic drugs), 44% were taking insulin at baseline (+/- other antidiabetic drugs).

This study was designed, due to FDA requirements, to establish that the drug liraglutide does not increase cardiovascular death in type 2 diabetes. To this end, all other parameters (most importantly: glycemic control and thus HbA1c) in the intervention and control group needed to be similar. So in both the liraglutide group and the placebo group, other antidiabetic agents could be added to achieve the desired HbA1c target (≤7% or individualized target).
Unfortunately this is very hard to achieve.
-In the liraglutide group, mean **HbA1c** dropped from about 8.7% at baseline to about 7.2% at 3 months. After that, HbA1c slowly increased over time to reach 7.6% at 36 months (results derived from graph). Whereas in the placebo group, HbA1c dropped from 8.7% at baseline slowly to about 8% at 36 months(results derived from graph). At the prespecified point of 36 months, HbA1c in the liraglutide group was lower than in the placebo group (mean difference -0.40% (95%CI -0.45 to -0.34). The patients in the placebo group did not achieve the same level of glycaemic control that the patients in the liraglutide group.
-In the placebo group, more patients **added (a new type of) insulin** to their treatment compared to the liraglutide group (43 % versus 29%). **Oral antidiabetic agents** were also started more often in the placebo group (3% more SU, about 1% more of each non-SU OAD).

It is difficult to interpret the results of this trial.
- First of all it seems safe to say **that liraglutide does not cause an increased cardiovascular risk**.
- With regards to lowering the cardiovascular risk compared to placebo:
It is unclear whether the benefit that is seen in the liraglutide group, is attributable to a beneficial protective effect of liraglutide, or whether it is due (or partly due) to the use in the placebo group of antidiabetic agents that may have elevated the cardiovascular risk, or due to the better glycaemic control and the lower weight that was achieved in the liraglutide group.
Because of these factors, it is not possible to conclude from this particular trial that liraglutide is cardioprotective in itself.
- This was a population with very high cardiovascular risk. It is unclear whether these results are applicable to a wider population with lower cardiovascular risk. It is likely, or can be hypothesized, that these effects will be less pronounced in a lower risk population.
- Liraglutide was added to the existing antidiabetic treatment (of which 44% insulin). We have insufficient information to determine what the benefit would be of adding liraglutide to a specific

existing antidiabetic regimen. This study cannot help us to determine the place of liraglutide as first-line, second line, third line.. treatment.
- The relative benefit on cardiovascular risk of liraglutide compared to a specific other antidiabetic agent, can also not be derived from this trial.

We assessed the quality of evidence as MODERATE. However, we want to add two important considerations:
- we did not downgrade for imprecision, because the estimate is precise enough, but it has to be noted that the upper boundary of the confidence intervals are very close to 1. So, apart from being statistically significant, we cannot be sure that there is actually a (clinically relevant) effect.
- Secondly, the authors did not make adjustments for multiple comparisons. Due to the large number of secondary endpoints, it is possible that some of the statistically significant results in the secondary endpoints are due to chance. It could therefore be argued that for secondary endpoints the quality of evidence should be downgraded to LOW. We did not downgrade, because, to our knowledge, this problem has not been described in the GRADE literature. It is also difficult to quickly assess the level of bias that is created by not adjusting for multiple comparisons. As we have already stated in the chapter 'Critical reflections', secondary endpoints are there to support the conclusions of the primary endpoint and to generate hypotheses. The authors of the LEADER trial call these endpoints justly 'exploratory endpoint'.

In patients with previous CV disease or high cardiovascular risk, who were inadequately controlled on their antidiabetic treatment, after a median duration of 3.8 years, the addition of liraglutide was **non-inferior and superior** to the addition of placebo to prevent a first event of a **composite of cardiovascular death, nonfatal MI, nonfatal stroke**.
66 patients would need to be treated for 3 years to prevent 1 first event (95%CI 39 to 285 patients).
GRADE: MODERATE quality of evidence

In patients with previous CV disease or high cardiovascular risk, who were inadequately controlled on their antidiabetic treatment, after a median duration of 3.8 years, the addition of liraglutide resulted in a statistically significant **decrease in death from cardiovascular causes and death from any cause** compared to the addition of placebo.
GRADE: MODERATE quality of evidence

In patients with previous CV disease or high cardiovascular risk, who were inadequately controlled on their antidiabetic treatment, after a median duration of 3.8 years, the addition of liraglutide resulted in a decrease of borderline statistical significance in **total myocardial infarction** compared to the addition of placebo.
GRADE: MODERATE quality of evidence

In patients with previous CV disease or high cardiovascular risk, who were inadequately controlled on their antidiabetic treatment, after a median duration of 3.8 years, the addition of liraglutide resulted in a statistically significant decrease in **microvascular events** compared to the addition of placebo.

The composite endpoint for microvascular events was defined by a number of renal and ocular outcomes, of which some are not a reliable reflection of microangiopathy.
GRADE: LOW quality of evidence

In patients with previous CV disease or high cardiovascular risk, who were inadequately controlled on their antidiabetic treatment, after a median duration of 3.8 years, the addition of liraglutide **did not** result in a statistically significant difference in **hospitalization for heart failure** compared to the addition of placebo.
GRADE: MODERATE quality of evidence

In patients with previous CV disease or high cardiovascular risk, who were inadequately controlled on their antidiabetic treatment at a median of 3.8 years, there was a statistically significant difference in **weight** change with the addition of liraglutide compared to the addition of placebo.
There was 2.3kg more weight loss with liraglutide than with placebo.
GRADE: MODERATE quality of evidence

Withdrawal from the study due to adverse events was seen in 9.5% with liraglutide and 7.3% with placebo. The difference was statistically significant.
GRADE: MODERATE quality of evidence

Discontinuation rates due to **diarrhea** were 0.6% with liraglutide and 0.1% with placebo. The difference was statistically significant.
Discontinuation rates due to **nausea** were1.6 % with liraglutide and 0.4% with placebo. The difference was statistically significant.
Discontinuation rates due to **vomiting** were 0.7% with liraglutide and <0.1 % with placebo. The difference was statistically significant.
GRADE: MODERATE quality of evidence

Severe hypoglycemia occurred in 2.4% with liraglutide and 3.3% with placebo. The difference was statistically significant.
GRADE: MODERATE quality of evidence

Systolic blood pressure in the liraglutide group was 0.6 mmHg lower than in the placebo group. The difference was statistically significant.

Pancreatitis, pancreatic cancer and thyroid cancer were reported. The difference with placebo did not reach statistical significance. More information on these rare endpoints is in the chapter: rare adverse events.

8.8 Liraglutide: other endpoints from the RCTs

8.8.1 Blood pressure

Blood pressure change from baseline was reported in all of the 19 trials that were eligible for this review.

All trials performed statistical tests for this outcome. In 9 trials, there was a statistically significant decrease in systolic blood pressure from baseline with liraglutide, compared to the comparator (placebo (N=5), insulin glargine (N=2), glimepiride (N=1), sitagliptin with glimepiride intensification (N=1)). Treatment differences were not always reported, and reported differences were small (≤5.5 mmHg).

There was no statistically significant difference of diastolic blood pressure change from baseline between liraglutide and comparator in any trial, with the exception of one study, where there was a larger decrease with sitagliptin compared to liraglutide at 26 weeks. This difference was no longer found at 52 weeks.

The level of evidence is LOW because of incomplete reporting and large drop-out in some of the included trials.

8.8.2 Injection site reactions

Injection site reactions (ISR) were reported in only 2 of 19 the trials that were eligible for this review. None performed statistical tests for this outcome:

Injection site reactions were reported in 0% to 2% of patients on liraglutide compared to 16 % of patients on exenatide twice daily and <1% of patients on dulaglutide.

The definition of what was considered to be an injection site reaction was not always specified.

8.8.3 Cardiovascular adverse events (including heart failure)

The LEADER(78) trial was designed, due to FDA requirements, to establish that the drug liraglutide does not increase cardiovascular death in type 2 diabetes. For an in-depth discussion of this trial, see 8.7.

Cardiovascular adverse events were not reported in most of the other trials that were eligible for this review. Statistical tests were not performed and would be of little value due to the relatively short duration of the trials and the low event rate.

8.8.4 Pancreatitis and thyroid cancer

Because of the low event rate of pancreatitis and thyroid cancer, these outcomes will be discussed in the chapter ‘rare safety outcomes’.

9 Lixisenatide – evidence tables and conclusions

9.1 Combination therapy with metformin

9.1.1 Lixisenatide (one-step or two step dose increase)+ metformin versus placebo + metformin

9.1.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Bolli 2014 - (79) GetGoal-F1 Design: RCT (DB) phase III Duration of follow-up:	n: 484 Mean age: 56 Prior/current treatment: metformin only Mean DMII duration: 6.0 Mean baseline HbA1c: 8.03% Mean BMI: 32.5 kg/m² Previous CV event: / Renal impairment: / <u>Inclusion</u>	Lixisenatide 20µg/day one-step dose increase (n = 161) vs Lixisenatide 20µg/day two-step dose increase (n = 161) vs placebo one-step dose increase (n = 82) vs placebo two-step dose increase (n = 80) in addition to this background treatment:	Efficacy		RANDO: Unclear: merely states randomized ALLOCATION CONC: unclear BLINDING : Participants: yes, received placebo or active treatment Personnel: unclear, states double blind Assessors: unclear Remarks on blinding method: Double blind with regard to active and placebo treatments, but not blinded to study drug volume FOLLOW-UP: <u>Study completers</u>: at 24 weeks:
			Change in HbA1c from baseline (PO) at 24 weeks (LOCF)	Lixisenatide 1-step: Least squares mean change: -0.9±0.10% LS mean change vs placebo: -0.5% (95% CI: -0.7 to -0.3) p<0.0001 Lixisenatide 2-step: Least squares mean change: -0.8 ± 0.1% LS mean change vs placebo: -0.4% (95% CI: -0,6 to -0,2); p<0.0001 Placebo (combined): Least squares mean change: -0.4 ± 0.1%	
			Body weight change from baseline at 24 weeks	Lixisenatide one-step: -2.6 ± 0.4 kg LS mean difference vs placebo:	

24 weeks (followed by a ≥52 week variable double blind period for safety endpoints)	- Type 2 diabetes for more than 1 year - Currently receiving at least 1.5 g of metformin as monotherapy for 3 months - HbA1c 53-86 mmol/mol (7-10%) <u>Exclusion</u> - Use of injectable or oral glucose-lowering agents (other than metformin) within 3 months prior to the time of screening - Fasting plasma glucose at screening >13.9 mmol/l (250 mg/dl) - history of unexplained pancreatitis - chronic pancreatitis - pancreatectomy - stomach/gastric surgery -IBD	metformin at least 1.5 g/day <u>Hyperglycaemia uptitration protocol:</u> one or two step protocol, see above <u>Hyperglycaemia rescue protocol</u>**:** not reported <u>Stratification:</u> by screening values of HbA1c < 64 mmol/mol, ≥ 64 mmol/mol (< 8%, ≥ 8%) and BMI (< 30 kg/m2, ≥ 30 kg/m2)	**(LOCF)**	-1.0 (p<0.01) Lixisenatide two-step: -2.7 ± 0.4 kg LS mean difference vs placebo: -1.1 (p<0.01) Placebo: -1.6 ± 0.4 kg	Lixisenatide one-step: 91% lixisenatide two-step: 89% placebo combined: 94% at 76 weeks: 81% in the lixisenatide one-step, 75% in the lixisenatide two-step and 80% in the placebo combined groups Reason described: yes/no <u>Discontinued treatment</u>: At week 24, discontinuation due to nausea or vomiting was reported in lixisenatide one-step: 6 (3.7%); lixisenatide two-step: 7 (4.3%); combined placebo: 0 <u>Uptitration of study medication</u>: - One step lixenatide uptitration: 10µg once daily for one week then 20µg once daily - Two-step lixenatice uptitration: 10 µg once daily for 1 week, then 15µg once daily for 1 week, then 20 µg once daily <u>Hyperglycaemic rescue</u>: Lixenatide one-step: 1.3% (n = 2) Lixenatide 2-step 3.1% (n = 5) Combined placebo groups: 4.4 (n = 7)
			Blood pressure change from baseline (SystBP/DiastBP)	/	
			Change in HbA1c from baseline <u>at 76 weeks</u>	Lixisenatide 1-step: -0.9 ± 0.9 % Lixisenatide 2-step: -0.9 ± 1.0 % Placebo combined: -0.6 ± 1.3% no test for statistical significance	
			Safety at 76 weeks		
			Death	Lixi 1-step: 1.2% (n =2) Lixi 2-step: 0.6% (n =1) Placebo: 1.3% (n =2)	
			Cardiovascular adverse events	not reported	
			Any adverse events	Lixi 1-step: 85.7% Lixi 2-step: 87.6% Placebo: 86.3%	
			Serious adverse	Lixi 1-step: 9.9%	

			events	Lixi 2-step: 13% Placebo: 13.8%	Statistical method for drop out/missing data: LOCF Data handling for rescued patients: LOCF ITT: **Efficacy** done on the modified intent-to-treat population, comprising all randomized participants who received at least one dose of double- blind investigational product and had a baseline and at least one post-baseline assessment for any primary or secondary efficacy variable SELECTIVE REPORTING: no Other important methodological remarks - 1 week placebo run-in Sponsor: Funded by Sanofi
			Adverse event leading to withdrawal	Lixi 1-step: 8.7% Lixi 2-step: 11.8% Placebo: 5.6%	
			Any gastro-intestinal adverse event	Lixi 1-step: 51.6% Lixi 2-step: 55.9% Placebo: 31.3%	
			Diarrhoea	Lixi 1-step: 9.9 % Lixi 2-step: 14.9% Placebo: 13.1%	
			Nausea	Lixi 1-step: 29.2% Lixi 2-step: 38.5% Placebo: 8.1%	
			Vomiting	Lixi 1-step: 13.0% Lixi2-step: 18.0% Placebo: 0.6%	
			Severe hypoglycaemia	Lixi 1-step: 0 Lixi 2-step: 0 Placebo: 0	
			Documented symptomatic hypoglycaemia	Lixi 1-step: 3.7% (6) Lixi 2-step: 7.5% (12) Placebo: 7.5% (12)	
			Injection site reactions	Lixi 1-step: 5.6% Lixi 2-step: 5.6% Placebo: 1.9%	
			Thyroid cancer	not reported	
			Pancreatitis	not reported	

Table 153

9.1.1.2 *Summary and conclusions*

Lixisenatide (20 µg/day) one or two-step dose-increase regimen + metformin versus placebo +metformin in patients with T2DM insufficiently controlled by metformin			
Bibliography: Bolli 2014 (79) GetGoal-F1			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO) **at 24 weeks** **1-step**	484 (1) 24 weeks	Lixisenatide 1-s: -0.9±0.10% Placebo: -0.4 ± 0.1% Difference: -0.5% (95%CI: -0.7, -0.3) p<0.0001 **SS in favour of lixisenatide one-step**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 for unclear rando misation and allocation Consistency: NA Directness:ok Imprecision:ok
HbA1c change from baseline (PO) **at 24 weeks** **2-step**	484 (1) 24 weeks	Lixisenatide 2-s: -0.8 ± 0.1% Placebo: -0.4 ± 0.1% Difference: -0.4% (95% CI: -0.6,-0.2) p<0.0001 **SS in favour of lixisenatide two-step**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 for unclear randomisation and allocation Consistency: NA Directness: OK Imprecision: OK
Body weight change from baseline **1 step**	484 (1) 24 weeks	Lixisenatide 1-S: -2.6 ± 0.4 kg Placebo: -1.6 ± 0.4 kg Difference: -1.0kg (95% CI: not shown) p < 0.01 **SS in favour of lixisenatide one-step**	⊕⊕⊖⊖ **LOW** Study quality: -1 for unclear randomisation and allocation Consistency: N/A Directness: ok Imprecision: -1, no 95% CI
Body weight change from baseline **2-step**	484 (1) 24 weeks	Lixisenatide 2-s: -2.7 ± 0.4 kg Placebo: -1.6 ± 0.4 kg Difference: -1.1kg (95%CI not shown) p < 0.01 **SS in favour of lixisenatide two-step**	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: N/A Directness: ok Imprecision: -1, no 95% CI
Adverse events leading to withdrawal	484 (1) 76 weeks	Lixi 1-step: 8.7% Lixi 2-step: 11.8% Placebo: 5.6%	NA

Diarrhea	484 (1) 76 weeks	Lixi 1-step: 9.9 % Lixi 2-step: 14.9% Placebo: 13.1%	NA
Nausea	484 (1) 76 weeks	Lixi 1-step: 29.2% Lixi 2-step: 38.5% Placebo: 8.1%	NA
Vomiting	484 (1) 76 weeks	Lixi 1-step: 13.0% Lixi2-step: 18.0% Placebo: 0.6%	NA
Severe hypoglycaemia	484 (1) 76 weeks	Lixi 1-step: 0 Lixi 2-step: 0 Placebo: 0	NA

Table 154

In this double blind, phase III RCT, 484 patients with type 2 diabetes, inadequately controlled by metformin (at least 1.5g/day), were randomized to lixisenatide in a one-step uptitration, lixisenatide in a two-step uptitration or to placebo for 24 weeks, followed by a double blind period for safety until at least 76 weeks. The mean age was 56, mean duration of diabetes 6 years, mean baseline HbA1c was 8.03% and mean BMI was 32.5 kg/m^2. It was unknown how many of the participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

In patients who were inadequately controlled on metformin, at 24 weeks, the addition of lixisenatide in a one-step uptitration regimen **resulted** in a statistically significant **decrease of HbA1c** compared to placebo.
GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on metformin, at 24 weeks, the addition of lixisenatide in a two-step uptitration regimen **resulted** in a statistically significant **decrease of HbA1c** compared to placebo.
GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on metformin, at 24 weeks, there was a statistically significant difference in weight change with the addition of lixisenatide compared to the addition of placebo.
There was **more weight loss with lixisenatide** than with placebo.
GRADE: MODERATE quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 8.7 % with lixisenatide 1-step, in 11.8% in lixisenatide 2-step and 5.6% with placebo.
GRADE: not applicable

Rates of diarrhea were 9.9 % with lixisenatide 1-step, 14.9% with lixisenatide 2-step and 13.1 % with placebo. It is not known if the difference was statistically significant.
Rates of nausea were 29.2% with lixisenatide 1-step, 28.5% with lixisenatide 2-step and 8.1% with placebo. It is not known if the difference was statistically significant.
Rates of vomiting were 13.0% with lixisenatide 1-step, 18.0% with lixisenatide 2-step and 0.6% with placebo. It is not known if the difference was statistically significant.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

9.1.2 Lixisenatide morning or evening dose + metformin versus placebo + metformin

9.1.2.1 *Clinical evidence profile*

Metformine + lixisenatide 20 µg/day (morning injection) / metformine + lixisenatide 20 µg/d (evening injection) versus metformine + placebo in patients with T2DM insufficiently controlled on metformin alone.

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Ahren 2013 (80) GetGOAL-M Design: RCT DB PG 4-arm Duration of follow-up: 24 weeks (+ 52 week placebo-controlled extension	n: 680 Mean age: 54.7 Prior/current treatment: metformin (mean: 1.971 mg/d) Mean DMII duration: 6.1 y Mean baseline HbA1c: 8.1% Mean BMI: 32.9 Previous CV event: unknown Renal impairment: unknown <u>Inclusion</u> Patients with type II diabetes inadequately controlled on	lixisenatide 20µg 1x/d (morning) (n = 255) vs lixisenatide 20µg 1x/d (evening) (n = 255) vs placebo (morning) (n = 85) vs placebo (evening) (n = 85) in addition to this background treatment: Metformin at least 1.5 g/day	Efficacy		RANDO: unclear, states randomized ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: unclear how, states double blind Assessors: unclear, except for allergic reaction adjudication committee clearly stated as blinded FOLLOW-UP: <u>Study completers</u>: 615 (drop-out of 9.6%) Reason described: yes <u>Discontinued treatment</u>: 65 patients in total Lixi morning: 8.6% Lixi evening: 12.2% Placebo: 7.1%
			Change in HbA1c from baseline (PO: morning lixi vs placebo) LS means	lixi morning: -0.9% (± 0.07) placebo (combined): -0.4% (± 0.08) LS mean differences: -0.5 ±0.09 95% CI: -0.66 to -0.31 p<0.0001	
			Change in HbA1c from baseline (SO: evening lixi vs placebo) LS means	Lixi evening: -0.8% ±0.07 Placebo (combined): -0.4% ±0.8 LS mean differences: -0.4% ±0.09 95% CI: -0.54 tot -0.19 p<0.0001	
			Body weight change from baseline LS mean changes	Lixi morning: -2.0 kg ±0.23 Lixi evening: -1.6 kg ± 0.24 Placebo (combined): -1.6 ±0.27 NS	
			Blood pressure change from baseline (SystBP/DiastBP)	unknown	
			Safety		
			Death	Lixi morning: 0 Lixi evening: 0	

for safety data)	metformin with a dose of at least 1.5g/day <u>Exclusion</u> use of oral or injectable glucose-lowering agents other than metformin within 3 months prior to the time of screening fasting plasma glucose at screening >13.9 mmol/L history of unexplained pancreatitis chronic pancreatitis pancreatectomy stomach/gastric surgery IBD history of metabolic acidosis, including diabetic ketoacidosis within 1 year prior to screening previous allergic reaction to any GLP-1 agonist; clinically relevant history of gastro-intestinal disease with prolonged nausea and vomiting during the previous 6	<u>Hyperglycaemia uptitration protocol:</u> <u>Hyperglycaemia rescue protocol</u>**:** If all the fasting self-monitored plasma glucose values in 3 consecutive days exceeded the prespecified limit. Sulfonylureas were the first option. Short term use (up to 5 days maximum) of insulin therapy not considered to be rescue therapy <u>Stratification:</u> By HbA1C values (<8.0 / ≥8.0)		Placebo (combined): 0	<u>Uptitration of study medication</u>: unknown <u>Hyperglycaemic rescue</u>: Lixi morning: 2.7% (vs placebo p=0.0007) Lixi evening: 3.9% (vs placebo p = 0.0063) Placebo: 10.6% <u>Statistical method for drop out/missing data</u>: LOCF <u>Data handling for rescued patients</u>: LOCF <u>ITT</u>: defined as all randomized patients who received at least one dose of double-blind study treatment and had both a baseline assessment and at least one post-baseline efficacy assessment SELECTIVE REPORTING: yes does not report on change from baseline in adiponectin or c-peptide
			Cardiovascular adverse events	unknown	
			Any adverse events	Lixi morning: 69.4% Lixi evening: 69.4% Placebo (combined): 60.0%	
			Serious adverse events	Lixi morning: 2.0% Lixi evening: 3.1% Placebo (combined): 1.2%	
			Adverse event leading to withdrawal	Lixi morning: 7.1% Lixi evening: 5.5% Placebo (combined): 1.2%	
			Any gastro-intestinal adverse event	Lixi morning: 36.5% Lixi evening: 41.2% Placebo (combined): 25.9%	
			Diarrhoea	Lixi morning: 10.6% Lixi evening: 10.6% Placebo (combined): 8.8	
			Nausea	Lixi morning: 22.7% Lixi evening: 21.2% Placebo (combined): 7.6%	
			Vomiting	Lixi morning: 9.4% Lixi evening: 13.3% Placebo (combined): 2.9%	

	months	by bmi (<30 kg/m² / ≥30 kg/m³)	**Severe hypoglycaemia**	Lixi morning: 0 Lixi evening: 0 Placebo (combined): 0	Other important methodological remarks: 2 week screening period and 1 week placebo run-in
			Documented symptomatic hypoglycaemia	Lixi morning: 2.4% Lixi evening: 5.1% Placebo (combined): 0.6%	Sponsor: Sanofi
			Injection site reactions	Lixi morning: 6.7% Lixi evening: 6.7% Placebo (combined): 3.5%	
			Thyroid cancer	none	
			Pancreatitis	none	

Table 155

9.1.2.2 *Summary and conclusions*

Lixisenatide 20 µg/d (morning / evening injection) + metformin versus placebo + metformin in patients with T2DM inadequately controlled on metformin alone			
Bibliography: Ahren 2013 (80) GetGoal-M			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO) **Morning injection**	425 for this comparison (1) 24 weeks	Lixisenatide: - 0.9% (± 0.07) Placebo: -0.4% (± 0.08) LS mean difference: **-0.5 ±0.09** **(95% CI: -0.66 to -0.31)** **p<0.0001** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: -1, unclear allocation, randomization and blinding Consistency: N/A Directness: ok Imprecision: ok
HbA1c change from baseline (PO) **Evening injection**	425 (1) 24 weeks	Lixisenatide: -0.8% ±0.07 Placebo: -0.4% ±0.8 LS mean difference: **-0.4% ±0.09** **(95% CI: -0.54 tot -0.19)** **p<0.0001** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: -1, unclear allocation, randomization and blinding Consistency: N/A Directness: ok Imprecision: ok
Body weight change from baseline **Morning injection**	425 (1) 24 weeks	Lixisenatide: -2.0 kg ±0.23 Placebo: -1.6 ±0.27 NS	⊕⊕⊖⊖ **LOW** Study quality:- 1 (see above) Consistency: n/a Directness: ok Imprecision: -1, no 95% CI, unable to assess
Body weight change from baseline **Evening injection**	425 (1) 24 weeks	Lixisenatide: -1.6 kg ± 0.24 Placebo: -1.6 ±0.27 NS	⊕⊕⊖⊖ **LOW** Study quality:- 1 (see above) Consistency: n/a Directness: ok Imprecision: -1, no 95% CI, unable to assess
Adverse events leading to withdrawal	680 (1) At least 76 weeks	Lixi morning: 7.1% Lixi evening: 5.5% Placebo (combined): 1.2% No statistical analysis	NA
Diarrhea	680 (1) At least 76 weeks	Lixi morning: 10.6% Lixi evening: 10.6% Placebo (combined): 8.8% No statistical analysis	NA
Nausea	680 (1) At least 76 weeks	Lixi morning: 22.7% Lixi evening: 21.2% Placebo (combined): 7.6% No statistical analysis	NA
Vomiting	680	Lixi morning: 9.4%	NA

	(1) At least 76 weeks	Lixi evening: 13.3% Placebo (combined): 2.9% No statistical analysis	
Severe hypoglycaemia	680 (1) At least 76 weeks	Lixi morning: 0 Lixi evening: 0 Placebo (combined): 0	NA

Table 156

In this double blind, 4 arm RCT, 680 patients with type 2 diabetes, inadequately controlled by at least 1.5 g of metformin, were randomized to morning or evening injection of 20 µg per day of lixisenatide for 24 weeks, with a double blind extension until at least 76 weeks. The mean age was 54, mean duration of diabetes 6.1 years, mean baseline HbA1c was 8.1% and mean BMI was 32.9 kg/m² kg/m^2. It is unknown how many of the participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

In patients who were inadequately controlled on at least 1.5g/day of metformin, at 24 weeks, the addition of a morning injection of lixisenatide **resulted** in a statistically significant decrease of HbA1c compared to placebo.
GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on at least 1.5g/day of metformin, at 24 weeks, the addition of an evening injection of lixisenatide **resulted** in a statistically significant decrease of HbA1c compared to placebo.
GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on at least 1.5g/day of metformin, at 24 weeks, there was **no** statistically significant **difference** in weight change with the addition of a morning injection of lixisenatide compared to placebo.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on at least 1.5g/day of metformin, at 24 weeks, there was **no** statistically significant **difference** in weight change with the addition of an evening injection of lixisenatide compared to placebo.
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 7.7% with lixisenatide morning injetions, 5.5% with lixisenatide evening injections and 1.2% with placebo.
GRADE: not applicable

Rates of diarrhea were 10.6% with lixisenatide morning injection, 10.6% with lixisenatide evening injections and 8.8% with placebo. It is not known if the difference was statistically significant.

Rates of nausea were10.6 % with lixisenatide morning injections, 10.6% with lixisenatide evening injections and 8.8 % with placebo. It is not known if the difference was statistically significant.
GRADE: not applicable

Rates of vomiting were 9.4% lixisenatide morning injection, 13.3% with lixisenatide evening injection and 2.9% with placebo. It is not known if the difference was statistically significant.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

9.1.3 Lixisenatide + metformin versus exenatide 2x/d + metformin

See Exenatide 6.2.3

9.1.4 Lixisenatide + metformin versus liraglutide + metformin

See **Fout! Verwijzingsbron niet gevonden.**.

9.2 Combination therapy with pioglitazone

9.2.1 Lixisenatide + pioglitazone versus placebo + pioglitazone

9.2.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref: Pinget 2013(81) GetGoal-P Design: RCT DB PG phase III study (Getgoal-P) Duration of follow-up: 24 weeks for primary endpoint	n:484 Mean age: 55.6 Prior/current treatment: pioglitazone (≥30 mg/day) (eventually metformin: 81% of patients) Mean DMII duration:8.1 Mean baseline HbA1c: 8.1±0.9 Mean BMI: 34.0 Previous CV event: / Renal impairment: patients with end stage renal disease and creatinine>1.4 mg/dl in women or >1.5 mg/dl in men were excluded	Lixisenatide 20µg (n = 323) vs placebo (n = 161) in addition to this background treatment: pioglitazone (≥30 mg/day) with or without metformin <u>Hyperglycaemia uptitration protocol:</u> unknown <u>Hyperglycaemia rescue protocol</u>**:** Patients above a specified FPG were eligible for	Efficacy		RANDO: unclear, states randomised ALLOCATION CONC: Adequate, with interactive voice response system BLINDING : States double blind with regard to active or placebo, not to study drug volume Participants: unclear Personnel: unclear Assessors: unclear FOLLOW-UP: <u>Study completers</u>: 24 weeks: Lixi: 89% Placebo: 85% 76 weeks: Lixi: 74% Placebo: 68% Reason described: yes
			Change in HbA1c from baseline (PO) LS square means	Lixisenatide: - 1.16% Placebo: -0.32% LS mean difference between lixisenatide and placebo: -0.56% (95% CI: -0.73 to -0.39) p < 0.0001 **SS in favour of lixisenatide**	
				Patients using metformin LS mean difference: −0.55% (95% CI: (−0.75, –0.36)	
				Patients who were not using metformin LS mean difference: −0.57% (95% CI: −0.97, –0.17) *No statistically significant difference between patients who were and who weren't using metformin*	
			Body weight change from baseline	Lixisenatide: -0.2 kg Placebo: +0.2kg Difference: -0.41 (95% CI: -1.03 to 0.20)	

+ ≥52 week extension period total of 76 weeks	<u>Inclusion</u> Adults with T2DM for at least 1 year and who were treated with pioglitazone at a stable dose of ≥30 mg/day with or without metformin for at least the previous 3 months, and with a HbA1c measurement of ≥7.0% and ≤10.0%, were eligible for inclusion. For patients who were receiving metformin, a stable dose (≥1.5 g/day) had to be maintained for at least 3months prior to screening. <u>Exclusion</u> The main exclusion criteria included use of oral or injectable glucose-lowering agents other than pioglitazone and metformin within 3months prior to the time of screening; fasting plasma glucose	rescue therapy (baseline to week 8, >15.0 mmol/l (270 mg/dl); from week 8 to 12 if FPG was >13.3 mmol/l (240 mg/dl); from week 12 to 24 if FPG was >11.1 mmol/l (200 mg/dl) or HbA1c >8.5%; and during the extension period if FPG was >10.0mol/l (180 mg/dl) or HbA1c >8%) <u>Stratification:</u> - by screening values of HbA1c (<8.0%; ≥8.0%) - by use of metformin at screening (yes / no)	LS square means	NS *Patients using metformin* Difference: -0.54kg (95% CI: -1.23 to 0.14) NS *Patients who were not using metformin* Difference: +0.13kg (95% CI: -1.27 to 1.53) NS	<u>Discontinued treatment</u>: lixisenatide: 10.8% (n = 35) Placebo: 14.9% (n = 24) <u>Uptitration of study medication</u>: two-step dose uptitration regimen, from 10 µg/day for a week, to 15 µg/day for a week, to 20µg/day <u>Hyperglycaemic rescue</u>: Lixisenatide: 3.8% Placebo: 11.3% <u>Statistical method for drop out/missing data</u>: LOCF <u>Data handling for rescued patients</u>: LOCF <u>ITT</u>: yes for safety (all 484 randomized patients included) mITT (modified) intention to treat for efficacy: all patients exposed to at least one dose of double-blind investigational product SELECTIVE REPORTING: no Other important methodological remarks :
			Blood pressure change from baseline (SystBP/DiastBP)	not reported	
			Safety		
			Death	Lixi: 0 Placebo: 0.6% (n = 1)	
			Cardiovascular adverse events	not reported	
			Any adverse events	Lixi: 72.4% (n = 234) Placebo: 72.7% (n = 117)	
			Serious adverse events	Lixi: 2.5% (n = 8) Placebo: 1.9% (n = 3)	
			Adverse event leading to withdrawal	Lixi: 6.5% (n = 21) Placebo: 5% (n= 8)	
			Any gastro-intestinal adverse event	Lixi: 36.5% (n = 118) Placebo: 28.6% (n = 46)	
			Diarrhoea	Lixi: 7.1% (n=76) Placebo: 10.6% (n = 17)	
			Nausea	Lixi: 23.5% (n = 76) Placebo: 10.6% (n = 17)	

	(FPG) at screening >250 mg/dl (13.9 mmol/l); history of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery or inflammatory bowel disease; end-stage renal disease and/or dialysis for patients treated only with pioglitazone and for patients treated with metformin in addition to pioglitazone, creatinine>1.4 mg/dl in women or>1.5 mg/dl in men; history of allergic reaction to any GLP-1RAs; and clinically relevant history of gastrointestinal disease, with prolonged nausea and vomiting during the previous 6 months.		**Vomiting**	Lixi: 6.8% (n = 22) Placebo: 3.7% (n = 6)	2 week screening period 1 week single-blind placebo run-in period Sponsor: Sanofi
			Severe hypoglycaemia	Lixi: 0 Placebo: 0	
			Documented symptomatic hypoglycaemia	Lixi: 3.4% (n = 11) Placbeo: 1.2% (n = 2)	
			Injection site reactions	not reported	
			Thyroid cancer	not reported	
			Pancreatitis	not reported	

Table 157

9.2.1.2 *Summary and conclusions*

Lixisenatide + pioglitazone (+ eventually metformin) vs placebo+ pioglitazone (+ eventually metformin) in patients with inadequately controlled TIIDM			
Bibliography: Pinget 2013(81) GetGoal-P			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	484 (1) 24 weeks	Lixisenatide: - 1.16% Placebo: -0.32% Difference: -0.56% (95% CI: -0.73 to -0.39) p < 0.0001 **SS in favour of lixisenatide**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: n/a Directness: -1, pioglitazone is not a first choice in Belgium, also population with and without metformin Imprecision: ok
Body weight change from baseline	484 (1) 24 weeks	Lixisenatide: -0.2 kg Placebo: +0.2kg Difference: -0.41 (95% CI: -1.03 to 0.20) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: n/a Directness: -1, pioglitazone is not a first choice in Belgium, also population with and without metformin Imprecision: ok
Adverse events leading to withdrawal	484 (1) ≥76 weeks	Lixi: 6.5% (n = 21) Placebo: 5% (n= 8)	NA
Diarrhea	484 (1) ≥76 weeks	Lixi: 7.1% (n=76) Placebo: 10.6% (n = 17)	NA
Nausea	484 (1) ≥76 weeks	Lixi: 235.5% (n = 76) Placebo: 10.6% (n = 17)	NA
Vomiting	484 (1) ≥76 weeks	Lixi: 6.8% (n = 22) Placebo: 3.7% (n = 6)	NA
Severe hypoglycaemia	484 (1) ≥76 weeks	Lixi: 0 Placebo: 0	NA

Table 158

In this double blind RCT, 484 patients with type 2 diabetes, inadequately controlled by pioglitazone (and eventually metformin), were randomized to lixisenatide or placebo for 24 weeks with a double blind extension until at least 76 weeks. The mean age was 55.6 years, mean duration of diabetes 8.1

years, mean baseline HbA1c was 8.1% and mean BMI was 34 kg/m^2. It is unknown how many participants had had a previous myocardial infarction. Patients with renal impairment were not allowed in the study, and a cut-off creatinine value was used.

The interpretation of these results is further limited because of the inclusion of patients with and without metformin (81% on metformin). Based on these results, it is difficult to make statements about the combination of a glp-1 receptor agonist with a specific oral antidiabetic agent. However, a subanalysis of the HbA1c PO and body weight endpoint according to metformin use was done. There were no statistically significant differences between the two groups.

In patients who were inadequately controlled on pioglitazone (and eventually metformin), at 24 weeks, the addition of lixisenatide **resulted** in a statistically significant decrease of HbA1c compared to placebo.
GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on pioglitazone (and eventually metformin), at 24 weeks, there was **no** a statistically significant **difference** in weight change with the addition of lixisenatide compared placebo.
GRADE: MODERATE quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 6.5% with lixisenatide and 5% with placebo.
GRADE: not applicable

Rates of diarrhea were 7.1% with lixisenatide and 10.6% with placebo. It is not known if the difference was statistically significant.
Rates of nausea were 23.5 % with lixisenatide and 10.6% with placebo. It is not known if the difference was statistically significant.
Rates of vomiting were 6.8% with lixisenatide and 3.7% with placebo. It is not known if the difference was statistically significant.
GRADE: not applicable

There were no events of severe hypoglycemia.
GRADE: not applicable

9.3 Combination therapy with SU with or without metformin

9.3.1 Lixisenatide + SU +/- MET versus placebo + SU +/- MET

9.3.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Rosenstock 2014 (82) Getgoal-S Design: RCT DB PG Duration of follow-up: 24 weeks + placebo controlled extension of at least 52 weeks (total at least 76	n: 859 Mean age: 57.4 Prior/current treatment: SU with or without metformin (85% on metformin) Mean DMII duration: 9.45 Mean baseline HbA1c: 8.25 Mean BMI: 30.25 Previous CV event: CV event within the previous 6 months was an exclusion criteria Renal impairment: patients on metformin with renal impairment were excluded	Lixisenatide 20 µg once daily vs placebo In addition to this background treatment: Sulfonylurea (SU) ± metformin Hyperglycaemia uptitration protocol: / Hyperglycaemia rescue protocol: If fasting SMPG value exceeded	Efficacy		RANDO: states randomized, no further information unclear ALLOCATION CONC: unclear BLINDING : States "double blind", no further information Participants: unclear Personnel: unclear Assessors: unclear FOLLOW-UP: Study completers: Lixisenatide: 499 (87.1%) Placebo: 255 (89.2%) Reason described: yes Discontinued treatment: Lixisenatide: 74 (12.9%) Placebo: 31 (10.8%)
			Change in HbA1c from baseline (PO)	LS mean decrease Lixi: -0.85% (SE: 0.06) LS mean decrease placebo: -0.10% (SE: 0.07) LS mean difference: -0.74% (95 CI: -0.867 to -0.621) p<0.0001	
			Body weight change from baseline	LS mean decrease lixi: -1.76 kg ±0.20 LE mean decrease placebo: -0.93 kg ±0.23 LS mean change difference: -0.84 kg (95% CI: -1.250 to -0.421) p<0.0001	
			Blood pressure change from baseline (SystBP/DiastBP)	not reported	
			Safety		
			Death	Lixi: 0.2% (n = 1) Placebo:0	
			Cardiovascular adverse events	not reported	
			Any adverse events	Lixi: 68.3% (n = 392)	

weeks)	Inclusion Male and female participants with T2DM aged 20-79 y receiving SU with or without metformin with an HbA1c level of 7-10% inclusive Exclusion Use of oral or injectable glucose lowering agents other than a SU or metformin within 3 months prior to the time of screening; fasting plasma glucose (FPG) at screening N250.0 mg/dL (N13.9 mmol/L); history of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery, or inflammatory bowel	the specific glycemic limit on three consecutive days, the patient was instructed to contact the investigator and a central laboratory FPG measurement (and HbA1c after Week 12) was performed Stratification: By HbA1C (<8%, ≥8%) and metformin use at screening (y/n)		Placebo:61.1% (n = 174)	Uptitration of study medication: lixisenatide once-daily or matching placebo were given in a 2-step dose-increase regimen (10 µg once-daily for 1 week, 15 µg once-daily for 1 week, then 20 µg once-daily). Hyperglycaemic rescue: Lixi: 23 (4%) Placebo: 36 (12.6%) p<0.0001 Statistical method for drop out/missing data: LOCF Data handling for rescued patients: Patients were censored for modified intent-to-treat (mITT) at the time that rescue medication was initiated. ITT:
			Serious adverse events	Lixi: 3.5% (n = 20) Placebo: 5.6% (n = 16)	
			Adverse event leading to withdrawal	Lixi: 9.8% (n = 56) Placebo: 4.9% (n = 14)	
			Any gastro-intestinal adverse event	Lixi: 40.9% (n = 235) Placebo: 20.0% (n = 57)	
			Diarrhoea	Lixi: 8.9% (n = 51) Placebo: 6.7% (n = 19)	
			Nausea	Lixi: 25.3% (n=145) Placebo:7.0% (n=20)	
			Vomiting	Lixi: 8.7% (n=50) Placebo:3.5% (n=10)	
			Severe hypoglycaemia	Lixi: 0.2% (n=1) Placebo:0	
			Documented symptomatic hypoglycaemia	Lixi: 15.3% (n=88) Placebo:12.3% (n=35)	
			Injection site reactions	not reported	
			Thyroid cancer	not reported	

	disease; history of gastrointestinal disease with prolonged nausea and vomiting in the 6 months prior to study initiation; history of metabolic acidosis, including diabetic ketoacidosis, within 1 year prior to screening; history of myocardial infarction, stroke, or heart failure requiring hospitalization within the previous 6 months; uncontrolled/inadequately controlled hypertension at the time of screening, with a resting systolic blood pressure of N180 mmHg or diastolic blood pressure N95 mmHg; amylase and/or lipase N3 times or aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase N2 times the upper limit of the normal laboratory range; and end-stage renal disease (defined by serum creatinine clearance of b15 mL/min) and/or		**Pancreatitis**	not reported	mITT: all randomized patients who received at least one dose of doubleblind investigational product and had both a baseline and at least one post-baseline assessment of any primary or secondary efficacy parameter The safety population comprised all randomized patients exposed to at least one dose of double-blind investigational product. SELECTIVE REPORTING: no Other important methodological remarks : 2 weeks screening and 1 week single blind run-in period Sponsor: Sanofi

	dialysis. In the case of treatment with metformin, patients with renal impairment (defined by creatinine of N1.4 mg/dL in women and N1.5 mg/dL in men)				

Table 159

9.3.1.2 *Summary and conclusions*

Lixisenatide once daily vs placebo in patients inadequately stabilized on sulfonylureas (±metformin)			
Bibliography: Rosenstock 2014 (82) GetGoal_S			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	859 (1) 24 weeks	Lixisenatide: -0.85% Placebo: -0.10% LS mean difference: -0.74% (95 CI: -0.867 to -0.621) p<0.0001 **SS in favour of lixisenatide**	⊕⊕⊖⊖ **LOW** Study quality: 1, unclear randomization, allocation concealment and blinding Consistency: N/A Directness: -1, patients with and without metformin, no subanalysis Imprecision: ok
Body weight change from baseline	859 (1) 24 weeks	Lixisenatide: -1.76 kg ±0.20 Placebo: -0.93 kg ±0.23 LS mean change difference: -0.84 kg (95% CI: -1.250 to -0.421) p<0.0001 **SS in favour of lixisenatide**	⊕⊕⊖⊖ **LOW** Study quality: 1, unclear randomization, allocation concealment and blinding Consistency: N/A Directness: -1, patients with and without metformin, no subanalysis Imprecision: ok
Adverse events leading to withdrawal	859 (1) 76 weeks	Lixi: 9.8% (n = 56) Placebo: 4.9% (n = 14)	Not applicable
Diarrhea	859 (1) 76 weeks	Lixi: 8.9% (n = 51) Placebo: 6.7% (n = 19)	Not applicable
Nausea	859 (1) 76 weeks	Lixi: 25.3% (n=145) Placebo:7.0% (n=20)	Not applicable
Vomiting	859 (1) 76 weeks	Lixi: 8.7% (n=50) Placebo:3.5% (n=10)	Not applicable
Severe hypoglycaemia	859 (1) 76 weeks	Lixi: 0.2% (n=1) Placebo:0	Not applicable

Table 160

In this double blind RCT, 859 patients with type 2 diabetes, inadequately controlled by sulfonylurea and eventually metformin, were randomized to lixisenatide or placebo for 24 weeks with a double blind extension until 76 weeks. The mean age was 57.4 years, mean duration of diabetes 9.45 years, mean baseline HbA1c was 8.25% and mean BMI was 30.25 kg/$m^{2.}$ Having had a myocardial infarction

in the 6 months prior to the study was an exclusion criterion. Patients on metformin and with renal impairment were excluded.

Our confidence in the estimate of the between-group differences is limited the fact that patients with and patients without metformin were analyzed together. There was no subgroup analysis available. Most patients used both metformin and sulfonylurea (85%).

In patients who were inadequately controlled on sulfonylurea ± metformin, at 24 weeks, the addition of lixisenatide **resulted** in a statistically significant decrease of HbA1c compared to placebo.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on sulfonylurea ± metformin, at 24 weeks, there was a statistically significant **difference** in weight change with the addition of lixisenatide compared to placebo. There was more weight loss with lixisenatide.
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 9.8% with lixisenatide and 4.9% with placebo.
GRADE: not applicable

Rates of diarrhea were 8.9% with lixisenatide and 6.7% with placebo. It is not known if the difference was statistically significant.
Rates of nausea were 25.3% with lixisenatide and 7.0% with placebo. It is not known if the difference was statistically significant.
Rates of vomiting were 8.7% with lixisenatide and 3.5% with placebo. It is not known if the difference was statistically significant.
GRADE: not applicable

There was only one event of severe hypoglycemia, in the lixisenatide group, 0 in the placebo group. It is not known if the difference was statistically significant.
GRADE: not applicable

9.4 Combination therapy with basal insulin with or without OAD

9.4.1 Lixisenatide + basal insulin +/- metformin versus placebo + basal insulin +/- metformin

9.4.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Riddle 2013(83) Getgoal-L Design: RCT DB PG Phase III Duration of follow-up: 24 weeks	n: 495 Mean age: 57 ± 10 Prior/current treatment: insulin therapy (100%) metformin use (79%) Mean DMII duration: 12.5y Mean baseline HbA1c: 8.4% Mean BMI: 32.1 ± 6.2 Previous CV event: unknown Renal impairment: unknown <u>Inclusion</u> Adults with type 2 diabetes diagnosed ≥1 AND basal insulin regimen	Lixisenatide 20µg (if tolerated) (n = 328) vs Placebo (n =167) in addition to this background treatment: basal insulin (± metformin) <u>Hyperglycaemia uptitration protocol:</u> preferably with rapid acting insulin, other possibility increase of basal insulin of >20% <u>Hyperglycaemia rescue protocol</u>**:** Rescue therapy, preferably with	Efficacy		RANDO: unclear, states "randomized", not by which method ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes Injected volume unblinded FOLLOW-UP: <u>Discontinued treatment</u>: Lixi: 16% Placebo: 12% Reason described: yes <u>Uptitration of study medication</u>: two-step dose-increase regimen (10 µg for 1 week, 15 µg for 1 week, and then 20 µg if tolerated) <u>Hyperglycaemic rescue</u>: Lixisenatide: 6% (n=19) Placebo: 7% (n=12)
			Change in HbA1c from baseline (PO)	Lixisenatide: -0.4%±0.1 Placebo: -0.7%±0.1 LS mean change difference: -0.4% 95% CI: -0.6 to -0.2 p = 0.0002 SS	
			Body weight change from baseline	Lixisenatide: -1.8 kg Placebo: -0.5 kg LS mean change difference: -1.3 kg (95% CI: -1.8 to -0.7) p<0.0001 SS	
			Blood pressure change from baseline (SystBP/DiastBP)	not reported	
			Safety		
			Death	Lixisenatide: 0.3% (n = 1) Placebo: 0	
			Cardiovascular adverse events	not reported	
			Any adverse events	Lixisenatide: 73.5% Placebo:68.3%	

	for ≥3months with a stable dose (±20%) ≥30 units/day for ≥2 months before screening and HbA1c = 7–10%. Candidates using metformin must have taken a stable dose of at least 1.5 g/day (South Korea, at least 1.0 g/day) for at least 3 months before screening. Exclusion FPG .13.9 mmol/L (250 mg/dL); BMI #20.0 kg/m2; weight change .5.0 kg over the 3 months before screening; history of unexplained pancreatitis, end-stage renal disease, or allergic reaction to any GLP-1RA in the past; or pregnancy.	rapid-acting insulin, was permitted if FPG was .15.0 mmol/L (270 mg/dL) any time between randomization and week 8, FPG was .13.3 mmol/L (240 mg/dL) from week 8 through 12, and FPGwas.11.1mmol/L (200 mg/dL) or HbA1c .8.5% from week 12 through 24 Stratification: by HbA1C (<8.0%; ≥8.0%) and by metformin use at screening	**Serious adverse events**	not reported	p=0.540) Statistical method for drop out/missing data: LOCF Data handling for rescued patients: Excluded from efficacy analysis ITT: mITT for **efficacy** endpoints: participants who received one or more doses of the allocated treatment and had a measurement at baseline (randomization) and at least one on-treatment measurement of any primary and secondary efficacy end point **Safety** endpoints , mITT as well: all randomized individuals who received at least one dose of the investigational product SELECTIVE REPORTING: yes presence of a cardiovascular event adjudication committee, but no report on cardiovascular events (except the one death which was attributed to cardiac arrest and deemed not treatment related by the investigator)
			Adverse event leading to withdrawal	Lixisenatide: 7.6% (n=25) Placebo: 4.8% (n=8)	
			Any gastro-intestinal adverse event	Lixi: 40.2% (n=132) Placebo: 20.4% (n=34)	
			Diarrhoea	Lixisenatide: 7.3% (n=24) Placebo: 5.4% (n=9)	
			Nausea	Lixisenatide: 26.2% (n=86) Placebo: 8.4% (n=14)	
			Vomiting	Lixi: 8.2% (n=27) Placebo: 0.6% (n=1)	
			Severe hypoglycaemia	Lixisenatide:1.2% (n=4) Placebo: 0	
			Documented symptomatic hypoglycaemia	Patients with hypoglycaemia with blood glucose <60 mg/dl: Lixisenatide: 26.5% (n = 87) Placebo: 21.0% (n = 35) p=0.174	
			Injection site reactions	Lixisenatide: 1.2% (n = 4) Placebo: 0.6% (n = 1)	
			Thyroid cancer		
			Pancreatitis		

					Other important methodological remarks: if HbA1c was ≤7.5% at screening, the daily dosage of basal insulin was initially reduced by 20% at randomization to limit the risk of hypoglycemia and thereafter progressively increased between weeks 4 and 12 to the dosage used at the screening visit, unless prevented by the occurrence of hypoglycemia. After week 12, no further dose adjustments of basal insulin were to be made except for reductions in response to hypoglycemia. Sponsor: Sanofi

Table 161

9.4.1.2 *Summary and conclusions*

Lixisenatide + basal insulin therapy (±metformin) vs placebo + basal insulin therapy (±metformin) in T2DM			
Bibliography: Riddle 2013(83) Getgoal-L			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	495 (1) 24 weeks	Lixisenatide: -0.4%±0.1 Placebo: -0.7%±0.1 LS mean change difference: -0.4% (95% CI: -0.6 to -0.2) p = 0.0002 **SS in favour of lixisenatide**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: N/A Directness: -1, participants with and without metformin use pooled together Imprecision: ok
Body weight change from baseline	495 (1) 24 weeks	Lixisenatide: -1.8 kg Placebo: -0.5 kg LS mean change difference: -1.3 kg (95% CI: -1.8 to -0.7) p<0.0001 **SS in favour of lixisenatide**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: N/A Directness: -1, participants with and without metformin use pooled together Imprecision: ok
Adverse events leading to withdrawal	495 (1) 24 weeks	Lixisenatide: 7.6% (n=25) Placebo: 4.8% (n=8)	Not applicable
Diarrhea	495 (1) 24 weeks	Lixisenatide: 7.3% (n=24) Placebo: 5.4% (n=9)	Not applicable
Nausea	495 (1) 24 weeks	Lixisenatide: 26.2% (n=86) Placebo: 8.4% (n=14)	Not applicable
Vomiting	495 (1) 24 weeks	Lixi: 8.2% (n=27) Placebo: 0.6% (n=1)	Not applicable
Severe hypoglycaemia	495 (1) 24 weeks	Lixisenatide:1.2% (n=4) Placebo: 0	Not applicable

Table 162

In this double blind, phase III RCT, 495 patients with type 2 diabetes, inadequately controlled by basal insulin therapy ± metformin, were randomized to lixisenatide or placebo for 24 weeks. The mean age was 57 years, mean duration of diabetes 12.5 years, mean baseline HbA1c was 8.4% and mean BMI was 32.1 kg/m^2. It is unknown how many participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

The interpretation of these results is limited because of the inclusion of patients with and without metformin oral therapy. Based on these results, it is difficult to make statements about the combination of a glp-1 receptor agonist with basal insulin specifically.

In patients who were inadequately controlled on basal insulin ± metformin, at 24 weeks, the addition of lixisenatide **resulted** in a statistically significant decrease of HbA1c compared to placebo.
GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on basal insulin ± metformin, at 24 weeks, there was a statistically significant difference in weight change with the addition of lixisenatide compared to placebo. There was more weight loss with lixisenatide.
GRADE: MODERATE quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 7.6% with lixisenatide and 4.8% with placebo.
GRADE: not applicable

Rates of diarrhea were 7.3% with lixisenatide and 5.4% with placebo. It is not known if the difference was statistically significant.
Rates of nausea were 26.2% with lixisenatide and 8.4% with placebo. It is not known if the difference was statistically significant.
Rates of vomiting were 8.2% with lixisenatide and 0.6% with placebo. It is not known if the difference was statistically significant.
GRADE: not applicable

There were 4 events of severe hypoglycemia.
Severe hypoglycemia occurred in 1.2% with lixisenatide and 0% with placebo. It is not known if the difference was statistically significant.
GRADE: not applicable

9.4.2 Lixisenatide + insulin glargine + OAD versus placebo + insulin glargine + OAD

9.4.2.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Riddle 2013(84) GetGoal-Duo1 Design: RCT DB PG phase III Duration of follow-up: 24 weeks	n:446 Mean age: 56 ± 10 Prior/current treatment: daily glargine of 44 units + metformin + oral therapy Mean DMII duration: 9.2 y Mean baseline HbA1c: 7.6% ±0.5 Mean BMI: 31.8 kg/m² Previous CV event: unknown Renal impairment: unknown <u>Inclusion</u> Adults with T2DM for at least 1 year use of metformin at a	Lixisenatide 20µg / day (n = 223) vs Placebo (n = 223) in addition to this background treatment: basal insulin glargine (44 units) <u>Hyperglycaemia uptitration protocol:</u> / <u>Hyperglycaemia rescue protocol</u>**:** Rescue therapy	Efficacy		RANDO: Adequate: centrally generated randomized treatment kit number list ALLOCATION CONC: Adequate: allocated using a centralized interactive voice response system BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: <u>Study completers</u>: Lixisenatide: 87% Placebo: 95% Reason described: yes <u>Discontinued treatment</u>: Lixisenatide: 13% (29) Placebo: 5% (12) <u>Uptitration of study medication</u>:
			Change in HbA1c from baseline (PO)	Lixisenatide: -0.74% Placebo:-0.4% LS mean difference: -0.32% 95%CI: -0.46 to -0.17 p<0.0001	
			Body weight change from baseline	Lixisenatide: -0.3 kg Placebo: +1.2kg Difference: -0.9 kg p = 0.0012	
			Blood pressure change from baseline (SystBP/DiastBP)	"no significant changes"	
			Safety		
			Death	Lixisenatide: 0 Placebo: 2	
			Cardiovascular adverse events	not reported	
			Any adverse events	Lixisenatide: 79.8% Placebo: 68.2%	
			Serious adverse events	Lixisenatide: 7.6% Placebo: 4.5%	
			Adverse event leading to withdrawal	Lixisenatide: 4% (n = 9) Placebo: 0	

	stable dose of at least 1.5 g/day for at least 3 months alone or in combination with a sulfonylurea or glinide or a thiazolidinedione (TZD), or a combination of these; HbA1c ≥7.0 and ≤10% (≥53 to ≤86 mmol/mol); and BMI .>20 kg/m2. <u>Exclusion</u> use of oral or injectable antihyperglycemic agents other than metformin, sulfonylureas, glinides, and TZDs within 3 months; use of weight-loss drugs if not at a stable dose for ≥3 months; history of hypoglycemia unawareness, gastrointestinal disease associated with prolonged nausea, and vomiting; and hypersensitivity to insulin glargine or	with short-acting insulin was permitted through week 8 if FPG was repeatedly >.11.1 mmol/L (200 mg/dL) or if HbA1c was >9.0% (75 mmol/mol), and after week 8 if FPG was.> 10.0mmol/L (180 mg/dL) or if HbA1c was .>8.5% (69 mmol/mol). <u>Stratification:</u> stratified by HbA1c values after the run-in (<8%, ≥8% [64 mmol/mol]) and TZD use (yes or no).	**Any gastro-intestinal adverse event**	Lixisenatide:39.9% (n = 89) Placebo: 16.1% (n = 36)	Morning administration of insulin glargine was started at 10 units daily and was titrated weekly, targeting a fasting range of 4.4–5.6 mmol/L (80–100 mg/dL). At completion of the 12-week run-in, participants were eligible for randomization if they had HbA1c $7% and #9% ($53 and #75 mmol/mol) and fasting self-measurement of plasma-referenced glucose (SMPG) for the past 7 days averaging# 7.0mmol/L (126mg/dL) early in the trial or #7.8 mmol/L (140 mg/dL) after a protocol amendment in July 2010. A two-step dosage increase was used with both placebo and lixisenatide (10 mg for 1 week, 15 mg for 1 week, and then 20-mg maintenance dosage if tolerated), with injections self-administered by participants ≤1 h before breakfast. Adjustment of dosage of insulin glargine was permitted throughout randomized treatment targeting fasting SMPG 4.4–5.6 mmol/L (80–100 mg/dL). <u>Hyperglycaemic rescue</u>: Lixisenatide: 1 person
			Diarrhoea	Lixisenatide: 6.7% (n = 15) Placebo: 3.1% (n = 7)	
			Nausea	Lixisenatide: 27.4 % (n = 61) Placebo: 4.9% (n = 11)	
			Vomiting	Lixisenatide: 9.4% (n = 21) Placebo: 1.3% (n = 3)	
			Severe hypoglycaemia	Lixisenatide: n = 1 Placebo: 0	
			Documented symptomatic hypoglycaemia	Lixisenatide: 20.2% Placebo: 11.7%	
			Injection site reactions	Lixisenatide: 6.7% (n = 15) Placebo: 2.2% (n = 5)	
			Thyroid cancer	not reported	
			Pancreatitis	Lixisenatide: n = 0 Placebo: n = 1	

	allergic reaction to any GLP-1RAs				Placebo: 1 person <u>Statistical method for drop out/missing data</u>: LOCF <u>Data handling for rescued patients</u>: LOCF <u>ITT</u>: **Efficacy** in a mITT population defined as: all randomized participants who received at least one dose of double-blind study drug, and had both a baseline assessment and at least one postbaseline assessment of any primary or secondary efficacy variables using the last observation carried forward procedure. **Safety** in all randomized participants exposed to at least one dose of the double-blind study drug, regardless of the amount of treatment administered SELECTIVE REPORTING: no Other important methodological remarks :

					Run-in of 12 weeks with a titration of glargine until a HbA1c of 7-9% was achieved, and a fasting glucose of ≤ 7.8 mmol/l Sponsor: Sanofi

Table 163

9.4.2.2 *Summary and conclusions*

Lixisenatide + Oral therapy (SU, glinide, thiazolidine or a combination)+ insulin glargine vs Placebo + oral therapy (SU, glinide, thiazolidine or a combination)+ insulin glargine			
Bibliography: Riddle 2013(84) GetGoal-Duo1			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	446 (1) 24 weeks	Lixisenatide: -0.74% Placebo:-0.4% LS mean difference: -0.32% 95%CI: -0.46 to -0.17 p<0.0001 **SS in favour of lixisenatide**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: n/a Directness: -1, "oral therapy" grouped together Imprecision: ok
Body weight change from baseline	446 (1) 24 weeks	Lixisenatide: -0.3 kg Placebo: +1.2kg Difference: -0.9 kg p = 0.0012 **SS in favour of lixisenatide**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: n/a Directness: -1, "oral therapy" grouped together Imprecision: ok
Adverse events leading to withdrawal	446 (1) 24 weeks	Lixisenatide: 4% (n = 9) Placebo: 0	Not applicable
Diarrhea	446 (1) 24 weeks	Lixisenatide: 6.7% (n = 15) Placebo: 3.1% (n = 7)	Not applicable
Nausea	446 (1) 24 weeks	Lixisenatide: 27.4 % (n = 61) Placebo: 4.9% (n = 11)	Not applicable
Vomiting	446 (1) 24 weeks	Lixisenatide: 9.4% (n = 21) Placebo: 1.3% (n = 3)	Not applicable
Severe hypoglycaemia	446 (1) 24 weeks	Lixisenatide: (0,4%) n = 1 Placebo: 0	Not applicable

Table 164

In this double blind RCT, 446 patients with type 2 diabetes, inadequately controlled by oral therapy and insulin glargine, were randomized to lixisenatide or placebo for 24 weeks. The mean age was 56 years, mean duration of diabetes 9,2 years, mean baseline HbA1c was 7.6% and mean BMI was 31.8 kg/m^2. It is unknown how many of the participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

The interpretation of these results is limited because of the inclusion of patients without specifying which exact oral antidiabetic therapy they were on. Based on these results, it is difficult to make statements about the combination of a glp-1 receptor agonist with a specific oral antidiabetic agent.

In patients who were inadequately controlled on oral therapy and insulin glargine, at 24 weeks, the addition of lixisenatide **resulted** in a statistically significant decrease of HbA1c compared to placebo.
GRADE: MODERATE quality of evidence

In patients who were inadequately controlled on oral therapy and insulin glargine, at 24 weeks, there was a statistically significant difference in weight change with the addition of lixisenatide compared with placebo.
The weight in the lixisenatide group was decreased compared to the placebo group (in which the weight had increased from baseline).
GRADE: MODERATE quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 4% with lixisenatide and 0% with placebo.
GRADE: not applicable

Rates of diarrhea were 6.7% with lixisenatide and 3.1% with placebo. It is not known if the difference was statistically significant.
Rates of nausea were 27.4% with lixisenatide and 4.9% with placebo. It is not known if the difference was statistically significant.
Rates of vomiting were 9.4% with lixisenatide and 1.3% with placebo. It is not known if the difference was statistically significant.
GRADE: not applicable

There were no events of severe hypoglycemia.
Severe hypoglycemia occurred in 0.4% with lixisenatide and 0% with placebo. It is not known if the difference was statistically significant.
GRADE: not applicable

9.4.3 Lixisenatide + insulin glargine +/- MET versus insulin glulisine + insulin glargine +/- MET

9.4.3.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Rosenstock 2016(85) GetGoal-Duo 2 Design: RCT OL Active comparator Duration of follow-up: 12 weeks of insulin glargine optimization + 26 weeks of active treatment or comparator + 3 days of follow up	n:894 Mean age: 59.8 y Prior/current treatment: metformin (87.3%), basal insulin, SU (46.1%), DPP-4 inhibitor (12%) Mean DMII duration: 12.2 y Mean baseline HbA1c: 8.5 ±0.7% Mean BMI: 32.2 kg/m² Previous CV event: unknown Renal impairment: unknown <u>Inclusion</u> Adults with T2DM for at least 1 year, a BMI of >20-40kg/m²	Lixisenatide 20µg once daily (n = 298) vs insulin glulisine once daily (n = 298) vs insulin glulisine 3x/day (n = 298) in addition to this background treatment: Insulin glargine Oral antidiabetic agents (but all OADs aside from metformin were discontinued) <u>Hyperglycaemia uptitration protocol:</u>	Efficacy		RANDO: Adequate ALLOCATION CONC: Open label BLINDING : Open label FOLLOW-UP: <u>Study completers</u>: Lixisenatide: 89.9% (n = 268) Insulin glulisine 1x/D : 94.3%(n = 281) Insulin glulisine 3x/D: 95.6% (n = 285) Reason described: yes <u>Discontinued treatment</u>: Lixisenatide: 10.1% (n = 30) Insulin glulisine 1x/D: 5.7% (n = 17) Insulin glulisine 3x/D: 4.0% (n = 4) <u>Uptitration of study medication</u>: Lixisenatide: 10 mg once daily for 2 weeks, followed by lixisenatide 20 mg once daily for the remainder of the study, injected 30–60 min before the main meal
			Change in HbA1c from baseline (PO)	Lixisenatide: -0.6 % ±0.1 Insulin glulisine once daily: -0.6 ±0.1 LS mean difference: -0.1 (95% CI: -0.17, 0.06) NS Insulin glulisine 3x/d: -0.8% ±0.1 LS mean difference: 0.2 (95% CI: 0.10,0.33) **SS** **In favour of insulin glulisine 3x/d**	
			Body weight change from baseline	Lixisenatide: -0.6 ± 0.3 kg Insulin glulisine once daily: 1.0±0.3kg LS mean difference: -1.7 (95% CI: -2.26, -1.06) **SS in favour of lixisenatide** Insulin glulisine thrice daily: 1.4±0.3kg LS mean difference: -2.0 (95% CI: -2.59, -1.40) **SS in favour of lixisenatide**	

	uncontrolled on ≥6 months basal insulin, alone or combined with stable doses of t 1-3 OADS(metformin [≥1.5 mg/day or maximum tolerated dose], a DPP-4 inhibitor, an SU, or a glinide) Patients receiving basal insulin alone or with metformin had to have HbA1c 7.5–10.0% (58–86 mmol/mol) at screening. Patients receiving basal insulin plus an SU and/or a DPP-4 inhibitor and/or a glinide had to have HbA1c 7.0–10.0% (53–86 mmol/mol) at screening <u>Exclusion</u> clinically relevant history of gastrointestinal disease or a history of unexplained/chronic pancreatitis. Patients were excluded if they had	<u>Hyperglycaemia rescue protocol</u>: <u>Stratification:</u> Stratified by baseline HbA1c (<8 or ≥8%) and metformin use			Insulin glargine: see "important methodological remarks" <u>Hyperglycaemic rescue</u>: N/A <u>Statistical method for drop out/missing data</u>: LOCF <u>ITT</u>: mITT for **efficacy**: (all randomized patients with at least one dose of study medication and a baseline assessment and at least one assessment after baseline of any primary or secondary efficacy end point For **safety**; (all randomized patients who received at least one dose of study medication regardless of the amount of treatment administered SELECTIVE REPORTING: yes/no (describe if yes) <u>Other important methodological remarks :</u> (*) Patients recruited were all on metformin + OADs but all OAD's aside from metformin were discontinued before trial started and insulin glargine was optimally
			Blood pressure change from baseline (SystBP/DiastBP)	not reported	
			Safety		
			Death	Lixisenatide: 0.3% (n = 1) Insulin glulisine 1x/d: 0 Insulin glulisine 3x/d: 0.7% (n = 2)	
			Cardiovascular adverse events	not reported	
			Any adverse events	Lixisenatide: 74.2% Insulin glulisine 1x/d: 73.8% Insulin glulisine 3x/d: 80.3%	
			Serious adverse events	Lixisenatide: 3.7% (n = 11) Insulin glulisine 1x/d: 3.7% (n = 11) Insulin glulisine 3x/d: 4.8% (n = 14)	
			Adverse event leading to withdrawal	Lixisenatide: 5.0% (n = 15) Insulin glulisine 1x/d: 0.7% (n = 2) Insulin glulisine 3x/d: 1.0% (n = 3.0)	
			Any gastro-intestinal adverse event	Lixisenatide: 35.2% (n = 105) Insulin glulisine 1x/d: 8.6% (n = 26) Insulin glulisine 3x/d: 7.5% (n = 22)	
			Diarrhoea	Lixisenatide: 6.7% (n = 20) Insulin glulisine 1x/d: 3.3% (n = 10) Insulin glulisine 3x/d: 1.4% (n = 4)	
			Nausea	Lixisenatide:25.2% (n = 70) Insulin glulisine 1x/d: 1.7% (n = 5) Insulin glulisine 3x/d: 1.0% (n = 3)	
			Vomiting	Lixisenatide: 8.7% (n = 26) Insulin glulisine 1x/d:1.7% (n = 5)	

	alanine/aspartate aminotransferase, amylase, or lipase levels more than three times the upper limit of normal or calcitonin levels >20 pg/mL			Insulin glulisine 3x/d: 2.0% (n = 6)	titrated during the run-in. If HbA1c was ≥7 and ≤9% and mean plasma glucose was ≤140 mg/dl patients were randomized. Insulin glargine doses were adjusted weekly to maintain fasting daily SMPG between 80 and 100 mg/dL (4.4 and 5.6 mmol/L) except during the 4 weeks after randomization when a stable insulin dose was maintained. Sponsor: Sanofi
			Severe hypoglycaemia	Lixisenatide: 0 Insulin glulisine 1x/d: 0.7% (n = 2) Insulin glulisine 3x/d: 0	
			Documented symptomatic hypoglycaemia	Lixisenatide: 35.9% (n = 107) Insulin glulisine 1x/d: 46.5% (n = 140) Insulin glulisine 3x/d: 52.4% (n = 154)	
			Injection site reactions	not reported	
			Thyroid cancer	not reported	
			Pancreatitis	not reported	

Table 165

9.4.3.2 *Summary and conclusions*

Lixisenatide once daily+ insulin glargine +metformin vs insulin glulisine once daily + insulin glargine +metformin			
Bibliography: Rosenstock 2016(85) GetGoal-Duo 2			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	596 (1) 26 weeks	Lixisenatide: -0.6 % ±0.1 Insulin glulisine once daily: -0.6 ±0.1 LS mean difference: -0.1 (95% CI: -0.17, 0.06) NS	⊕⊕⊖⊖ **LOW** Study quality: -1, open label Consistency: n/a Directness: -1, unclear if inadequate control on OAD Imprecision: ok
Body weight change from baseline	596 (1) 26 weeks	Lixisenatide: -0.6 ± 0.3 kg Insulin glulisine once daily: 1.0±0.3kg LS mean difference: -1.7 (95% CI: -2.26, -1.06) **SS in favour of lixisenatide**	⊕⊕⊖⊖ **LOW** Study quality: -1, open label Consistency: n/a Directness: -1, unclear if inadequate control on OAD Imprecision: ok
Adverse events leading to withdrawal	596 (1) 26 weeks	Lixisenatide: 5.0% (n = 15) Insulin glulisine 1x/d: 0.7% (n = 2)	Not applicable
Diarrhea	596 (1) 26 weeks	Lixisenatide:6.7% (n = 20) Insulin glulisine 1x/d: 3.3% (n = 10)	Not applicable
Nausea	596 (1) 26 weeks	Lixisenatide:25.2% (n = 70) Insulin glulisine 1x/d: 1.7% (n = 5)	Not applicable
Vomiting	596 (1) 26 weeks	Lixisenatide:8.7% (n = 26) Insulin glulisine 1x/d:1.7% (n = 5)	Not applicable
Severe hypoglycaemia	596 (1) 26 weeks	Lixisenatide: 0 Insulin glulisine 1x/d: 0.7% (n = 2)	Not applicable

Table 166

Lixisenatide once daily+ insulin glargine +metformin vs insulin glulisine thrice daily + insulin glargine + metformin			
Bibliography: Rosenstock 2016(85) GetGoal-Duo 2			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
HbA1c change from baseline (PO)	596 (1) 26 weeks	Lixisenatide: -0.6 % ±0.1 Insulin glulisine 3x/d: -0.8% ±0.1 LS mean difference: 0.2 (95% CI: 0.10,0.33) **SS** **In favour of insulin glulisine 3x/d**	⊕⊕⊖⊖ **LOW** Study quality: -1, open label Consistency: n/a Directness: -1, unclear if inadequate control on OAD Imprecision: ok
Body weight change from baseline	596 (1) 26 weeks	Lixisenatide: -0.6 ± 0.3 kg Insulin glulisine thrice daily: 1.4±0.3kg LS mean difference: -2.0 (95% CI: -2.59, -1.40) **SS in favour of lixisenatide**	⊕⊕⊖⊖ **LOW** Study quality: -1, open label Consistency: n/a Directness: -1, unclear if inadequate control on OAD Imprecision: ok
Adverse events leading to withdrawal	596 (1) 26 weeks	Lixisenatide: 5.0% (n = 15) Insulin glulisine 3x/d: 1.0% (n = 3)	Not applicable
Diarrhea	596 (1) 26 weeks	Lixisenatide:6.7% (n = 20) Insulin glulisine 3x/d: 1.4% (n = 4)	Not applicable
Nausea	596 (1) 26 weeks	Lixisenatide:25.2% (n = 70) Insulin glulisine 3x/d: 1.0% (n = 3)	Not applicable
Vomiting	596 (1) 26 weeks	Lixisenatide: 8.7% (n = 26) Insulin glulisine 3x/d: 2.0% (n = 6)	Not applicable
Severe hypoglycaemia	596 (1) 26 weeks	Lixisenatide: 0 Insulin glulisine 3x/d: 52.4% (n = 154)	Not applicable

In this open label RCT, 894 patients with type 2 diabetes, inadequately controlled by oral therapy, were stabilized on insulin glargine after discontinuation of all oral medication except metformin until they reached a HbA1c value of ≥7% and ≤9%. They were then randomized to insulin glulisine 1x/day, insulin glulisine 3x/day or lixisenatide for 26 weeks. The mean age was 59.8 years, mean duration of diabetes 12.2 years, mean baseline HbA1c was 8.5±0.7% and mean BMI was 32.2 kg/m^2. It is unknown how many of the participants had had a previous myocardial infarction. Patients with mild renal impairment were allowed in the study, but it is unclear how many of these patients were actually included.

Our confidence in the estimate of the between-group differences is limited by the lack of knowledge of previous treatment and if patients were inadequately controlled on those treatments or not, and the fact the study was open label.

In patients who were inadequately controlled on metformin and insulin glargine, at 26 weeks, the addition of lixisenatide **did not result** in a statistically significant decrease of HbA1c compared to the addition of insulin glulisine once daily.
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin and insulin glargine, at 26 weeks, there was a statistically significant difference in **decrease of HbA1c** with the addition of lixisenatide compared to the addition of insulin glulisine thrice daily (**there was a bigger decrease with insulin glulisine**).
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin and insulin glargine, at 26 weeks, there was a statistically **significant difference in weight change** with the addition of lixisenatide compared to the addition of insulin glulisine **once daily**.
The weight in the lixisenatide group was decreased compared to the insulin glulisine once daily group (in which the weight had increased from baseline).
GRADE: LOW quality of evidence

In patients who were inadequately controlled on metformin and insulin glargine, at 26 weeks, there was a statistically **significant difference in weight change** with the addition of lixisenatide compared to the addition of insulin glulisine **thrice daily**.
The weight in the lixisenatide group was decreased compared to the insulin glulisine thrice daily group (in which the weight had increased from baseline).
GRADE: LOW quality of evidence

Adverse events were reported, but no statistical testing was performed or reported. Therefore, GRADE cannot be applied.

Withdrawal from the study due to adverse events was seen in 5% with lixisenatide, in 0.7% with insulin glulisine once daily and 13% with insulin glulisine thrice daily.

GRADE: not applicable

Rates of diarrhea were 6.7% with lixisenatide, 3.3% with insulin glulisine once daily and 1.4% with insulin glulisine thrice daily.
Rates of nausea were 25.2% with lixisenatide, 1.7% with insulin glulisine once daily and 1.0% with insulin glulisine thrice daily.
Rates of vomiting were 8.7% with lixisenatide, 1.7% with insulin glulisine once daily and 2.0% with insulin glulisine thrice daily.
GRADE: not applicable

There were 2 events of severe hypoglycemia, both with Insulin glulisine once daily. No events were reported for lixisenatide or insulin glulisine thrice daily.
GRADE: not applicable

9.5 Lixisenatide versus placebo (in addition to standard care): hard endpoints

9.5.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Pfeffer 2015(86) ELIXA Design: RCT (DB) (PG) non-inferiority trial Duration of follow-up: median 25 months	n:6068 Race/Ethnicity: 75% Caucasian Mean age: 60y (34%≥65y) Prior/current treatment: Insulin 39%, metformin 66%, SU 33%, TZD 1.6% DMII duration:9.3y Baseline HbA1c: 7.7% Mean BMI: 30.2kg/m2 Previous MI before index case: 22% Renal impairment: mean eGFR 76ml/min/1.73m2 qualifying event: 39% NSTEMI; 44% STEMI, 17% unstable angina <u>Inclusion</u> type 2 diabetes,	Lixisenatide max 20µg/day vs placebo in addition to this background treatment: standard OAD treatment see left for baseline data <u>Hyperglycaemia uptitration protocol:</u> Glycemic control was managed by the investigators in accordance with local clinical practice guidelines by	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: <u>Study completers</u>: 96.2% (of patients who did not die) <u>Discontinued treatment during study</u>: 27.5% lixi and 24% pla <u>Uptitration of other antidiabetic medication</u>: not reported in this study SELECTIVE REPORTING: not all
			Composite (death from cardiovascular causes, nonfatal MI, non-fatal stroke, hospitalization for unstable angina)(PO)	lixi: 13.4% pla:13.2% HR:1.02 (95%CI 0.89-1.17) **noninferiority of lixisenatide to placebo** **(P<0.001)** p=0.81 for superiority 'sensitivity analyses showed similar results' 'No significant study-group interactions were observed for the primary end point in the prespecified subgroups or in the post hoc subgroups'	
			Composite (death from cardiovascular causes, nonfatal MI, non-fatal stroke, hospitalization for unstable angina, hospitalization for heart failure)(SO)	lixi:15.0% pla:15.5% HR: 0.97 (95% CI 0.85–1.10) NS	

	acute coronary event within 180 days before screening <u>Exclusion</u> < 30 , percutaneous coronary intervention within the previous 15 days, coronary-artery bypass graft surgery for the qualifying event, planned coronary revascularization procedure within 90 days after screening, eGFR of less than 30 ml per minute per 1.73 m2 , HbA1c of less than 5.5% or more than 11.0%	the adjustment of concomitant glucose-lowering agents or the addition of new antidiabetic medications with the exception of other incretin therapies. This approach was expected to yield similar glycemic control in the two study groups.	**Composite (death from cardiovascular causes, nonfatal MI, non-fatal stroke, hospitalization for unstable angina, hospitalization for heart failure or coronary revascularization)(SO)**	lixi:21.8% pla:21.7% HR:1.00 (95% CI 0.90 to 1.11) NS	adverse events registered (or reported). No information on concomitant antidiabetic medication during trial. No information on injections site reactions although specified in protocol Other important methodological remarks 1 week run-in before randomisation non-inferiority if upper boundary of the 95% confidence interval of the hazard ratio is less than 1.3 and the superiority would be shown if the upper boundary was less than 1.0 Sensitivity analyses were conducted in which events that occurred more than 30 days after the discontinuation of lixisenatide or placebo were excluded; in addition, a post hoc Cox proportional-hazards analysis was conducted with a model that was adjusted for nominally significant baseline imbalances. Sponsor: Sanofi
			All-cause mortality	lixi:7.0% pla:7.4% HR: 0.94 (95% CI 0.78–1.13) NS	
			Cardiovascular mortality	lixi:5.1% pla:5.2% HR: 0.98 (95% CI 0.78–1.22) NS	
			Myocardial infarction	lixi:8.9% pla:8.6% HR: 1.03 (95% CI 0.87–1.22) NS	
			Stroke	lixi:2.2% pla:2.0% HR: 1.12 (95% CI 0.79–1.58) NS	

			Hospitalisation for heart failure	lixi:4.0% pla:4.2% HR: 0.96 (95% CI 0.75 to 1.23) NS subgroup of patients with heart failure at baseline and subgroup without heart failure at baseline : similar results, no interaction between subgroups	
			Change in HbA1c from baseline (PO) MMRM	at 12 w: lixi:-0.6% pla: -0.2% MD across all visits −0.27% (95% CI −0.31 to −0.22) P<0.001) SS in favour of lixisenatide	
			Body weight change from baseline	at 12 weeks lixi:-0.6kg pla:-0.0kg 'average between-group difference (lixisenatide minus placebo) across all visits −0.7 kg (95% CI, −0.9 to −0.5; P<0.001)' representation in figure. Before 32 weeks: SS difference between lixi and pla. After 32 weeks: overlapping CIs	
			Blood pressure change from baseline (SystBP/DiastBP)	SBP: 'average difference across all visits of −0.8 mm Hg (95% CI, −1.3 to −0.3) in favor of lixisenatide (P = 0.001)'	

				representation in figure. After 24 months: overlapping CIs	
			Safety		
			Any adverse events	NR	
			Serious adverse events	lixi:20.6% pla:22.1%	
			Adverse event leading to withdrawal	lixi:11.4% pla:7.2% p<0.001	
			Any gastro-intestinal adverse event	NR	
			Withdrawal due to GI adverse events	lixi:4.9% pla:1.2% p<0.001	
			Severe hypoglycaemia (requiring assistance from another person)	lixi:n= 14 pla:n=24 'numerically less frequent with lixisenatide'	
			hypoglycaemia (not defined) – see below for definition in protocol	lixi:16.6% of patients pla:15.2% of patients p=0.14 NS	
			Injection site reactions	NR	
			Thyroid cancer	NR	

			Pancreatitis independent adjudication	lixi:n=5 (0.2%) pla:n=8 (0.3%)	

Table 167

In protocol:
Symptomatic hypoglycemia is defined as an event with clinical symptoms that are considered to result from a hypoglycemic episode (e.g., sweating, palpitations, hunger, restlessness, anxiety, fatigue, irritability, headache, loss of concentration, somnolence, psychiatric or visual disorders, transient sensory or motor defects, confusion, convulsions, or coma) with an accompanying plasma glucose < 60 mg/dL (3.3 mmol/L) or associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration if no plasma glucose measurement is available. Symptoms with an associated plasma glucose measurement ≥ 60 mg/dL (3.3 mmol/L) should not be reported as a hypoglycaemia, unless the glucose value is only obtained after the event was treated, and the event otherwise satisfies the definition of a symptomatic hypoglycaemia event above

'No significant study-group interactions were observed for the primary end point in the prespecified subgroups or in the post hoc subgroups, including the subgroup defined according to history or no history of heart failure'.
Note: It is unclear which subgroups were prespecified. Subgroups reported were, amongst others: age < or > 65y, baseline BMI < or > 30kg/m2, duration of diabetes < or > 10 y, eGFR (3 categories), HbA1c < 7.5 or > 7.5%

9.5.1.2 *Summary and conclusions*

Lixisenatide 20µg/d + standard antidiabetic treatment versus placebo + standard antidiabetic treatment in patients with a recent myocardial infarction			
Bibliography: Pfeffer 2015(86) ELIXA			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Composite (death from cardiovascular causes, nonfatal MI, non-fatal stroke, hospitalization for unstable angina) (PO)	6068 (1) median 25 months	lixi: 13.4% pla:13.2% HR:1.02 (95%CI 0.89-1.17) **lixisenatide is non-inferior to placebo** **(P<0.001)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 very specific population, no information on added antidiabetic treatment other than lixi or placebo Imprecision: ok
Death from any cause	6068 (1) median 25 months	lixi:7.0% pla:7.4% HR: 0.94 (95% CI 0.78–1.13) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 very specific population, no information added on antidiabetic treatment other than lixi or placebo Imprecision: ok
Death from cardiovascular causes	6068 (1) median 25 months	lixi:5.1% pla:5.2% HR: 0.98 (95% CI 0.78–1.22) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -1 very specific population, no information on antidiabetic treatment other than lixi or placebo Imprecision: -1 lower boundry of CI includes appreciable benefit, upper boundry includes appreciable harm
Myocardial infarction	6068 (1) median 25 months	lixi:8.9% pla:8.6% HR: 1.03 (95% CI 0.87–1.22) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -1 very specific population, no information on antidiabetic treatment other than lixi or placebo Imprecision: -1 lower boundry of CI includes appreciable benefit, upper boundry includes appreciable harm
Hospitalization for heart failure	6068 (1) median 25 months	lixi:4.0% pla:4.2% HR: 0.96 (95% CI 0.75 to 1.23) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -1 very specific population, no information on antidiabetic treatment other than lixi or placebo

			Imprecision: -1 lower boundry of CI includes appreciable benefit, upper boundry includes appreciable harm
HbA1c change from baseline (PO)	6068 (1) median 25 months	MD across all visits −0.27% (95%CI −0.31 to −0.22) P<0.001 **SS in favour of lixisenatide**	GRADE not applied. See note
Body weight change from baseline	6068 (1) median 25 months	'average between-group difference across all visits ' −0.7 kg (95% CI, −0.9 to −0.5) P<0.001	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 very specific population, no information on antidiabetic treatment other than lixi or placebo Imprecision: ok
Adverse events leading to withdrawal	6068 (1) median 25 months	lixi:11.4% pla:7.2% p<0.001	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 very specific population, no information on antidiabetic treatment other than lixi or placebo Imprecision: unable to assess
Gastro-intestinal events leading to discontinuation of trial	6068 (1) median 25 months	lixi:4.9% pla:1.2% p<0.001	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 very specific population, no information on antidiabetic treatment other than lixi or placebo Imprecision: unable to assess
Severe hypoglycaemia	6068 (1) median 25 months	lixi:n= 14 pla:n=24 'numerically less frequent with lixisenatide'	unable to assess

Table 168

In this double blind, non-inferiority RCT, 6,068 patients with a recent acute coronary event and type 2 diabetes, were randomized to lixisenatide or placebo for a median of 25 months.
The mean age was 60y, mean duration of diabetes 9.3 y, mean baseline HbA1c was 7.7% and mean BMI was 30.2 kg/m^2. For 83% of participants the qualifying event was a myocardial infarction, for 17% it was unstable angina.
66% of patients were taking metformin at baseline (+/- other antidiabetic drugs), 39% were taking insulin at baseline (+/- other antidiabetic drugs).

This study was designed, due to FDA requirements, to establish that the drug lixisenatide does not increase cardiovascular death in type 2 diabetes. To this end, all other parameters (most importantly: glycemic control and thus HbA1c) in the intervention and control group needed to be similar. In both the lixisenatide group and the placebo group, other antidiabetic agents could be added to achieve the desired HbA1c target. No specific target was defined by the authors (target was defined 'according to local practice').

At the 12-week time-point and as an average difference across all visits, the **HbA1c was lowered more with lixisenatide compared to placebo** (MD across all visits−0.27% (95% CI −0.31 to −0.22), but by 24 months until the end of the trial, the difference no longer appeared statistically significant (interpreted from graph).

No information is available about the additional antidiabetic treatments that were started during the trial.

When interpreting this trial, one needs to take into account the following items (see also chapter Liraglutide and LEADER):
- Participants did not need to have inadequate glycaemic control to be eligible for this trial. The mean HbA1c is therefore lower than in most of the other trials in our report.
- Lixisenatide was added to the existing antidiabetic treatment (of which 39% insulin). We have insufficient information to determine what the effect would be of adding lixisenatide to a specific existing antidiabetic regimen. This study cannot help us to determine the place of lixisenatide as first-line, second line, third line… treatment.
- The relative benefit or harm on cardiovascular risk of lixisenatide compared to another specific antidiabetic agent, can also not be derived from this trial.

In type 2 diabetic patients with a recent acute coronary event, after a median duration of 25 months, the addition of lixisenatide was **non-inferior** to the addition of placebo to prevent a first event of a **composite of cardiovascular death, nonfatal MI, nonfatal stroke and hospitalization for unstable angina**.
GRADE: MODERATE quality of evidence

In type 2 diabetic patients with a recent acute coronary event, after a median duration of 25 months, the addition of lixisenatide **did not result** in a statistically significant difference **in death from cardiovascular causes** or **death from any cause** compared to the addition of placebo.
GRADE: LOW (cardiovascular causes) and MODERATE (any cause) quality of evidence

In type 2 diabetic patients with a recent acute coronary event, after a median duration of 25 months, the addition of lixisenatide, **did not** result in a statistically significant difference in **myocardial infarction** compared to the addition of placebo.
GRADE: LOW quality of evidence

In type 2 diabetic patients with a recent acute coronary event, after a median duration of 25 months, the addition of lixisenatide **did not** result in a statistically significant difference in **hospitalization for heart failure** compared to the addition of placebo
GRADE: LOW quality of evidence

In type 2 diabetic patients with a recent acute coronary event, there was a statistically significant difference in **weight** change with the addition of liraglutide compared to the addition of placebo

when considered across a median of 25 months (average between-group difference across all visits −0.7 kg; 95% CI, −0.9 to −0.5).
GRADE: not applied

Withdrawal from the study due to adverse events was seen in 11.4% with liraglutide and 7.2% with placebo. The difference was statistically significant.
GRADE: MODERATE quality of evidence

Discontinuation rates due to **gastro-intestinal events** were 4.9% with liraglutide and 1.2% with placebo. The difference was statistically significant.
GRADE: MODERATE quality of evidence

Severe hypoglycemia occurred in 14 patients with lixisenatide and 24 patients with placebo.
GRADE: not applicable

Systolic blood pressure across all visits was 0.8 mmHg lower in the lixisenatide group than in the placebo group. The difference was statistically significant.

Pancreatitis, pancreatic cancer and thyroid cancer were reported. No statistical testing was reported. More information on these rare endpoints is in the chapter: rare adverse events.

9.6 Lixisenatide: other endpoints from the RCTs

9.6.1 Blood pressure change

Blood pressure change from baseline was reported in 1 of the 8 trials with HbA1c decrease as primary endpoint that we included for this review. One trial with a composite cardiovascular primary endpoint also reported on blood pressure changes.

Both RCTs that reported blood pressure changes performed statistical tests for this outcome. Nauck 2016(70) found no statistically significant difference in the blood pressure change at 24 weeks between liraglutide and lixisenatide, when added to metformin. Pfeffer 2015(86) (ELIXA found an average difference across all visits of −0.8 mm Hg (95% CI, −1.3 to −0.3) in favor of lixisenatide, when compared to placebo, but CI overlap after 24 months.

The level of evidence for lixisenatide versus liraglutide is LOW to VERY LOW because of lack of reporting, very large CI, and the fact that the only study reporting this was open label.

9.6.2 Injection site reactions

Injection site reactions were reported in 4 of the 9 trials that were eligible for this review.

No trial performed a statistical analysis, it was therefore not possible to apply GRADE.

The definition of what was considered to be an injection site reaction was usually not specified.

9.6.3 Cardiovascular adverse events (including heart failure)

Aside from the study specifically researching the cardiovascular effects of lixisenatide versus placebo, none of the 8 trials reported on cardiovascular endpoints.

9.6.4 Pancreatitis and thyroid cancer

Because of the low event rate of pancreatitis and thyroid cancer, these outcomes will be discussed in the chapter ‘rare safety outcomes’.

It is however useful to note that 3 out of 9 lixisenatide trials reported on pancreatitis, but none of them did a statistical analysis, and no trial reported on thyroid cancer.

10 Rare adverse events from RCTs and observational studies

This chapter is based on information from RCTs and observational (cohort) studies. Our source document to find observational studies was the 2016 AHRQ comparative effectiveness review(87) 'Diabetes Medications for adults with type 2 diabetes: an update'. AHRQ searched for RCTs and observational studies for safety endpoints. In the final report, AHRQ included only observational studies that were assessed medium or high quality according to a specific assessment tool (Downs and Black).

10.1 Bone fracture

RCTs

- The RCTs included in this review did not report the risk of bone fracture. The AHRQ 2016 report did not find any information on bone fracture for included trials with GLP-1 receptor agonists.
- We found a systematic search and meta-analysis of RCTs by Su 2015(88) that evaluated risk of bone fracture associated with GLP-1 receptor agonists exenatide and liraglutide. The mean age in the RCTs ranged from 45.9 to 59.5 years
  - A pooled analysis of 16 RCTs, including a total of 11206 patients, found **no significant difference in bone fracture** with GLP-1 receptor agonists compared to other antidiabetic treatment or placebo (Odds Ratio OR 1.05, 95 % CI 0.59–1.87).
  - When 8 RCTs with liraglutide were pooled (including a total of 5912 patients) a statistically significantly lower fracture rate was found with liraglutide compared to other antidiabetic treatment or placebo, but this difference became non-significant when 2 trials that used exenatide as the comparator, were excluded.
  - Pooling of 10 RCTs (including 5294 patients) with exenatide found a (borderline significant) higher fracture rate with exenatide compared to other antidiabetic treatment or placebo (OR 2.09, 95 % CI 1.03–4.21). When 2 studies that used liraglutide as the comparator were excluded, the results were no longer statistically significant (OR 1.71; 95 % CI 0.80–3.67).

Observational

- AHRQ 2016(87) did not find any medium or high quality observational studies (based on risk of bias assessment) for this outcome.
- We found a population based cohort study in the UK(89) that followed 216,816 patients with at least 1 prescription for a non-insulin antihyperglycemic drug for a maximum of 5 years. 8,354 used a GLP-1 RA. **No significant difference in bone fracture risk** was found when comparing the use of GLP-1 RA to no use of GLP-1 RA (adjusted HR 0.99, 95 % CI 0.82–1.19). No dose-response relationship could be found. The duration of GLP-1 use (median 1.2 years) was rather short.

Conclusion

Based on sparse data, GLP-1 receptor agonists do not seem to have an impact on risk of fracture.

GRADE: VERY LOW quality of evidence

The level of evidence for this outcome is VERY LOW, because of the short follow-up of most studies (10 RCTs ≤ 26 weeks), the wide confidence interval in the meta-analysis, the low event rate, the young age of the participants and the pooling of different comparators.

10.2 All cancer

The AHRQ 2016(87) report states that the strength of evidence for cancer outcomes is LOW to INSUFFICIENT, because of lack of active ascertainment, lack of reporting and high withdrawal rates.

10.3 Colorectal cancer

We found a US cohort study by Htoo 2016(90), that followed 5,600 new GLP-1 RA users and compared them to 54,767 new long acting insulin users. All were older than 65 years. The median follow up was 0.8 and 1.2 years respectively. No statistically significant difference in colorectal cancer rates was found (adjusted HR 0.98; 95%CI 0.74, 1.30).

Conclusion: there is limited evidence that GLP-1 receptor agonists are not associated with an increased risk of colorectal cancer. More data are needed before we can make a definite statement.

GRADE: VERY LOW quality of evidence

The short follow-up lowers our confidence in the results of this observational study.

10.4 Thyroid cancer

RCTs

- For this review, thyroid cancer events that were reported in the individual RCTs can be found in the detailed evidence tables of the full document. Individual RCTs are not powered to detect differences in thyroid cancer rates.
- The LEADER trial randomized 9340 patients to liraglutide or placebo, on top of their current antidiabetic treatment and followed them for a median of 3.8 years. No patients taking liraglutide and 1 patient taking placebo developed thyroid cancer. The difference was not statistically significant.
- The 2016 AHRQ(87) reports thyroid cancer outcomes for the following comparisons:
  SU versus GLP-1 RA; MET + GLP-1 RA versus MET, MET + DPP-4 i, MET + SU, MET + TZD.
  No statistical testing was performed (low event rate). Overall, the level of evidence for these comparisons was considered by AHRQ as INSUFFICIENT to LOW, because of lack of reporting, lack of ascertainment of the outcomes and imprecision.

- Karagiannis 2015(23) performed a systematic review and meta-analysis of all RCTs of once-weekly GLP-1 RA and found no statistically significant difference in thyroid cancer rates between GLP-1 RA and all comparators (OR 1.03; 95%CI 0.45 to 2.32).
- An older systematic review and meta-analysis of longitudinal studies by Alves 2012(91) found no reported thyroid malignancies with exenatide twice daily and no statistically significant incrased risk with liraglutide (OR 1.54, 95% CI 0.40-6.02).

Observational studies

- AHRQ 2016(87) did not find any medium or high quality observational studies (based on their risk of bias assessment) for this outcome.

Conclusion
We have very limited evidence that GLP-1 RA are not associated with an increased risk of thyroid cancer. More data are needed before we can make a definite statement.

GRADE for this outcome VERY LOW, because of imprecision, selective reporting, duration of follow-up, pooling of different comparators.

10.5 Pancreatic cancer

RCTs

- For this review, pancreatic cancer events that were reported in the individual RCTs can be found in the detailed evidence tables of the full document. All these trials individually are not large enough or have inadequate follow-up time to reliably assess pancreatic cancer outcomes.
- The LEADER trial randomized 9340 patients to liraglutide or placebo, on top of their current antidiabetic treatment and followed them for a median of 3.8 years. 0.3% of patients taking liraglutide and 0.1% of patients taking placebo experienced pancreatic cancer. The difference was not statistically significant (p= 0.06).
- The ELIXA trial randomized 6068 patients to lixisenatide or placebo, on top of their current antidiabetic treatment and followed them for a median of 25 months. 3 patients taking lixisenatide and 9 patients taking placebo experienced pancreatic cancer. The difference was not statistically significant.
- AHRQ 2016 stated that the body of evidence for pancreatic cancer was insufficient.
- Karagiannis 2015(23) performed a systematic review and meta-analysis of all RCTs of once-weekly GLP-1 RA and found no statistically significant difference in pancreatic cancer rates between GLP-1 RA and all comparators (OR 1.07; 95%CI 0.46 to 2.52).

Observational studies

- AHRQ 2016(87) did not find any medium or high quality observational studies (based on their risk of bias assessment) for this outcome.
- We included 1 recent observational study. A population-based cohort study in the UK by Knapen 2016(92) did not find a statistically significant association between GLP-1 RA use and

non-insulin, non-incretin use, when adjusting for all possible confounders (adjusted HR 1.18; 95% CI 0.52–2.69).
The results were based on 11,206 person-years of exposure to GLP-1 RA. The mean duration of follow-up was 4.1 years for incretin users.

The current evidence does not suggest an increased risk of pancreatic cancer with the use of GLP-1 receptor agonists. More data are needed before we can make a definite statement.

GRADE: VERY LOW quality of evidence.
The information from RCTs was downgraded because of imprecision, selective reporting, duration of follow-up, pooling of different comparators. The information from observational studies was also downgraded because of imprecision.

10.6 Pancreatitis

RCTs

- For this review, pancreatitis events that were reported in the RCTs can be found in the detailed evidence tables of the full document. All these trials individually are not large enough or have inadequate follow-up time to reliably assess pancreatitis outcomes.
- The LEADER trial randomized 9340 patients to liraglutide or placebo, on top of their current antidiabetic treatment and followed them for a median of 3.8 years. 0.4% of patients taking liraglutide and 0.5% of patients taking placebo experienced pancreatitis. The difference was not statistically significant.
- The ELIXA trial randomized 6068 patients to lixisenatide or placebo, on top of their current antidiabetic treatment and followed them for a median of 25 months. 0.2% of patients taking lixisenatide and 0.3% of patients taking placebo experienced pancreatitis. The difference was not statistically significant.
- AHRQ 2016(87) reports on pancreatitis for the following comparisons:
  - monotherapy: MET, TZD, SU and DPP-4 i vs GLP-1 RA
  - combination therapy: MET + GLP-1 RA vs MET + pla, MET + SU, MET + DPP-4 i
  No statistical testing was performed. The strength of evidence was considered LOW for all comparisons, mainly due to the low event rates and the fact that for most comparisons there was only a single study available.
- We found several meta-analyses of RCTs for this outcome.
  - Karagiannis 2015(23) performed a systematic review and meta-analysis of all RCTs of once-weekly GLP-1 RA and found no statistically significant difference in pancreatitis rates between these GLP-1 RA and all comparators (placebo or active treatment) (OR 1.17; 95%CI 0.61 to 2.22). Note that in some included trials, the active comparator was a DPP-4 inhibitor.
  - Other meta-analyses have been performed by Li 2014(93) and Monami 2014(94) (both with search date march 2013).
  Li 2014 found no statistically significant difference in pancreatitis events with GLP-1 RA compared to control (placebo or active treatment, but no DPP-4 inhibitors). 14,562 patients

from 29 trials were included (OR 1.05, 95% CI 0.37 to 2.94). Li remarked that the rate of pancreatitis in RCTs (0.11%) was lower than the rate seen in observational studies (0.47%), which can be explained by the exclusion of at risk patients from RCTs.
Monami 2014 found similar results (glp-1 RA versus comparators: OR 1.01; 95%CI 0.37 to 2.76).

Observational studies

- AHRQ 2016(87) did not find any medium or high quality observational studies (based on their risk of bias assessment) for this outcome.
- We were not required to search for observational studies for this outcome.

Conclusion
The current evidence does not suggest an increased risk of pancreatitis with the use of GLP-1 receptor agonists. More data are needed before we can make a definitive statement.

GRADE: LOW quality of evidence.
Our confidence in these findings is mainly limited due to imprecision (a wide confidence interval that does not exclude clinically relevant harm) and the exclusion from the RCTs of patients that are at risk of pancreatitis (directness).

10.7 Heart failure

RCTs

- For this review, heart failure events that were reported in the RCTs can be found in the detailed evidence tables of the full document . In most trials, heart failure events were not reported. When they were reported, study duration and/or sample size did not allow any firm conclusions.
- The LEADER trial randomized 9340 patients to liraglutide or placebo, on top of their current antidiabetic treatment and followed them for a median of 3.8 years. 4.7% of patients taking liraglutide and 5.3% of patients taking placebo were hospitalized for heart failure. The difference was not statistically significant.
- The ELIXA trial randomized 6068 patients to lixisenatide or placebo, on top of their current antidiabetic treatment and followed them for a median of 25 months. 4.0% of patients taking lixisenatide and 4.2% of patients taking placebo were hospitalized for heart failure. The difference was not statistically significant.
- AHRQ did not find any information from RCTs on heart failure with GLP-1 RA.
- A recent systematic review and meta-analysis by Li 2016(95) examined the risk of heart failure with GLP-1 receptor agonists. RCTs and observational studies were included. GRADE was performed. Based on information from 20 RCTs, Li found no evidence of a difference in risk of heart failure between GLP-1 agonists and control (odds ratio (OR) 0.62, 95 % CI 0.31 to 1.22).

Observational studies

- AHRQ 2016(87) did not find any medium or high quality observational studies (based on their risk of bias assessment) for this outcome.
- Three cohort studies found by Li 2016(95) comparing GLP-1 agonists to alternative agents concluded that GLP-1 agonists were not associated with the incidence of heart failure. (GRADE for observational studies as assessed by Li: VERY LOW quality of evidence)

Conclusion: The current evidence does not find an increased risk of **heart failure** with the use of GLP-1 RA.
GRADE: LOW quality of evidence.
Our confidence in the estimate for heart failure is mainly limited by the short duration of the included trials, the pooling of different comparators and the imprecision of the estimate.

The current evidence does not find an increased risk of **hospitalization for heart failure** with the use of liraglutide and lixisenatide.
GRADE: MODERATE to LOW quality of evidence
Our confidence in the estimate for hospitalization for heart failure is limited by the very specific population and the fact that the placebo group added more and different antidiabetic drugs. For lixisenatide, it is also limited by imprecision of the estimate.

10.8 Cardiovascular adverse events

A lot of meta-analyses about cardiovascular events have been published, comparing all GLP-1 RA to placebo or any other antidiabetic treatment (the most recent is Wang 2016(96)). All these have the same problem: they included RCTs that were not primarily designed for this outcome, they included RCTs with a short duration and they pooled RCTs with different concomitant treatments and different comparators. None of these meta-analysis could find an increased risk of cardiovascular events between GLP-1 receptor agonists and comparator. We decided not to report these in detail. More information on cardiovascular events can be found in the chapters of the individual GLP-1 receptor agonists.

11 Adverse effects of GLP-1 agonists from other sources

Because GLP-1 RA are new drugs, almost no information was found in Meyler's Side Effects of Drugs (15th edition) and other of our usual sources. Most of the information in this chapter is derived from the BCFI/CBIP website (www.bcfi.be – www.cbip.be) and from the Summary of the Product Characteristics.

11.1 In general[2]

- Gastrointestinal disorders, especially nausea: common
- Hypoglycaemia, especially in association with a sulphonylurea (or a basal insulin)
- Angioneurotic oedema, anaphylaxis: very rare
- Injection site reactions (more frequent with the once weekly injection)
- An increased risk of pancreatitis and of pancreatic and thyroid cancer has been suggested, but at this time there is no proof of a causal relationship.
- Formation of antibodies, possibly resulting in the reduction of the hypoglycemic effect and in increased injection site reactions
- Liraglutide: thyroid disorders (cancer, increased serum calcitonin, goitre): rare

Patient frequencies below are defined as: very common ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000; very rare: <1/10,000 and not known (cannot be estimated from the available data), including isolated reports.

11.2 Albiglutide[3]

System/organ class	Frequency of occurence		
	Very common	**Common**	**Uncommon**
Infections en infestations		Pneumonia	
Metabolism and nutrition disorders	Hypoglycaemia (when Eperzan is used in combination with insulin or sulphonylurea)	Hypoglycaemia (when Eperzan is used as monotherapy or in combination with metformin or pioglitazone)	
Cardiac disorders		Atrial fibrillation/ flutter	
Gastrointestinal disorders	Diarrhoea, nausea	Vomiting, constipation, dyspepsia, gastrooesophageal reflux disease	Pacreatitis, intestinal obstruction
General disorders and administration site conditions	Injection site reactions		

Table 169: frequency of adverse reactions in albiglutide

[2] Bcfi/cbip
[3] Summary of Product Characteristics of Eperzan©

11.3 Dulaglutide[4]

System/organ class	Frequency of occurence			
	Very common	**Common**	**Uncommon**	**Rare**
Metabolism and nutrition disorders	Hypoglycaemia* (when used in combination with prandial insulin, metformin§ or metformin plus glimepiride)	Hypoglycaemia * (when used as monotherapy or in combination with metformin plus pioglitazone)		
Gastrointestinal disorders	Nausea, diarrhoea, vomiting§, abdominal pain§	Decreased appetite, dyspepsia, constipation, flatulence, abdominal distention, gastroesophageal reflux disease, eructation		Acute pancreatitis
General disorders and administration site conditions		Fatigue	Injection site reactions	
Investigations		Sinus tachycardia, first degree atrioventricular block (AVB)		

Table 170: frequency of adverse reactions of dulaglutide

*Documented, symptomatic hypoglycaemia and blood glucose ≤3.9 mmol/L.
§Dulaglutide 1.5 mg dose only. For dulaglutide 0.75 mg, adverse reaction met frequency for next lower incidence grouping.

11.4 Exenatide 2x/day[5]

System/organ class/AE terms	Frequency of occurence					
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Immune system disorders						
Anaphylactic reaction					X3	
Metabolism and nutrition disorders						
Hypoglycaemia (with metformin and a sulphonylurea)[2]	X1					
Hypoglycaemia (with a sulphonylurea)	X1					
Decreased appetite		X1				

[4] Summary of Product Characteristics of Trulicity©
[5] Summary of Product Characteristics of Byetta©

Dehydration, generally associated with nausea, vomiting and/or diarrhoea				X3		
Nervous system disorders						
Headache[2]		X1				
Dizziness		X1				
Dysgeusia			X3			
Somnolence				X3		
Gastrointestinal disorders						
Intestinal obstruction				X4		
Nausea	X1					
Vomiting	X1					
Diarrhoea	X1					
Dyspepsia		X1				
Abdominal pain		X1				
Gastroesophageal reflux disease		X1				
Abdominal distension		X1				
Acute pancreatitis				X3		
Eructation			X3			
Constipation			X3			
Flatulence			X3			
Skin and subcutaneous tissue disorders						
Hyperhidrosis[2]		X1				
Alopecia				X3		
Macular and papular rash				X3		
Pruritus, and/or urticaria				X3		
Angioneurotic oedema				X3		
Renal and urinary disorders						
Altered renal function, including acute renal failure, worsened chronic renal failure, renal impairment, increased serum creatinine				X3		
General disorders and administration site conditions						
Feeling jittery		X1				
Asthenia[2]		X1				
Injection site reactions		X1,3				
Investigations						
Weight decreased		X1				
International normalised ratio increased with concomitant warfarin, some reports associated with bleeding						X

Table 171: frequency of adverse reactions of exenatide twice daily.

X1 Data from comparator-controlled phase 3 trials versus placebo, insulin glargine, or 30% soluble insulin aspart/70% insulin aspart protamin in cristallin form (biphasic insulin aspart), in which

participants received metformin, thiazolidinediones, or sulphonylurea as a background treatment. (N= 1788 with Byetta©-treated intent-to-treat (ITT) patients.) The data from a 30-week study in which Byetta© was compared to insulin lispro, when added to an existing basal insulin therapy (insulin glargine), were not included.
X2 In controlled trials with insulin as a comparator, and in which metformin and a sulphonylurea were administered as a background treatment, the incidence of these adverse effect was comparable between participants treated with insulin and Byetta©.
X3 Adverse events reported after market release
X 4 Incidence based on Byetta© clinical study database n=5227 (including all completed long-term trials investigating effectiveness and safety).

11.5 Exenatide 1x/week[6]

System/organ class/AE	Frequency of occurence					
	Very common	Common	Uncommon	Rare	Very rare	Unknown
Immune system disorders						
Anaphylactic reaction						X2
Metabolism and nutrition disorders						
Hypoglycaemia (with sulphonylurea)	X1,3					
Decreased appetite		X1,3				
Nervous system disorders						
Headache		X1,3				
Dizziness		X1,3				
Gastrointestinal disorders						
Acute pancreatitis						X2
Nausa	X1,3					
Vomiting	X1,3					
Diarrhea	X1,3					
Dyspepsia		X1,3				
Abdominal pain		X1,3				
Gastroesophageal reflux disease		X1,3				
Abdominal distension		X1				
Eructation		X1				
Constipation	X1					
Flatulence		X1,3				
Renal and urinary disorders						
Altered renal function including acute renal failure, worsened chronic renal failure, increased serum creatinine						X2
Skin and subcutaneous tissue disorders						
Macular and papular rash						X2

[6] Summary of Product Characteristics of Bydureon©

Pruritus and/or urticaria			X1			
Angioneurotic oedema						X2
General disorders and administration site conditions						
Injection site pruritus	X1					
Asthenia		X1,3				
Injection site erythema		X1				
Injection site rash		X1				
Somnolence		X1				

Table 172: frequency of adverse reactions of exenatide once weekly

X1 Frequencies based on clinical study data with BYDUREON© n=592 total, (patients using sulphonylurea n=135)

X2 Frequencies based on spontaneously reported data with BYDUREON©.

X3 Adverse events were in same frequency-interval in exenatide twice daily treatment group

11.6 Liraglutide[7]

System/organ class	**Frequency of occurence**				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Infections and infestations		Nasopharyngitis Bronchitis			
Immune system disorders				Anaphylactic reactions	
Metabolism and nutrition disorders		Hypoglycaemia Anorexia Appetite decreased	Dehydratation		
Nervous system disorders		Headache Dizziness			
Cardiac disorders		Increased heart rate			
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Dyspepsia Abdominal pain Constipation Gastritis Flatulence Abdominal distension Gastroesophageal reflux disease Abdominal discomfort Toothache		Intestinal obstruction	Pancreatitis (including necrotising pancreatitis)
Skin and subcutaneous		Rash	Urticaria Pruritus		

[7] Summary of Product Characteristics of Victoza

tissue disorder					
Renal and urinary disorders			Renal impairment Acute renal failure		
General disorders and administration site conditions		Fatigue Injection site reactions	Malaise		

Table 173: frequency of adverse reactions of liraglutide

11.7 Lixisenatide[8]

System/organ class	Frequency of occurence		
	Very common	**Common**	**Uncommon**
Infections and infestations		Influenza Upper respiratory tract infection Cystitis Viral infection	
Immune system disorders			Anaphylactic reaction
Metabolism and nutrition disorders	Hypoglycaemia (in combination with a sulphonylurea and/or a basal insulin)	Hypoglycaemia (in combination with metformin alone)	
Nervous system disorders	Headache	Dizziness Somnolence	
Gastrointestinal disorders	Nausea Vomiting Diarrhoea	Dyspepsia	
Skin and subcutaneous tissue disorders			Urticaria
Musculoskeletal and connective tissue disorders		Back pain	
General disorders and administration site conditions		Injection site pruritus	

Table 174: frequency of adverse reactions of lixisenatide

[8] Summary of Product Characteristics of Lyxumia©

12 Appendix 1 - Search strategy

12.1 Cochrane library search

12.1.1 Cochrane Database of Systematic Reviews-CDSR

Search date 5/2/2016
Search term: type 2 diabetes
Number of hits: 108
Number exported to reference manager: 10
Number withheld: 1 (after new scope of consensus conference)

12.1.2 Database of Abstracts of Reviews of Effects – DARE

Search date 5/2/2016
Search term: type 2 diabetes AND glucagon-like peptide 1
Number of hits: 31
Number exported to reference manager: 21 (2010 – present)

12.2 Pubmed systematic search for RCTs, SRs, MAs

12.2.1 Source document to start our search

Shyangdan DS, Royle P, Clar C, et al. Glucagon-like peptide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev 2011:Cd006423. DOI: 10.1002/14651858.CD006423.pub2.

Search date of this SR: march 2011

All relevant references extracted and entered into reference manager.

Systematic search in Medline (pubmed) developed from januari 2011 (slight overlap with Shyandang search date) up to 1st july 2016.

12.2.2 Pubmed search string

((((("Glucagon-Like Peptides"[Mesh] OR "rGLP-1 protein" [Supplementary Concept] OR "dulaglutide" [Supplementary Concept] OR "exenatide" [Supplementary Concept] OR "Liraglutide"[Mesh] OR "ZP10A peptide" [Supplementary Concept] OR ((glucagon-like peptide 1[TIAB] OR glp-1[TIAB])AND agonist*[TIAB]) OR Albiglutide[TIAB] OR Dulaglutide[TIAB] OR exenatide[TIAB] OR Liraglutide[TIAB] OR Lixisenatide[TIAB])))) AND ((("Diabetes Mellitus, Type 2"[Mesh] OR NIDDM OR (diabetes AND ("type II" OR "type 2 "))))) AND (((randomized controlled trial OR random*[TIAB] OR placebo[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])))) AND ("2011/01/01"[Date - Entrez] : "2016/07/01"[Date - Entrez])

Number of references found: 806

12.3 Additional search for observational studies

12.3.1 Source document to start our search

Bolen S, Tseng E, Hutfless S, et al. AHRQ Comparative Effectiveness Reviews. Diabetes Medications for Adults With Type 2 Diabetes: An Update 2016

Search date of this SR: april 2015

All relevant references extracted and entered into reference manager.

Systematic search in Medline (pubmed) developed from march 2015 up to 1st july 2016.

12.3.2 Pubmed search string

(((Cohort*[tiab] OR Longitudinal[TIAB] OR Prospective[TIAB] OR Retrospective[TIAB] OR observational[TIAB] OR "Observational Study"[Publication Type]) AND ("Glucagon-Like Peptides"[Mesh] OR "rGLP-1 protein" [Supplementary Concept] OR "dulaglutide" [Supplementary Concept] OR "exenatide" [Supplementary Concept] OR "Liraglutide"[Mesh] OR "ZP10A peptide" [Supplementary Concept] OR ((glucagon-like peptide 1[TIAB] OR glp-1[TIAB]) AND (agonist*[TIAB] or analogue*[TIAB])) OR Albiglutide[TIAB] OR Dulaglutide[TIAB] OR exenatide[TIAB] OR Liraglutide[TIAB] OR Lixisenatide[TIAB] OR incretin*[TIAB]))) AND ("2015/03/01"[Date - Entrez] : "2016/07/01"[Date - Entrez])

Number of references found: 99

13 Appendix 2-List of excluded publications

The following publications were excluded after reviewing the full text. The reason for exclusion is stated in **bold.**

1. *Abdul-Ghani MA, Williams K, Kanat M, et al. Insulin vs GLP-1 analogues in poorly controlled Type 2 diabetic subjects on oral therapy: a meta-analysis. J Endocrinol Invest 2013;36:168-73.**n. not SR: incomplete search***
2. *Ahren B, Vorokhobina N, Souhami E, et al. Equal improvement in glycaemia with lixisenatide given before breakfast or the main meal of the day. J Diabetes Complications 2014;28:735-41.**n. not a research question***
3. *Alves C, Batel-Marques F, Macedo AF. A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer. Diabetes Res Clin Pract 2012;98:271-84.**n. old search date. AHRQ 2016 is a more recent source for this outcome***
4. *Anonymous. [Type 2 diabetes. Lixisenatide - effective in combination]. MMW Fortschr Med 2013;155:62-3.**n. not SR***
5. *Anonymous. Two new GLP-1 receptor agonists for diabetes. Med Lett Drugs Ther 2014;56:109-11.**n. not SR***
6. *Anyanwagu U, Mamza J, Mehta R, et al. Cardiovascular events and all-cause mortality with insulin versus glucagon-like peptide-1 analogue in type 2 diabetes. Heart 2016.**n. no observational studies for this outcome***
7. *Araki E, Inagaki N, Tanizawa Y, et al. Efficacy and safety of once-weekly dulaglutide in combination with sulphonylurea and/or biguanide compared with once-daily insulin glargine in Japanese patients with type 2 diabetes: a randomized, open-label, phase III, non-inferiority study. Diabetes Obes Metab 2015;17:994-1002.**n. 100% japanese patients***
8. *Armstrong MJ, Houlihan DD, Rowe IA, et al. Safety and efficacy of liraglutide in patients with type 2 diabetes and elevated liver enzymes: individual patient data meta-analysis of the LEAD program. Aliment Pharmacol Ther 2013;37:234-42.**n. not a subgroup of interest***
9. *Aroda VR, Henry RR, Han J, et al. Efficacy of GLP-1 receptor agonists and DPP-4 inhibitors: meta-analysis and systematic review. Clin Ther 2012;34:1247-58.e22.**n. old search, we have more recent sources***
10. *Avogaro A, Schernthaner G. Achieving glycemic control in patients with type 2 diabetes and renal impairment. Acta Diabetol 2013;50:283-91.**n. not SR and old review.***
11. *Azoulay L. Incretin-based drugs and adverse pancreatic events: almost a decade later and uncertainty remains. Diabetes Care 2015;38:951-3.**n. not SR***
12. *Azoulay L, Filion KB, Platt RW, et al. Incretin based drugs and the risk of pancreatic cancer: international multicentre cohort study. Bmj 2016;352:i581.**n. nested case control. not a pure cohort study***
13. *Balena R, Hensley IE, Miller S, et al. Combination therapy with GLP-1 receptor agonists and basal insulin: a systematic review of the literature. Diabetes Obes Metab 2013;15:485-502.**n. old search. newer trial have been published since then. we have all included trials.***
14. *Bell PM, Cuthbertson J, Patterson S, et al. Additive hypoglycaemic effect of nateglinide and exogenous glucagon-like peptide-1 in type 2 diabetes. Diabetes Res Clin Pract 2011;91:e68-70.**n. not available in belgium***
15. *Bennett WL, Balfe LM, Faysal JM. AHRQ's comparative effectiveness research on oral medications for type 2 diabetes: a summary of the key findings. J Manag Care Pharm 2012;18:1-22.**n. there is a new version of this SR***
16. *Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med 2011;154:602-13.**n. we have a newer version of this SR.***
17. *Bennett WL, Wilson LM, Bolen S, et al. AHRQ Comparative Effectiveness Reviews - Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update. 2011.**n. there is a newer version of this SR***

18. *Bentley-Lewis R, Aguilar D, Riddle MC, et al. Rationale, design, and baseline characteristics in Evaluation of LIXisenatide in Acute Coronary Syndrome, a long-term cardiovascular end point trial of lixisenatide versus placebo. Am Heart J 2015;169:631-8.e7.**n. is description of methods***
19. *Berlie H, Hurren KM, Pinelli NR. Glucagon-like peptide-1 receptor agonists as add-on therapy to basal insulin in patients with type 2 diabetes: a systematic review. Diabetes Metab Syndr Obes 2012;5:165-74.**n. old review. newer trials have been published since then. we have all included trials***
20. *Best JH, Rubin RR, Peyrot M, et al. Weight-related quality of life, health utility, psychological well-being, and satisfaction with exenatide once weekly compared with sitagliptin or pioglitazone after 26 weeks of treatment. Diabetes Care 2011;34:314-9.**n. quality of life outcomes are not a research question***
21. *Blonde L, Pencek R, MacConell L. Association among weight change, glycemic control, and markers of cardiovascular risk with exenatide once weekly: a pooled analysis of patients with type 2 diabetes. Cardiovasc Diabetol 2015;14:12.**n. MA not based on systematic search. pooling of studies with different background OAD. no added value for intermediate endpoints. exploratory analyses***
22. *Bloomgarden ZT, Handelsman Y. SGLT-2 INHIBITION ADDED TO GLP-1 AGONIST THERAPY FOR TYPE 2 DIABETES: WHAT IS THE BENEFIT? Endocr Pract 2015;21:1442-4.**n. not a research question***
23. *Bode B. An overview of the pharmacokinetics, efficacy and safety of liraglutide. Diabetes Res Clin Pract 2012;97:27-42.**n. not SR***
24. *Bode BW, Brett J, Falahati A, et al. Comparison of the efficacy and tolerability profile of liraglutide, a once-daily human GLP-1 analog, in patients with type 2 diabetes >/=65 and <65 years of age: a pooled analysis from phase III studies. Am J Geriatr Pharmacother 2011;9:423-33.**n. pooled analysis without systematic search***
25. *Boland CL, Degeeter M, Nuzum DS, et al. Evaluating second-line treatment options for type 2 diabetes: focus on secondary effects of GLP-1 agonists and DPP-4 inhibitors. Ann Pharmacother 2013;47:490-505.**n. incomplete search***
26. *Brady EM, Davies MJ, Gray LJ, et al. A randomized controlled trial comparing the GLP-1 receptor agonist liraglutide to a sulphonylurea as add on to metformin in patients with established type 2 diabetes during Ramadan: the Treat 4 Ramadan Trial. Diabetes Obes Metab 2014;16:527-36.**n. ramadan. not a research question.***
27. *Brice KR, Tzefos MK. The Clinical Efficacy and Safety of Glucagon-Like Peptide-1 (GLP-1) Agonists in Adults with Type 2 Diabetes Mellitus. Clin Med Insights Endocrinol Diabetes 2011;4:13-24.**n. old review, searched in only 1 database.***
28. *Bronden A, Naver SV, Knop FK, et al. Albiglutide for treating type 2 diabetes: an evaluation of pharmacokinetics/pharmacodynamics and clinical efficacy. Expert Opin Drug Metab Toxicol 2015;11:1493-503.**n. not SR***
29. *Burgmaier M, Heinrich C, Marx N. Cardiovascular effects of GLP-1 and GLP-1-based therapies: implications for the cardiovascular continuum in diabetes? Diabet Med 2013;30:289-99.**n. incomplete search. old(er) review.***
30. *Buse JB, Peters A, Russell-Jones D, et al. Is insulin the most effective injectable antihyperglycaemic therapy? Diabetes Obes Metab 2015;17:145-51.**n. post hoc***
31. *Bush MA. Glucagon-like peptide-1 receptor agonists for intensifying diabetes treatment. J Fam Pract 2011;60:S11-20.**n. old review.***
32. *Campbell RK. Clarifying the role of incretin-based therapies in the treatment of type 2 diabetes mellitus. Clin Ther 2011;33:511-27.**n. old review.***
33. *Carris NW, Taylor JR, Gums JG. Combining a GLP-1 receptor agonist and basal insulin: study evidence and practical considerations. Drugs 2014;74:2141-52.**n. not SR***
34. *Charbonnel B, Bertolini M, Tinahones FJ, et al. Lixisenatide plus basal insulin in patients with type 2 diabetes mellitus: a meta-analysis. J Diabetes Complications 2014;28:880-6.**n. MA not based on systematic search. pooling of studies with different background OAD. no added value for intermediate endpoints***
35. *Chaudhuri A, Dandona P. Effects of insulin and other antihyperglycaemic agents on lipid profiles of patients with diabetes. Diabetes Obes Metab 2011;13:869-79.**n. not SR. not a research question***
36. *Cohen D. Two drugs for type 2 diabetes seem to raise risk of acute pancreatitis, study shows. Bmj 2013;346:f1304.**n. not SR***
37. *Dai X, Wang H, Jing Z, et al. The effect of a dual combination of noninsulin antidiabetic drugs on lipids: a systematic review and network meta-analysis. Curr Med Res Opin 2014;30:1777-86.**n. outcome***

38. *Davidson JA, Brett J, Falahati A, et al. Mild renal impairment and the efficacy and safety of liraglutide. Endocr Pract 2011;17:345-55.* ***n. MA not based on systematic search. analysis post hoc in nature.***
39. *Davidson MH. Potential impact of dipeptidyl peptidase-4 inhibitors on cardiovascular pathophysiology in type 2 diabetes mellitus. Postgrad Med 2014;126:56-65.* ***n. dpp4***
40. *Davies ML, Pham DQ, Drab SR. GLP1-RA Add-on Therapy in Patients with Type 2 Diabetes Currently on a Bolus Containing Insulin Regimen. Pharmacotherapy 2016.* ***n. we have all included trials in our report.***
41. *de Heer J, Goke B. Are incretin mimetics and enhancers linked to pancreatitis and malignant transformations in pancreas? Expert Opin Drug Saf 2014;13:1469-81.* ***n. not SR***
42. *de Wit HM, Te Groen M, Rovers MM, et al. The placebo response of injectable GLP-1 receptor agonists versus oral DPP-4 inhibitors and SGLT-2 inhibitors: a systematic review and meta-analysis. Br J Clin Pharmacol 2016.* ***n. not a research question***
43. *de Wit HM, Vervoort GM, Jansen HJ, et al. Liraglutide reverses pronounced insulin-associated weight gain, improves glycaemic control and decreases insulin dose in patients with type 2 diabetes: a 26 week, randomised clinical trial (ELEGANT). Diabetologia 2014;57:1812-9.* ***n. sample size***
44. *Deacon CF, Mannucci E, Ahren B. Glycaemic efficacy of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors as add-on therapy to metformin in subjects with type 2 diabetes-a review and meta analysis. Diabetes Obes Metab 2012;14:762-7.* ***n. old search, incomplete search. pooling of different. GLP-1 receptor agonists and DPP4 inhibitors***
45. *Dejgaard TF, Knop FK, Tarnow L, et al. Efficacy and safety of the glucagon-like peptide-1 receptor agonist liraglutide added to insulin therapy in poorly regulated patients with type 1 diabetes--a protocol for a randomised, double-blind, placebo-controlled study: the Lira-1 study. BMJ Open 2015;5:e007791.* ***n. type 1 diabetes***
46. *Derosa G, Cicero AF, Franzetti IG, et al. Effects of exenatide and metformin in combination on some adipocytokine levels: a comparison with metformin monotherapy. Can J Physiol Pharmacol 2013;91:724-32.* ***n. primary endpoint of the study was adipocytokine levels.***
47. *Derosa G, Franzetti IG, Querci F, et al. Exenatide plus metformin compared with metformin alone on beta-cell function in patients with Type 2 diabetes. Diabet Med 2012;29:1515-23.* ***n. primary endpoint = beta cell function***
48. *Derosa G, Franzetti IG, Querci F, et al. Variation in inflammatory markers and glycemic parameters after 12 months of exenatide plus metformin treatment compared with metformin alone: a randomized placebo-controlled trial. Pharmacotherapy 2013;33:817-26.* ***n. the primary endpoint of the study was inflammatory markers.***
49. *Desouza CV, Gupta N, Patel A. Cardiometabolic Effects of a New Class of Antidiabetic Agents. Clin Ther 2015;37:1178-94.* ***n. we have all included trials in our report***
50. *DeVries JH, Bain SC, Rodbard HW, et al. Sequential intensification of metformin treatment in type 2 diabetes with liraglutide followed by randomized addition of basal insulin prompted by A1C targets. Diabetes Care 2012;35:1446-54.* ***n. the comparison was insulin vs placebo.***
51. *Distiller LA, Nortje H, Wellmann H, et al. A 24-week, prospective, randomized, open-label, treat-to-target pilot study of obese type 2 diabetes patients with severe insulin resistance to assess the addition of exenatide on the efficacy of u-500 regular insulin plus metformin. Endocr Pract 2014;20:1143-50.* ***n. sample size***
52. *Downes MJ, Bettington EK, Gunton JE, et al. Triple therapy in type 2 diabetes; a systematic review and network meta-analysis. PeerJ 2015;3:e1461.* ***n. indirect comparison. network MA***
53. *Drab SR. Glucagon-Like Peptide-1 Receptor Agonists for Type 2 Diabetes: A Clinical Update of Safety and Efficacy. Curr Diabetes Rev 2015.* ***n. incomplete search.***
54. *Drucker DJ, Sherman SI, Bergenstal RM, et al. The safety of incretin-based therapies--review of the scientific evidence. J Clin Endocrinol Metab 2011;96:2027-31.* ***n. old review***
55. *Du Q, Wang YJ, Yang S, et al. Liraglutide for the treatment of type 2 diabetes mellitus: a meta-analysis of randomized placebo-controlled trials. Adv Ther 2014;31:1182-95.* ***n. pooling of studies with different background OAD. no added value for intermediate endpoints***
56. *Einecke D. [Basal insulin and GLP-1 agonist potentiate each other (interview by Dr. med Dirk Einecke)]. MMW Fortschr Med 2012;154:28.* ***n. publication type***
57. *Ekstrom N, Svensson AM, Miftaraj M, et al. Cardiovascular Safety of Glucose-Lowering Agents as Add-on Medication to Metformin Treatment in Type 2 Diabetes:Report from the Swedish National Diabetes Register (NDR). Diabetes Obes Metab 2016.* ***n. cohort starting GLP-1 ra too small (n=219)***

58. *Eng C, Kramer CK, Zinman B, et al. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet 2014;384:2228-34.**n. pooling of different comparators, no information on individual glp-1 agonists or comparators. we have all included trials***
59. *Esposito K, Chiodini P, Bellastella G, et al. Proportion of patients at HbA1c target <7% with eight classes of antidiabetic drugs in type 2 diabetes: systematic review of 218 randomized controlled trials with 78 945 patients. Diabetes Obes Metab 2012;14:228-33.**n. this is observational analysis***
60. *Esposito K, Chiodini P, Ceriello A, et al. A nomogram to estimate the proportion of patients at hemoglobin A1c target <7% with noninsulin antidiabetic drugs in type 2 diabetes: a systematic review of 137 randomized controlled trials with 39,845 patients. Acta Diabetol 2014;51:305-11.**n. this is observational analysis***
61. *Esposito K, Mosca C, Brancario C, et al. GLP-1 receptor agonists and HBA1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials. Curr Med Res Opin 2011;27:1519-28.**n. old review***
62. *Fahrbach JL, Fu H, Shurzinske L, et al. Network meta-analysis accurately predicted the outcome of a subsequent randomised trial comparing once weekly dulaglutide 1.5 mg and once daily liraglutide 1.8 mg. Int J Clin Pract 2016;70:218-21.**n. indirect comparison. network MA***
63. *Fakhoury WK, LeReun C, Wright D. A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretin-based medications in patients with type 2 diabetes (Structured abstract). Pharmacology 2010;86:44-57.**n. old review. more recent MAs and RCTs have been published since***
64. *Filion KB, Azoulay L, Platt RW, et al. A Multicenter Observational Study of Incretin-based Drugs and Heart Failure. N Engl J Med 2016;374:1145-54.**n. nested case control. not a pure cohort study***
65. *Filippatos TD, Elisaf MS. Effects of glucagon-like peptide-1 receptor agonists on renal function. World J Diabetes 2013;4:190-201.**n. incomplete search. screened for additional references anyway.***
66. *Fonseca VA, Devries JH, Henry RR, et al. Reductions in systolic blood pressure with liraglutide in patients with type 2 diabetes: insights from a patient-level pooled analysis of six randomized clinical trials. J Diabetes Complications 2014;28:399-405.**n. MA not based on systematic search. pooling of studies with different background OAD and different comparators. no added value for intermediate endpoints***
67. *Fournier M, Germe M, Theobald K, et al. Indirect comparison of lixisenatide versus neutral protamine Hagedorn insulin as add-on to metformin and sulphonylurea in patients with type 2 diabetes mellitus. Ger Med Sci 2014;12:Doc14.**n. network meta-analysis: indirect comparisons***
68. *Franks AS, Lee PH, George CM. Pancreatitis: a potential complication of liraglutide? Ann Pharmacother 2012;46:1547-53.**n. we have more recent references with better search strategy for this outcome.***
69. *Gallo M. Thyroid safety in patients treated with liraglutide. J Endocrinol Invest 2013;36:140-5.**n. older review. not SR.***
70. *Gamble JM, Clarke A, Myers KJ, et al. Incretin-based medications for type 2 diabetes: an overview of reviews. Diabetes Obes Metab 2015;17:649-58.**n. screened but not used: not enough detail of included SRs and included trials***
71. *Garber AJ. Novel incretin-based agents and practical regimens to meet needs and treatment goals of patients with type 2 diabetes mellitus. J Am Osteopath Assoc 2011;111:S20-30.**n. old review***
72. *Gautier JF, Martinez L, Penfornis A, et al. Effectiveness and Persistence with Liraglutide Among Patients with Type 2 Diabetes in Routine Clinical Practice--EVIDENCE: A Prospective, 2-Year Follow-Up, Observational, Post-Marketing Study. Adv Ther 2015;32:838-53.**n. observational. no comparator group.***
73. *Germino FW. Noninsulin treatment of type 2 diabetes mellitus in geriatric patients: a review. Clin Ther 2011;33:1868-82.**n. not SR, old review***
74. *Giorda CB, Nada E, Tartaglino B. Pharmacokinetics, safety, and efficacy of DPP-4 inhibitors and GLP-1 receptor agonists in patients with type 2 diabetes mellitus and renal or hepatic impairment. A systematic review of the literature. Endocrine 2014;46:406-19.**n. incomplete search strategy. only 1 report on GLP-1 receptor agonists which was already found by our search.***
75. *Giorda CB, Nada E, Tartaglino B, et al. A systematic review of acute pancreatitis as an adverse event of type 2 diabetes drugs: from hard facts to a balanced position. Diabetes Obes Metab 2014;16:1041-7.**n. incomplete search. we have more recent and more complete SRs***
76. *Giorda CB, Sacerdote C, Nada E, et al. Incretin-based therapies and acute pancreatitis risk: a systematic review and meta-analysis of observational studies. Endocrine 2015;48:461-71.**n. incomplete search. we have more complete sources***

77. *Gluud LL, Knop FK, Vilsboll T. Effects of lixisenatide on elevated liver transaminases: systematic review with individual patient data meta-analysis of randomised controlled trials on patients with type 2 diabetes. BMJ Open 2014;4:e005325.**n. not a research question***
78. *Goldenberg R. Insulin plus incretin agent combination therapy in type 2 diabetes: a systematic review. Curr Med Res Opin 2014;30:431-45.**n.older review***
79. *Goldenberg RM. Management of unmet needs in type 2 diabetes mellitus: the role of incretin agents. Can J Diabetes 2011;35:518-27.**n. old review***
80. *Goldman-Levine JD. Combination therapy when metformin is not an option for type 2 diabetes. Ann Pharmacother 2015;49:688-99.**n. not SR***
81. *Gorter KJ, van de Laar FA, Janssen PG, et al. Diabetes: glycaemic control in type 2 (drug treatments). BMJ Clin Evid 2012;2012.**n. screened but not used, newer SRs available***
82. *Gray LJ, Dales J, Brady EM, et al. Safety and effectiveness of non-insulin glucose-lowering agents in the treatment of people with type 2 diabetes who observe Ramadan: a systematic review and meta-analysis. Diabetes Obes Metab 2015;17:639-48.**n. ramadan. not a research question***
83. *Gross JL, Kramer CK, Leitao CB, et al. Effect of antihyperglycemic agents added to metformin and a sulfonylurea on glycemic control and weight gain in type 2 diabetes: a network meta-analysis. Ann Intern Med 2011;154:672-9.**n. indirect comparison. network MA***
84. *Guo X, Yang Q, Dong J, et al. Tumour Risk with Once-Weekly Glucagon-Like Peptide-1 Receptor Agonists in Type 2 Diabetes Mellitus Patients: A Systematic Review. Clin Drug Investig 2016.**n. searched in only 1 database. article not available in 3 university libraries.***
85. *Gurung T, Shyangdan DS, O'Hare JP, et al. A novel, long-acting glucagon-like peptide receptor-agonist: dulaglutide. Diabetes Metab Syndr Obes 2015;8:363-86.**n. we found all included trials. read and compared for risk of bias assessment***
86. *Haluzik M, Trachta P, Mraz M. [Cardiovascular effects of GLP-1 receptor agonist treatment: focus on liraglutide]. Vnitr Lek 2015;61:635-40.**n. language***
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94. *Jensen TM, Saha K, Steinberg WM. Is there a link between liraglutide and pancreatitis? A post hoc review of pooled and patient-level data from completed liraglutide type 2 diabetes clinical trials. Diabetes Care 2015;38:1058-66.**n. post hoc review***
95. *Jeong KH, Yoo BK. The efficacy and safety of liraglutide. Int J Clin Pharm 2011;33:740-9.**n. old SR. we already found all included studies***
96. *Jeong KH, Yoo BK. The efficacy and safety of liraglutide (Provisional abstract). International Journal of Clinical Pharmacy 2011;33:740-9.**n. old review. new RCTs and SRs have been published since then***

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105. *Kayaniyil S, Lozano-Ortega G, Bennett H, et al. Exenatide Once Weekly Plus Metformin for the Treatment of Type 2 Diabetes Mellitus: A Network Meta-Analysis of Randomised Controlled Trials. Value Health 2015;18:A597-8.**n. indirect comparison. network MA***
106. *Kayaniyil S, Lozano-Ortega G, Bennett HA, et al. A Network Meta-analysis Comparing Exenatide Once Weekly with Other GLP-1 Receptor Agonists for the Treatment of Type 2 Diabetes Mellitus. Diabetes Ther 2016.**n. indirect comparison. network MA***
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116. *Liutkus J, Rosas Guzman J, Norwood P, et al. A placebo-controlled trial of exenatide twice-daily added to thiazolidinediones alone or in combination with metformin. Diabetes Obes Metab 2010;12:1058-65.**n. all participants took TZD (rosiglitazone or pioglitazone). unknown how many patients took rosiglitazone (no longer available in Belgium)***

117. *Lorenzi M, Ploug UJ, Vega G, et al. Liraglutide vs Other Daily GLP-1 Analogues in People with Type 2 Diabetes: A Network Meta-Analysis. Value Health 2015;18:A598-9.**n. indirect comparison: network MA***

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132. *Milicevic Z, Anglin G, Harper K, et al. Low Incidence of Anti-Drug Antibodies in Type 2 Diabetes Patients Treated with Once Weekly GLP-1 Receptor Agonist Dulaglutide. Diabetes Obes Metab 2016.**n. pooling but no systematic search.***

133. *Miyagawa J, Odawara M, Takamura T, et al. Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide is non-inferior to once-daily liraglutide and superior to placebo in Japanese patients with type 2 diabetes: a 26-week randomized phase III study. Diabetes Obes Metab 2015;17:974-83.**n. 100% japanese patients***
134. *Monami M, Cremasco F, Lamanna C, et al. Glucagon-like peptide-1 receptor agonists and cardiovascular events: a meta-analysis of randomized clinical trials. Exp Diabetes Res 2011;2011:215764.**n. old SR. we have more recent SRs for this outcome.***
135. *Monami M, Cremasco F, Lamanna C, et al. Glucagon-like peptide-1 receptor agonists and cardiovascular events: a meta-analysis of randomized clinical trials (Structured abstract). Experimental Diabetes Research 2011;2011:215764.**n. old review. newer RCTs and MAs have been published since then.***
136. *Monami M, Dicembrini I, Marchionni N, et al. Effects of glucagon-like peptide-1 receptor agonists on body weight: a meta-analysis. Exp Diabetes Res 2012;2012:672658.**n. pooling of different comparators; pooling of studies with different background OAD. no added value for intermediate endpoints***
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138. *Montanya E, Fonseca V, Colagiuri S, et al. HbA improvement evaluated by baseline BMI: a meta-analysis of the liraglutide phase 3 clinical trial programme. Diabetes Obes Metab 2015.**n. MA not based on systematic search. post hoc evaluation.***
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140. *Murphy CE. Review of the safety and efficacy of exenatide once weekly for the treatment of type 2 diabetes mellitus. Ann Pharmacother 2012;46:812-21.**n. old SR. we have more recent sources to find RCTs***
141. *Narushima D, Kawasaki Y, Takamatsu S, et al. Adverse events associated with incretin-based drugs in Japanese spontaneous reports: a mixed effects logistic regression model. PeerJ 2016;4:e1753.**n. not a cohort study***
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144. *Neumiller JJ. Clinical pharmacology of incretin therapies for type 2 diabetes mellitus: implications for treatment. Clin Ther 2011;33:528-76.**n. not SR***
145. *Nikfar S, Abdollahi M, Salari P. The efficacy and tolerability of exenatide in comparison to placebo; a systematic review and meta-analysis of randomized clinical trials. J Pharm Pharm Sci 2012;15:1-30.**n. pooling of studies with different background OAD. no added value for intermediate endpoints. old(er) MA***
146. *Niswender K, Pi-Sunyer X, Buse J, et al. Weight change with liraglutide and comparator therapies: an analysis of seven phase 3 trials from the liraglutide diabetes development programme. Diabetes Obes Metab 2013;15:42-54.**n. MA not based on systematic search. pooling of studies with different background OAD. no added value for intermediate endpoints***
147. *Norwood P, Liutkus JF, Haber H, et al. Safety of exenatide once weekly in patients with type 2 diabetes mellitus treated with a thiazolidinedione alone or in combination with metformin for 2 years. Clin Ther 2012;34:2082-90.**n. single arm study. no comparator***
148. *Odawara M, Miyagawa J, Iwamoto N, et al. Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide significantly decreases glycated haemoglobin compared with once-daily liraglutide in Japanese patients with type 2 diabetes: 52 weeks of treatment in a randomized phase III study. Diabetes Obes Metab 2016;18:249-57.**n. 100% japanese population***
149. *Onishi Y, Koshiyama H, Imaoka T, et al. Safety of exenatide once weekly for 52 weeks in Japanese patients with type 2 diabetes mellitus. J Diabetes Investig 2013;4:182-9.**n. noncomparative extension study***
150. *Onishi Y, Niemoeller E, Ikeda Y, et al. Efficacy and safety of lixisenatide in Japanese patients with type 2 diabetes mellitus inadequately controlled by sulfonylurea with or without metformin: Subanalysis of GetGoal-S. J Diabetes Investig 2015;6:201-9.**n. subanalysis of japanese patients in GetGoal S.***

151. *Ovalle F. Cardiovascular implications of antihyperglycemic therapies for type 2 diabetes. Clin Ther 2011;33:393-407.**n. not SR***
152. *Patorno E, Everett BM, Goldfine AB, et al. Comparative Cardiovascular Safety of Glucagon-Like Peptide-1 Receptor Agonists versus Other Antidiabetic Drugs in Routine Care: a Cohort Study. Diabetes Obes Metab 2016.**n. no observational studies for this outcome***
153. *Paul S, Best J, Klein K, et al. Effects of HbA1c and weight reduction on blood pressure in patients with type 2 diabetes mellitus treated with exenatide*. Diabetes Obes Metab 2012;14:826-34.**n. exploratory analyses, no systematic search.***
154. *Pendergrass M, Fenton C, Haffner SM, et al. Exenatide and sitagliptin are not associated with increased risk of acute renal failure: a retrospective claims analysis. Diabetes Obes Metab 2012;14:596-600.**n. dates from before search date of AHRQ and was not included***
155. *Peters KR. Liraglutide for the treatment of type 2 diabetes: a clinical update. Am J Ther 2013;20:178-88.**n. old review***
156. *Pinelli NR, Hurren KM. Efficacy and safety of long-acting glucagon-like peptide-1 receptor agonists compared with exenatide twice daily and sitagliptin in type 2 diabetes mellitus: a systematic review and meta-analysis. Ann Pharmacother 2011;45:850-60.**n. old review. newer trial have been published since then.***
157. *Pinelli NR, Hurren KM. Efficacy and safety of long-acting glucagon-like peptide-1 receptor agonists compared with exenatide twice daily and sitagliptin in type 2 diabetes mellitus: a systematic review and meta-analysis (Structured abstract). Annals of Pharmacotherapy 2011;45:850-60.**n. old review. newer RCTs and SRs have been published since then.***
158. *Potts JE, Gray LJ, Brady EM, et al. The Effect of Glucagon-Like Peptide 1 Receptor Agonists on Weight Loss in Type 2 Diabetes: A Systematic Review and Mixed Treatment Comparison Meta-Analysis. PLoS One 2015;10:e0126769.**n. indirect comparison. network MA***
159. *Pratley RE, Nauck MA, Bailey T, et al. Efficacy and safety of switching from the DPP-4 inhibitor sitagliptin to the human GLP-1 analog liraglutide after 52 weeks in metformin-treated patients with type 2 diabetes: a randomized, open-label trial. Diabetes Care 2012;35:1986-93.**n. noncomparative extension study***
160. *Probstfield JL, Hirsch I, O'Brien K, et al. Design of FLAT-SUGAR: Randomized Trial of Prandial Insulin Versus Prandial GLP-1 Receptor Agonist Together With Basal Insulin and Metformin for High-Risk Type 2 Diabetes. Diabetes Care 2015;38:1558-66.**n. no results yet.***
161. *Raccah D, Gourdy P, Sagnard L, et al. Lixisenatide as add-on to oral anti-diabetic therapy: an effective treatment for glycaemic control with body weight benefits in type 2 diabetes. Diabetes Metab Res Rev 2014;30:742-8.**n. MA not based on systematic search. pooling of studies with different background OAD. no added value for intermediate endpoints***
162. *Raccah D, Lin J, Wang E, et al. Once-daily prandial lixisenatide versus once-daily rapid-acting insulin in patients with type 2 diabetes mellitus insufficiently controlled with basal insulin: analysis of data from five randomized, controlled trials. J Diabetes Complications 2014;28:40-4.**n. MA not based on systematic search. pooling of studies with different background OAD. no added value for intermediate endpoints***
163. *Raccah D, Miossec P, Esposito V, et al. Efficacy and safety of lixisenatide in elderly (>/=65 years old) and very elderly (>/=75 years old) patients with type 2 diabetes: an analysis from the GetGoal phase III programme. Diabetes Metab Res Rev 2015;31:204-11.**n. MA not based on systematic search. pooling of studies with different background OAD. this is a post hoc analysis.***
164. *Ratner R, Han J, Nicewarner D, et al. Cardiovascular safety of exenatide BID: an integrated analysis from controlled clinical trials in participants with type 2 diabetes. Cardiovasc Diabetol 2011;10:22.**n. no systematic search, retrospective adjudication***
165. *Ridge T, Moretto T, MacConell L, et al. Comparison of safety and tolerability with continuous (exenatide once weekly) or intermittent (exenatide twice daily) GLP-1 receptor agonism in patients with type 2 diabetes. Diabetes Obes Metab 2012;14:1097-103.**n. no systematic search***
166. *Rigato M, Fadini GP. Comparative effectiveness of liraglutide in the treatment of type 2 diabetes. Diabetes Metab Syndr Obes 2014;7:107-20.**n. not SR***
167. *Rizos EC, Ntzani EE, Papanas N, et al. Combination therapies of DPP4 inhibitors and GLP1 analogues with insulin in type 2 diabetic patients: a systematic review. Curr Vasc Pharmacol 2013;11:992-1000.**n. searched only 1 database. we have other sources to find RCTs***

168. *Rizos EC, Ntzani EE, Papanas N, et al. Combination therapies of DPP4 inhibitors and GLP1 analogues with insulin in type 2 diabetic patients: a systematic review (Provisional abstract). Current Vascular Pharmacology 2013;11:992-1000.**n. older review. newer RCTs have been published since then.***
169. *Robinson LE, Holt TA, Rees K, et al. Effects of exenatide and liraglutide on heart rate, blood pressure and body weight: systematic review and meta-analysis. BMJ Open 2013;3.**n. pooling of different comparators; pooling of studies with different background OAD. no added value for intermediate endpoints***
170. *Rosenstock J, Rodbard HW, Bain SC, et al. One-year sustained glycemic control and weight reduction in type 2 diabetes after addition of liraglutide to metformin followed by insulin detemir according to HbA1c target. J Diabetes Complications 2013;27:492-500.**n. compares insulin vs no insulin.***
171. *Ross SA, Ballantine J. Early use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in type 2 diabetes. Curr Med Res Opin 2013;29:1617-26.**n.old search.***
172. *Rotz ME, Ganetsky VS, Sen S, et al. Implications of incretin-based therapies on cardiovascular disease. Int J Clin Pract 2015;69:531-49.**n. we have a more recent SR for these outcomes (AHRQ)***
173. *Roussel R, Lorraine J, Rodriguez A, et al. Overview of Data Concerning the Safe Use of Antihyperglycemic Medications in Type 2 Diabetes Mellitus and Chronic Kidney Disease. Adv Ther 2015;32:1029-64.**n. no information on RCTs***
174. *Russell S. Incretin-based therapies for type 2 diabetes mellitus: a review of direct comparisons of efficacy, safety and patient satisfaction. Int J Clin Pharm 2013;35:159-72.**n. old review. newer trial have been published since then. we have all included trials***
175. *Ryan GJ, Foster KT, Jobe LJ. Review of the therapeutic uses of liraglutide. Clin Ther 2011;33:793-811.**n. old review. newer trial have been published since then. screened for additional references***
176. *Ryder RE. The potential risks of pancreatitis and pancreatic cancer with GLP-1-based therapies are far outweighed by the proven and potential (cardiovascular) benefits. Diabet Med 2013;30:1148-55.**n. no mention of SR. inadequate distinction between dpp4 and glp1-ra***
177. *Saulsberry WJ, Coleman CI, Mearns ES, et al. Comparative efficacy and safety of antidiabetic drug regimens added to stable and inadequate metformin and thiazolidinedione therapy in type 2 diabetes. Int J Clin Pract 2015;69:1221-35.**n. indirect comparison: network MA. we have all included rcts***
178. *Savvidou S, Karatzidou K, Tsakiri K, et al. Circulating adiponectin levels in type 2 diabetes mellitus patients with or without non-alcoholic fatty liver disease: Results of a small, open-label, randomized controlled intervention trial in a subgroup receiving short-term exenatide. Diabetes Res Clin Pract 2016.**n. primary aim of study = adiponectin levels***
179. *Schauerhamer MB, Gurgle H, McAdam-Marx C. Once-weekly exenatide as a treatment for Type 2 diabetes. Expert Rev Cardiovasc Ther 2015;13:611-26.**n. not SR***
180. *Scheen AJ. [Albiglutide (Eperzan): a new once-weekly agonist of glucagon-like peptide-1 receptors]. Rev Med Liege 2015;70:207-14.**n. not SR***
181. *Schernthaner G, Rosas-Guzman J, Dotta F, et al. Treatment escalation options for patients with type 2 diabetes after failure of exenatide twice daily or glimepiride added to metformin: results from the prospective European Exenatide (EUREXA) study. Diabetes Obes Metab 2015;17:689-98.**n. no comparator to exenatide***
182. *Schernthaner G, Schernthaner-Reiter MH, Schernthaner GH. EMPA-REG and Other Cardiovascular Outcome Trials of Glucose-lowering Agents: Implications for Future Treatment Strategies in Type 2 Diabetes Mellitus. Clin Ther 2016;38:1288-98.**n. not SR. insufficient information on GLP1 ra***
183. *Schmidt LJ, Habacher W, Augustin T, et al. A systematic review and meta-analysis of the efficacy of lixisenatide in the treatment of patients with type 2 diabetes. Diabetes Obes Metab 2014;16:769-79.**n. pooling of studies with different background OAD. no added value for intermediate endpoints. used as additional reference source for lixisenatide. PANCREATITIS UITZONDERING?***
184. *Schwartz S. Evidence-based practice use of incretin-based therapy in the natural history of diabetes. Postgrad Med 2014;126:66-84.**n. not SR***
185. *Schwartz SS, Jellinger PS, Herman ME. Obviating much of the need for insulin therapy in type 2 diabetes mellitus: A re-assessment of insulin therapy's safety profile. Postgrad Med 2016:1-11.**n. not SR. focus = insulin***
186. *Scott DA, Boye KS, Timlin L, et al. A network meta-analysis to compare glycaemic control in patients with type 2 diabetes treated with exenatide once weekly or liraglutide once daily in comparison with insulin glargine, exenatide twice daily or placebo. Diabetes Obes Metab 2013;15:213-23.**n. indirect comparison. network MA***

187. *Scott DA, Boye KS, Timlin L, et al. A network meta-analysis to compare glycaemic control in patients with type 2 diabetes treated with exenatide once weekly or liraglutide once daily in comparison with insulin glargine, exenatide twice daily or placebo (Structured abstract). Diabetes Obesity and Metabolism 2013;15:213-23.**n. indirect comparison. network MA***
188. *Seino Y. Understanding the incretin effect. J Clin Endocrinol Metab 2011;96:934-5.**n. old review.***
189. *Seino Y, Ikeda Y, Niemoeller E, et al. Efficacy and Safety of Lixisenatide in Japanese Patients with Type 2 Diabetes Insufficiently Controlled with Basal Insulin+/-Sulfonylurea: A Subanalysis of the GetGoal-L-Asia Study. Horm Metab Res 2015;47:895-900.**n. subanalysis for japanese patients in 100% asian population study.***
190. *Seino Y, Min KW, Niemoeller E, et al. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). Diabetes Obes Metab 2012;14:910-7.**n. 100% asian patients***
191. *Seino Y, Rasmussen MF, Clauson P, et al. The once-daily human glucagon-like peptide-1 analog, liraglutide, improves beta-cell function in Japanese patients with type 2 diabetes. J Diabetes Investig 2012;3:388-95.**n. 100% japanese population. endpoints.***
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14 Appendix 3 – AGREE scores

14.1 Detailed scoring

CDA 2013	Item	Rating	Comment
Systematic methods were used to search for evidence	7	5	search terms used were not described; no full strategy
The criteria for selecting the evidence are clearly described	8	3	in- and exclusion criteria not described; in methodology the selection of relevant outcomes is described in general terms, without specifics
The strengths and limitations of the body of evidence are clearly described	9	5	GRADE methodology was used; but no evidence tables provided, no clear descriptions of limitations
The methods for formulating the recommendations are clearly described	10	4	No formal method used; each recommendation had to be approved by the Steering and Executive Committee, with 100% consensus
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	6	Yes, described in methodology from onset; description in tekst
There is an explicit link between the recommendations and the supporting evidence.	12	7	Yes, references cited/GRADE applied/ lack of evidence or consensus described
The guideline has been externally reviewed by experts prior to its publication	13	6	Yes, by stakeholders, experts and methodological panel; no description of changes made by external review
A procedure for updating the guideline is provided	14	7	Yes, process will be published in 2018; update will commence within 5 years, sooner in the event of significant changes in evidence supporting the recommendations
NICE 2015	**Item**	**Rating**	**Comment**
Systematic methods were used to search for evidence	7	7	yes, full search provided in appendix
The criteria for selecting the evidence are clearly described	8	7	yes, in/exclusion criteria described, full list of excluded studies provided in appendix
The strengths and limitations of the body of evidence are clearly described	9	7	yes, evidence tables provided, GRADE methodology used to assess; discussion in full guideline
The methods for formulating the recommendations are clearly described	10	4	Not clear in this guideline; general guidelines manual describes informal decision process
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	6	yes, studies were selected for these outcomes; discussion spread throughout guideline
There is an explicit link between the recommendations and the supporting evidence.	12	7	yes, discussion of body of evidence before each recommendation
The guideline has been externally reviewed by experts prior to its publication	13	5	there is a consultation process for stakeholder comments, described in manual but not in guideline
A procedure for updating the guideline is provided	14	5	manual: usually need for update is reviewed every three years; no description in guideline
Domus 2015	**Item**	**Rating**	**Comment**
Systematic methods were used to search for evidence	7	4	not described in guideline, available upon request; ADAPTE procedure, guidelines were searched via GIN en guideline.gov
The criteria for selecting the evidence are clearly described	8	4	criteria for selecting guidelines described (standard procedure, without details), target population described; no description of selection criteria for studies
The strengths and limitations of the body of evidence are clearly described	9	5	GRADE was used to evaluate body of evidence (no evidence tables of individual studies)
The methods for formulating the recommendations are clearly described	10	5	informal consensus techniques
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	7	harms/side effects/ risks are described in discussion after each recommendation
There is an explicit link between the recommendations and the supporting evidence.	12	7	GRADE/references provided, it is described when evidence is lacking

The guideline has been externally reviewed by experts prior to its publication	13	6	yes, well described. No methodological expert
A procedure for updating the guideline is provided	14	7	yes literature will be reviewed in 2 years, update in 5
ADA 2016	**Item**	**Rating**	**Comment**
Systematic methods were used to search for evidence	7	4	"PPC members systematically searched MEDLINE" studies since 1 january 2015
The criteria for selecting the evidence are clearly described	8	4	"human studies related to each section"
The strengths and limitations of the body of evidence are clearly described	9	5	recommendations are graded; no evaluation of individual studies
The methods for formulating the recommendations are clearly described	10	3	informal methods/ not well described
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	7	has been described after each recommendation
There is an explicit link between the recommendations and the supporting evidence.	12	7	grading system/references provided
The guideline has been externally reviewed by experts prior to its publication	13	5	Reviewed by ADA board of directors, readers were invited to comment; yet no formal external expert review
A procedure for updating the guideline is provided	14	6	"They are updated every 5 years or as needed."
EASD/ADA 2015	**Item**	**Rating**	**Comment**
Systematic methods were used to search for evidence	7	1	" there was not a published search strategy. Committee members were asked to submit papers that they believed to be germane to the topic to be reviewed by the group."
The criteria for selecting the evidence are clearly described	8	1	not described
The strengths and limitations of the body of evidence are clearly described	9	1	no LoE/GoR; no evaluation of quality of evidence
The methods for formulating the recommendations are clearly described	10	1	no formal methods, only described as "face-to-face meeting"
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	7	Benefits, risks and side effects are described
There is an explicit link between the recommendations and the supporting evidence.	12	4	References provided
The guideline has been externally reviewed by experts prior to its publication	13	2	Reviewed by experts, but methods and contributions not described
A procedure for updating the guideline is provided	14	3	"the recommendations will need to be updated in future years", but no method or timeline provided
AACE 2015	**Item**	**Rating**	**Comment**
Systematic methods were used to search for evidence	7	1	Not described
The criteria for selecting the evidence are clearly described	8	1	Not described
The strengths and limitations of the body of evidence are clearly described	9	6	LoE/GoR are provided after each recommendation
The methods for formulating the recommendations are clearly described	10	1	Not described
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	7	described in tekst
There is an explicit link between the recommendations and the supporting evidence.	12	7	references provided, best level of evidence
The guideline has been externally reviewed by experts prior to its publication	13	4	yes but no description
A procedure for updating the guideline is provided	14	5	In protocol "every 3 years"
ERBP 2015			

Systematic methods were used to search for evidence	7	7	Cochrane database of systematic reviews, DARE, CENTRAL, Medline; may 2014; full strategies in appendix
The criteria for selecting the evidence are clearly described	8	7	yes, clearly described (6,6,2 selection)
The strengths and limitations of the body of evidence are clearly described	9	7	evidence tables in appendix; quality rating AMSTAR (SR), Cochrane risk of bias (RCT), Newcastle Ottawa sce for cohort and case-control, QUADAS for diagnostic test accuracy; GRADE for body of evidence
The methods for formulating the recommendations are clearly described	10	6	plenary meetings, discussion, consensus, voting with 80% positive vote required if no consensus
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	7	yes, in evidence tables, discussion, reflected in recommendations
There is an explicit link between the recommendations and the supporting evidence.	12	7	GRADE; discussion underneath recommendations, references
The guideline has been externally reviewed by experts prior to its publication	13	5	yes, by email, meeting; no description of the information gathered
A procedure for updating the guideline is provided	14	7	yes, every 5 years or earlier, methods described
ESC/EASD 2013			
Systematic methods were used to search for evidence	7	3	protocol: must be based on "formal literature review", but method not elaborated upon
The criteria for selecting the evidence are clearly described	8	3	"only peer reviewed published literature" (protocol)
The strengths and limitations of the body of evidence are clearly described	9	6	yes, LoE/GoR of recommendations (body of evidence)
The methods for formulating the recommendations are clearly described	10	3	protocol: different processes possible; no description in guideline
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	7	benefits, side effects and risks are discussed; risk-benefit ratio specifically discussed
There is an explicit link between the recommendations and the supporting evidence.	12	7	yes, LoE/GoR and references
The guideline has been externally reviewed by experts prior to its publication	13	4	yes, reviewed by experts, names are available but no further info
A procedure for updating the guideline is provided	14	5	In protocol, every 2 to 4 years

14.2 Summary

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score
CDA 2013	5	3	5	4	6	7	6	7	**43**	**0,767857143**
NICE 2015	7	7	7	4	6	7	5	5	**48**	**0,857142857**
Domus 2016	4	4	5	5	7	7	6	7	**45**	**0,803571429**
ADA 2016	4	4	5	3	7	7	5	6	**41**	**0,732142857**
EASD/ADA 2015	1	1	1	1	7	4	2	3	**20**	**0,357142857**
AACE 2015	1	1	6	1	7	7	4	5	**32**	**0,571428571**
AACE 2016									**0**	**0**
ERBP 2015	7	7	7	6	7	7	5	7	**53**	**0,946428571**
ESC/EASD 2013	3	3	6	3	7	7	4	5	**38**	**0,678571429**
Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain.										

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