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MALADIE-INVALIDITE
SERVICE DES SOINS DE SANTE
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médicales en matière de médicaments

THE EFFICIENT DRUG MANAGEMENT OF TYPE 2 DIABETES IN PRIMARY CARE

Systematic literature review: full report

Consensus conference
November 29th 2012
Auditorium Lippens (Royal Library)
Brussels

This literature review was performed by vzw Farmaka asbl and was followed-up by a reading committee.

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List of abbreviations

ACS: acute coronary syndrome
AE: adverse events
AHRQ: Agency for Healthcare Research and Quality
ALT: Alanine aminotransferase
AP: alkaline phosphatase
ARR: absolute risk reduction
AST: Aspartate aminotransferase
Bid: twice a day
CI : confidence interval
CO: crossover RCT
DMII: diabetes mellitus type 2
DM2: diabetes mellitus type 2
DPP-4: Dipeptidyl peptidase-4
FAS: functional analysis set
FPG: fasting plasma glucose
GGT: gamma glutamyl transpeptidase
GI: Gastrointestinal
GLA: glucose lowering agents
GLP-1 Glucagon-like peptide-1
HbA1c : Hemoglobin A1c
HR: Hazard ratio
IGT: impaired glucose tolerance
ITT: intention-to-treat analysis
IU: International units
Kg: Kilograms
LOCF: last observation carried forward
MA: meta-analysis
mg/dL: Milligrams per deciliter
MI :Myocardial infarction
n: number of patients
NNH: number needed to harm
NNT: number needed to treat
NPH: Neutral protamine Hagedorn
NR: not reported
NS: not statistically significant
NT: no statistical test
OAD: oral antidiabetic drug
OHA: oral hypoglycemic agents
OR: Odds ratio
P: parallel RCT
PE: primary endpoint
PG: parallel group RCT
Pla: placebo
PP: per protocol
PPS: per protocol set
PVD: peripheral vascular disease

Py (person years)
Qd: once a day
RCT: Randomised controlled trial
RR: Relative risk
SU: sulfonylurea
TNR: statistical test not reported
TZD: thiazolidinediones
UKPDS: United Kingdom Prospective Diabetes Study

1. Methodology

1.1. Introduction and scope

This systematic literature review was conducted in preparation of the consensus conference on 'Appropriate pharmacological treatment in type 2 diabetes in primary care' which will take place on November 29th 2012.

The last consensus conference on oral antidiabetic agents dates from 2003. Since then, many new studies and evidence-based guidelines on type-2 diabetes have been published. The evidence-based guidelines in primary care are almost unanimous in their choice of metformin as first line treatment in most patients.
Rather than to (re)conduct a systematic review on metformin as first line treatment, the organisation committee has decided to consider metformin first choice initial treatment, based on the study and discussion of these recent guidelines. The questions then posed to the literature group and the jury are to clarify the best course of action when metformin cannot be used or when metformin monotherapy provides inadequate diabetes control.

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 (French/Dutch)

Epidemiology – glycemic norm

Jury question 1:
- pour évaluer l'efficacité en respectant la sécurité d'un traitement antidiabétique, quelle valeur d'HbA1c faut-il viser et en fonction de quelles caractéristiques du patient ?
- naar welke HbA1c-waarde moet men zich richten en dit in functie van welke patiëntenkenmerken, om de doeltreffendheid te evalueren waarbij rekening wordt gehouden met de veiligheid van een antidiabetische behandeling?

Treatment of type 2 diabetes

MONOTHERAPY

Jury question 2:
- Quelles sont les **contre-indications** absolues et relatives de la metformine et quelles sont les alternatives ?
- Wat zijn absolute en relatieve **contra-indicaties** voor metformine en wat zijn dan de alternatieven

Jury question 3:
- Comment utiliser la metformine de manière optimale et quelles sont les alternatives en cas d'**intolérance** ?
- Wat is de optimale manier om metformine te gebruiken en wat zijn de alternatieven bij **intolerantie**?

WHAT IF METFORMIN ALONE IS NOT SUFFICIENT?

Jury Question 4:
- Quels sont les antidiabétiques à associer à la metformine quand la cible thérapeutique n'est pas atteinte ?
- Welke antidiabetica kunnen aan metformine worden geassocieerd wanneer de doelstellingen niet bereikt worden?

Jury Question 5:
- Quelles sont les indications d'associer une (des) insuline(s) et laquelle (lesquelles) initialement ?
- Wat zijn de indicaties voor het toevoegen van insulines en met welke insuline moet er worden gestart?

Treatment of pre diabetes

Jury question 6:
- Prédiabète: quels sont les critères de définition et quelles sont les conséquences à long échéance en termes de survenue de diabète ET de morbidité cardiovasculaire ?
- Wanneer kan men spreken over prediabetes en wat zijn de gevolgen op lange termijn met name op gebied van progressie naar diabetes en op gebied van cardiovasculaire morbiditeit?

Jury Question 7:
- En cas de prédiabète, quels antidiabétiques utiliser pour freiner un passage au diabète ET améliorer le pronostic cardiovasculaire ?
- Welke antidiabetica kunnen gebruikt worden bij prediabetes om de progressie naar overte diabetes af te remmen en de cardiovasculaire prognose van prediabetes te verbeteren?

Mechanisms pro and contra

Jury question 8:
- Traitement du diabète de type 2 : facteurs d'amélioration et obstacles dans la pratique quotidienne?
- Behandeling van type 2 diabetes: verbeteringsfactoren en obstakels in de dagelijkse praktijk?

1.1.2. Research task of the literature group

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

Populations

The following populations are to be evaluated

- Adults with type 2 diabetes
- Adults with pre-diabetes

Endpoints

The following endpoints are to be reported

- Type 2 diabetes
    - Mortality and cardiovascular events
    - Surrogate endpoints
        - HbA1c
        - Weight loss/influence on weight
    - Safety

- Cancer incidence
- Other important safety endpoints

- Pre-diabetes
    - Same endpoints as in type 2 diabetes, plus
    - Progression to type 2 diabetes

Interventions: pharmacological treatment

Only products with a registered indication in Belgium, or products that will shortly appear on the Belgian marked are to be studied.

The following drugs are to be discussed in the literature review

- Biguanides: metformin
- Sulphonylureas: glibenclamide, gliclazide, glimepiride, glipizide, gliquidone
- Meglitinides: repaglinide
- Thiazolidinediones: pioglitazone
- DPP-4 inhibitors: saxagliptin, sitagliptin, vildagliptin, linagliptin
- Incretin mimetics (GLP-1 analogues): exenatide, liraglutide
- Insulin: only intermediate acting NPH and long-acting insulin analogues: insulin glargine, insulin detemir

The next drugs will not be included in the literature review

- Alpha-glucosidase inhibitors: acarbose
- Other insulin preparations

Lifestyle interventions are not to be studied as a separate intervention, only in comparison to pharmacological interventions.

Comparisons to be studied: Type 2 diabetes

- **HbA1c targets**

Studies that compare different targets of HbA1c or different intensities of treatment that have hard endpoints as the primary endpoint.

- **Monotherapy: alternatives to metformin**

The following comparisons are to be included in the literature review (marked grey):

	Met	SU	Meglit	TZD	DPP-4	Glp-1	Ins
Placebo	(1)	(2)					

(1) Only studies with hard endpoints

(2) Only SU that can be used in severe renal insufficiency

- **Combination therapy: What to do when monotherapy fails?**

The following comparisons are to be included in the literature review (marked grey)[1]

	Met+SU	Met+Meglit	Met+TZD	Met+DPP-4	Met+Glp-1	Met+Ins	SU+DPP-4	Met+SU+Glp-1	Met+SU+Ins
Met									
Met+SU									
Met+Meglit									
Met+TZD									
Met+DPP-4									
Met+Glp-1									
Met+Ins						(1)			
SU							(2)		
Met+SU+Glp-1									
Met+SU+Ins									(1)

(1) Only Ins NPH vs long-acting insulin analogues (glargin or detemir)

(2) Only linagliptin

We will focus on studies in which patients were previously on monotherapy (metformin). Studies in which treatment-naive patients receive initial combination therapy will not be included[1].

Comparisons to be studied: Pre-diabetes

The following comparisons are to be included in the literature review (marked grey):

	Met	SU	Meglit	TZD	DPP-4	Glp-1	Ins
Placebo							(1)
Lifestyle intervention							

(1) At the request of the organising committee, the recent ORIGIN trial was also included

Study criteria

- Efficacy
    - Design
        - RCT
        - Minimum single blind for oral therapy
        - Open label permitted for injectable agents and lifestyle measures
    - Duration of RCT: at least 24 weeks of intervention[1]
    - Minimum number of participants: minimum 200 for both arms of study together[1]. For studies with multiple treatment arms, we looked at the number of participants in comparisons relevant to our search.

- Safety

[1] Exceptions to these inclusion criteria could be made for

- A study that is included in a meta-analysis that provides an answer to one of our research questions, and that includes mostly studies that meet our inclusion criteria.
- Studies that report hard endpoints as primary endpoint

- Information from the selected RCTs
- Handbook Meyler's Side Effects of Drugs, Fifteenth Edition (for most products we searched the BCFI's website, which is based on Meyler's, amongst other sources)
- Additional information from large observational studies

Guidelines

Only guidelines that report levels of evidence/recommendation are to be selected.
Only guidelines from 2008 onwards are to be selected.
Guidelines were selected and agreed upon through discussion with the organising committee, based on relevance for the Belgian situation.
Similarities and discrepancies between guidelines are to be reported.
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.

1.2. Search strategy

1.2.1. Principles of systematic search

Relevant literature was searched in a stepwise approach.

- Firstly, sources that report and discuss data from systematic reviews, meta-analyses and original trials, like Clinical Evidence were consulted. Guidelines were consulted to look up additional relevant references.
- In a second step we have searched for large systematic reviews from reliable EMB-producers (NICE, AHRQ,…) that answer our research questions. One or more systematic reviews were selected as our basic source. From these sources, references of relevant publications were screened manually.
- In a third step, we conducted a systematic search for (double)blind 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

Guidelines were searched through the link "evidence-based guidelines" on the website of vzw Farmaka asbl (www.farmaka.be). This section contains links to the national and frequently consulted international guidelines, as well as links to 'guideline search engines' such as National Guideline Clearinghouse. All of these were searched.

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),…

1.2.2. Search strategy details

Type 2 diabetes

The following systematic reviews or meta-analyses were selected: see below. We then searched Medline (Pubmed) for RCTs that were published after the search date of these publications.

- Bennett WL. Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update. Comparative Effectiveness Review No. 27. (Prepared by Johns Hopkins University Evidence-based Practice Center under Contract No. 290-02-0018.)
  AHRQ Publication No. 11-EHC038-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2011. Available on: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

For comparisons that weren't included in the above review, we selected relevant references from the following guideline, that was developed on the basis of a systematic review of good quality:

- Scottish Intercollegiate Guidelines Network. Management of diabetes. National clinical guideline 116. March 2010. http://www.sign.ac.uk/pdf/sign116.pdf

A search strategy was developed in Pubmed to find relevant RCTs that appeared after the search date of the above publications (http://www.ncbi.nlm.nih.gov/pubmed/).
In some cases, when the selected systematic reviews were not sufficient (e.g. no search for all drugs), an additional search was conducted for RCTs that appeared before the search date of the selected systematic review.

The following search strategy was used:

("Diabetes Mellitus, Type 2"[Mesh] OR NIDDM OR (diabetes AND ("type II" OR "type 2")))
AND
(Metformin* OR Glibenclamide OR glyburide OR Gliclazide OR Glimepiride OR Glipizide OR Gliquidone OR sulfonylurea OR sulphonylurea OR meglitinide OR repaglinide OR "NPH insulin" OR glargine OR detemir OR (insulin AND (long acting OR intermediate acting OR isophane)) OR Pioglitazone OR Sitagliptin* OR Saxagliptin* OR Vildagliptin* OR linagliptin* OR dpp-4 OR dpp4 OR dpp-iv OR "glucagon-like peptide 1" OR Exenatide OR Liraglutide[Title/Abstract])
AND
(randomised controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
Filters: Publication date from 2009/11/01

Searched up to 2012/07/12

Pre-diabetes

The following systematic reviews were selected. We then searched Pubmed for RCTs that were published after the search date of these publications.

- SCHARR Public Health Collaborating Centre. Preventing the progression of pre-diabetes to type 2 diabetes in adults. Systematic review and meta-analysis of lifestyle, pharmacological and surgical interventions. 2012. Commissioned by NICE Centre for Public Health Excellence.
  http://www.nice.org.uk/nicemedia/live/12163/57043/57043.pdf

To find relevant RCTs that appeared after the search date of above publications, a search strategy was developed in Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/).

The following search strategy was used:

((prediabetes OR pre-diabetes OR impaired glucose tolerance OR impaired fasting glucose[Title/Abstract])
OR
(("Diabetes Mellitus, Type 2"[Mesh] OR NIDDM OR (diabetes AND ("type II" OR "type 2"))) AND Prevention))
AND
(pioglitazone OR metformin OR exenatide OR liraglutide[Title/Abstract])
AND
(randomised controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
Filters: Publication date from 2011/07/01

Searched up to 2012/07/12

1.3. Selection procedure

Inclusion criteria used to select relevant *meta-analyses and systematic reviews*:

- Research question in selected publication matched research question for this literature review
- Systematic search
- Systematic reporting of results
- Inclusion of randomised controlled trials
- Reporting of clinically relevant outcomes

Inclusion criteria for *randomised controlled trials (RCTs)* are mentioned in chapter 1.1. with relevant interventions, endpoints and study criteria.

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.

Some publications were excluded for practical reasons:

- Publications unavailable in Belgian libraries
- Publications in languages other than Western European

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 has no influence on the quality of the evidence. The GRADE system[3,4,5] 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 assciation (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

***Consistency** refers to the similarity of estimates of effect across studies. if there is an important unexplained inconsistency in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the size of the differences in effect, and the significance of the differences guide the (inevitably somewhat arbitrary) decision about whether important inconsistency exists.

****Directness:** there are two types of indirectness of evidence. The first occurs when considering, for example, use of one of two active drugs. Although randomised comparisons of the drugs may be unavailable, randomised trials may have compared one drug with placebo and the other with placebo. Such trials allow indirect comparisons of the magnitude of effect of both drugs. Such evidence is of lower quality than that provided by head to head comparisons of the drugs.
The second type of indirectness of evidence includes differences between the population, intervention, comparator to the intervention, and outcome of interest, and those included in the relevant studies.

*****Imprecision**: When studies include relatively few patients and few events and thus have wide confidence intervals, a guideline panel will judge the quality of the evidence to be lower.

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

In this literature review the criterium 'publication bias' and the criteria specifically intended for observational studies (see table above) have not been assessed. This adapted version of GRADE therefore evaluates the following criteria:

Study design	+ 4	RCT
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
SUM	4	HIGH quality of evidence
	3	MODERATE quality of evidence
	2	LOW quality of evidence
	1	VERY LOW quality of evidence

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

Study design

In this literature review, all studies are RCTs (inclusion criterium). "Study design" is therefore not reported specifically in this report.

Study quality

To assess the methodological quality of RCTs, the Jadad score was used, in combination with the assessment of an "intention-to-treat"(ITT) analysis (all randomised patients in efficacy analysis). 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.

Jadad score:

1a	Was the study described as randomised (this includes the use of words such as randomly, random and randomisation)?	Yes	1
		No	0
1b	If the method of generating the randomisation sequence was described, was it adequate (table of random numbers, computer-generated, coin tossing, etc.) or inadequate (alternating, date of birth, hospital number, etc.)?	Not described / NA	0
		Adequate	1
		Inadequate	-1
2	Was the study described as double-blind?	Yes	1
		No	0
2a	If the method of blinding was described, was it adequate (identical placebo, active placebo, etc.) or inadequate (comparison of tablet vs injection without double dummy)?	Not described / NA	0
		Adequate	1
		Inadequate	-1

3	Was there a description of withdrawals and drop-outs?	Yes	1
		No	0

(Table reprinted from Duke University, Center for Clinical Health Policy Research. Drug Treatments for the Prevention of Migraine. AHCPR February 1999.)

Application in GRADE:
The following principle was applied as a minimal rule: 1 quality point was deducted if there was a problem with item 3 of the Jadad score ("was there a description of withdrawals and drop-outs"). Since randomisation was an inclusion criterium, no point was deducted here, even if the method (item 1a and 1b of Jadad) was inadequately described. Apart from Jadad, we also assessed whether an ITT analysis was performed. If this was not the case, a point was deducted. Points were only deducted for absence of ITT if follow-up was less than 80%. If follow-up percentage was not known, no extra point was deducted for ITT.
Other factors that can influence the assessment: moderate drop-out in studies with low event rates, problems with construction of study, selective outcome reporting,…

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 study endpoints are not relevant, points can be deducted here. When indirect comparisons are made, a point is also deducted.

Imprecision

If we consider systematic reviews or meta-analyses that include studies with <40 patients per study-arm (for a cross-over study: <40 patients in the complete study), a point is deducted for imprecision.

For meta-analyses and in comparisons with only one study: a point is deducted when power is inadequate (depends also on the sample size).

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 results. If 1 smaller study of poor quality confirms the results of 2 large studies of good quality, no points are deducted.

1.5. Synopsis of study results

The complete report contains per research question

- 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

- 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 different discussions with 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
2. Minerva is a journal for evidence-based medicine published in Belgium. Website: www.minerva-ebm.be
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 literature group

Populations

Inclusion criteria in studies were often narrow, excluding 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.

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).

Outcomes

The vast majority of studies was designed for intermediary or surrogate endpoints. Most studies report changes in HbA1c, other glycemic endpoints, and often weight change. These markers do not necessarily reflect a change in clinically meaningful, hard outcome measures.

Information on hard endpoints is very rare: only 7 of all included trials report hard endpoints as primary outcome. Five of these trials were designed to examine the 'optimal' HbA1c target.

The aim of using glucose lowering drugs, apart from avoiding symptoms of hyperglycemia, is ultimately to lower the risk of cardiovascular disease, stroke, microvascular disease and premature death. Information on these endpoints however, is very sparse.

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

Studies reporting only quality of life outcomes were not included in this review. Nevertheless quality of life can be a deciding factor in selecting a specific treatment. Quality of life e.g. could be lower with insulin, or a lower HbA1c value does not necessarily mean a better quality of life.

Trial duration

Trial duration is often short. Type 2 diabetes is a chronic condition usually resulting in the lifelong use of antidiabetic (and other) drugs. Some adverse events may take years to develop. Information on hard endpoints or long-term safety can only be established through longer follow-up.

Setting

Very few studies adequately reported setting. For most of the evidence, it is unclear whether the study took place in a first-line or second-line setting.

Methodological problems

- Practically all studies were industry sponsored.
- The quality of study design was often compromised because of unclear or no reporting of randomisation procedure or blinding procedure. Studies with insulin or GPL-1 analogues were open label, as were studies that included lifestyle-interventions in one arm. This is understandable due to the nature of the intervention but decreases the methodological quality of the studies.

- Often studies use a run-in period (placebo or titration/stabilisation of active drug), to avoid enrolling patients with adverse effects or poor adherence. This decreases applicability of the results.
- Studies were not primarily designed to evaluate safety.
- The included meta-analyses are often graded low quality and lack applicability mainly due to heterogeneity of included interventions and due to inclusion of low quality studies.

The reading committee and literature group would like to draw attention to the following issues when critically appraising evidence:

- Studies using composite endpoints pose multiple problems. Sometimes the endpoint is composed of both serious events (e.g. mortality) and less serious, clinician-driven events (e.g. the need for retinal photocoagulation). If less serious events are more common, they can affect the clinical meaningfulness of the composite outcome.
- Studies are designed around a primary endpoint. If multiple secondary endpoints (e.g. UKPDS, PROactive) are reported, caution is needed. Only when the primary outcome of the study is statistically significant, a significant result in a secondary endpoint can be considered as supportive evidence of the primary outcome.
- 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.

Target

Fixing a target for HbA1c in an intervention study is arbitrary and the target has changed throughout the years. E.g. the target for intensive treatment in the UKPDS trial is comparable to the target for standard treatment in newer trials.

Monotherapy

This literature review tried to find evidence for alternatives to metformin as a first line treatment, when intolerance or contra-indications for metformin exist.
However, patients with contra-indications for metformin (renal disease, liver disease and heart failure) were often excluded from trials. Therefore, these trials are less useful in this area.
Besides, no studies with sulphonylurea in monotherapy met our inclusion criteria.
Long term studies and comparative studies with newer antidiabetics are sparse. More studies are needed with information on hard endpoints and safety.

Combination Therapy

Dual therapy versus monotherapy:
(Older) studies with sulphonylurea often did not meet inclusion criteria.
There is insufficient evidence to determine whether the addition of a second drug to ongoing monotherapy will decrease morbidity and mortality.
Dual therapy versus dual therapy:
Again, information on hard endpoints is lacking. Information on (long-term) safety is lacking or inadequately reported.

Pre-diabetes

The body of evidence for prevention of diabetes with antidiabetic drugs is not large. The studies are generally of low quality and the external validity is low. The heterogeneity of the study populations, intensity of lifestyle interventions, acceptability of medication and outcomes used in studies diminish the general applicability.

Studies in populations with pre-diabetes were designed to measure prevention or delay of type 2 diabetes as primary endpoint. However, the question is: is the diabetes really prevented (disease-modifying) or is it just not apparent due to the use of the antihyperglycemic drugs?

The definition of diabetes is a convention. This definition has changed through the years.

If the scientific community accepts that diabetes is defined purely by 'glycemic' criteria, an endpoint that considers this strict definition in 'prevention of type 2 diabetes' is in itself correct. All the same, it is not a real clinical event. We must ask ourselves: what can we do to reduce the (elevated) cardiovascular risk in these patients?

No studies consider hard endpoints as primary outcome measures. Only the ORIGIN trial included a small subpopulation of patients with pre-diabetes, but no conclusions can be drawn from this trial in this subpopulation for hard endpoints.

3. Summary of the guidelines

3.1. Criteria for guideline selection

In order to be included, the guideline had to be of recent date (not older than 5 years) and had to report levels of evidence and/or grades of recommendation.
The following guidelines fulfilled these criteria:

3.2. Diabetes

3.2.1. Selected guidelines

American College of Physicians	Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2012;156:218-231
SIGN Scottish Intercollegiate Guidelines Network	Management of Diabetes: A national clinical guideline. March 2010 www.sign.ac.uk
NICE The National Collaborating Centre for Chronic Conditions	-Type 2 Diabetes National clinical guideline for management in primary and secondary care (update). London: Royal College of Physicians, 2008. -Type 2 Diabetes: newer agents for blood glucose control in type 2 diabetes. May 2009 -Liraglutide for the treatment of type 2 diabetes mellitus. October 2010 www.nice.org.uk
American Diabetes Association	Standards of Medical Care in Diabetes - 2012 Diabetes Care, vol 35, suppl 1, January 2012
Agencia de Evaluación de Tecnologías Sanitarias del País Vasco (OSTEBA)	Clinical Practice Guideline for type 2 Diabetes Grupo de trabajo de la Guía de Práctica Clínica sobre Diabetes tipo 2. Guía de Práctica Clínica sobre Diabetes tipo 2. Madrid: Plan Nacional para el SNS del MSC. Agencia de Evaluación de Tecnologías Sanitarias del País Vasco; 2008. Guías de Práctica Clínica en el SNS: OSTEBA Nº 2006/08
Domus Medica	Aanbeveling voor goede medische praktijkvoering: Diabetes Mellitus type 2. WVVH-VDV BERCHEM/GENT, 2005. Opvolgrapport 2007 en 2009. www.domusmedica.be. Validated by CEBAM

3.2.2. Levels of evidence / grades of recommendation

American College of Physicians	American College of Physicians guideline grading system	
	Strong Recommendation High Quality Evidence	Benefits clearly outweigh risks and burden or vice versa RCTs without important limitations or overwhelming evidence from observational studies
	Strong recommendation Moderate-quality evidence	Benefits clearly outweigh risks and burden or vice versa RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
	Strong recommendation Low-quality evidence	Benefits clearly outweigh risks and burden or vice versa Observational studies or case series
	Weak recommendation High-quality evidence	Benefits closely balanced with risks and burden RCTs without important limitations or overwhelming evidence from observational studies
	Weak recommendation Moderate-quality evidence	Benefits closely balanced with risks and burden RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
	Weak recommendation Low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risks, and burden may be closely balanced Observational studies or case series
	Insufficient	Balance of benefits and risks cannot be determined Evidence is conflicting, poor quality, or lacking

SIGN Scottish Intercollegiate Guidelines Network	Levels of evidence	
	1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
	1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
	1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
	2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
	2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
	2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
	3	Non-analytic studies e.g. case reports, case series
	4	Expert opinion
	Grades of Recommendation	
	A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
	B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
	C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
	D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2+
	Good Practice Points	
	Recommended best practice based on the clinical experience of the guideline development group	

NICE The National Collaborating Centre for Chronic Conditions	Levels of evidence	
	1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
	1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
	1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
	2++	High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal.
	2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.
	2-	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal.
	3	Non-analytic studies e.g. case reports, case series
	4	Expert opinion, formal consensus
	No Grades of Recommendation	

American Diabetes Association	Levels of evidence	
	A	Clear evidence from well-conducted generalisable RCTs that are adequately powered, including: • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Compelling non-experimental evidence e.g. “all or none” rule developed by Center for Evidence Based Medicine at Oxford. Supportive evidence from well-conducted randomised controlled trials that are adequately powered, including: • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
	B	Supportive evidence from well-conducted cohort studies • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study
	C	Supportive evidence from poorly controlled or uncontrolled studies • Evidence from RCTs with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
	E	Expert consensus or clinical experience
	No grades of recommendation	

Agencia de Evaluación de Tecnologías Sanitarias del País Vasco (OSTEBA)	Levels of evidence	
	1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
	1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
	1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
	2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
	2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
	2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
	3	Non-analytic studies, eg case reports, case series
	4	Expert opinion
	Grades of Recommendation	
	A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
	B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
	C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
	D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2+
	Good Practice Points	
	Recommended best practice based on the clinical experience of the guideline development group	

Domus Medica	Levels of evidence	
	1	At least two independently conducted studies with similar results belong to one of the following types: -an RCT of good quality -an independent blind comparison of a diagnostic test with the reference test of good quality -a prospective cohort study of good quality with a follow-up of 80% or more -a systematic review or meta-analysis of this type of articles with a high degree of consistency
	2	At least two independently conducted studies with similar results exist which belong to one of the following types: -an RCT of moderate quality -an independent blind comparison of a diagnostic test with the reference test of moderate quality -a retrospective cohort study of moderate quality or case-control study -a systematic review or meta-analysis of this of type articles with a high degree of consistency
	3	Where comparative evidence of good quality is missing level 3 evidence is used. This means: -no RCTs of good quality -only one study of moderate quality and no meta-analyses of studies with moderate quality -results of RCTs or meta-analyses are contradictory -This level also includes the consistent opinion of at least two experts, recommendation or conclusion obtained after reviewing all available material and a consensus within the authorship.
	No grades of recommendations	

3.2.3. Included populations – Interventions – Outcomes

American College of Physicians 2012	- Adults with type 2 diabetes - Oral pharmacologic treatment for hyperglycemia in type 2 diabetes (Combination therapies with more than 2 agents are not included in the review. Data on α-glucosidase inhibitors excluded.) - All-cause mortality, hemoglobin A1c levels, cardiovascular morbidity and mortality, weight, cerebrovascular morbidity, plasma lipid levels, neuropathy, nephropathy, retinopathy, adverse effects
SIGN Scottish Intercollegiate Guidelines Network 2010	- People with type 1 and type 2 diabetes - Oral and injectable glucose-lowering agents and insulins - Mortality, hemoglobin A1c levels, cardiovascular disease, microvascular morbidity, hypoglycemia, weight gain, adverse effects
NICE The National Collaborating Centre for Chronic Conditions 2008, 2009, 2010	- People with type 2 diabetes - Oral and injectable glucose-lowering agents and insulins - Mortality, hemoglobin A1c levels, cardiovascular disease, microvascular morbidity, hypoglycemia, weight gain, fasting plasma glucose, lipid profile, quality of life, adverse effects
American Diabetes Association 2012	- People with type 1 and type 2 diabetes, including children - Oral and injectable glucose-lowering agents and insulins - Mortality, cardiovascular events, hypoglycemia, weight, adverse effects, lipid profile
Agencia de Evaluación de Tecnologías Sanitarias del País Vasco (OSTEBA) 2008	- People with type 2 diabetes. Focus on outpatient context. Exclusion of gestational diabetes. - Oral and injectable glucose-lowering agents and insulins - Mortality, microvascular complications, macrovascular complications, amputations, weight, adverse events
Domus Medica 2009	- Adult patients with type 2 diabetes - Oral and injectable glucose-lowering agents and insulins - Mortality, microvascular complications, macrovascular complications, amputations, weight, adverse events

3.2.4. Members of development group - Target population

American College of Physicians 2012	-NA -Internists, family physicians, other clinicians
SIGN Scottish Intercollegiate Guidelines Network 2010	-Multidisciplinary (physicians, nurses, general practitioners, dietitians, health psychologists, pharmacists) groups of practising clinicians. Involvement of patient representatives. -People with diabetes, their carers and those who interact with people with diabetes outside of the NHS
NICE The National Collaborating Centre for Chronic Conditions 2008, 2009, 2010	-Healthcare professionals (general practitioners, specialists, nurses, primary care pharmacists), health economists, chemical pathologists and patient groups -All healthcare professionals, people with type 2 diabetes and their parents and carers, patient support groups, commissioning organisations and service providers
American Diabetes Association 2012	-Health care professionals, scientists and lay people -Clinicians, patients, researchers, payers.
Agencia de Evaluación de Tecnologías Sanitarias del País Vasco (OSTEBA) 2008	-Primary care (medicine, nursing, pharmacy), specialised care (endocrinologists and nursing educators on diabetes) and professionals experienced in the creation of a Clinical Practice Guideline. -Diabetes educators, family physicians, primary care and specialised nursing professionals, endocrinologists and other professionals who attend these patients in outpatient visits (ophthalmologists, internists, cardiologists, nephrologists, chiropodists, general and vascular surgeons, etc.)
Domus Medica 2009	-General practitioners, endocrinologists, cardiologists, ophthalmologists, nurses, diabetes educators, dieticians, members of the Flemisch Diabetes association -Primary care for people with type 2 diabetes

3.2.5. Recommendations

American College of Physicians 2012	Recommendation 1: ACP recommends that clinicians add oral pharmacologic therapy in patients diagnosed with type 2 diabetes when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglykemia. (Grade: strong recommendation; high-quality evidence) The goal for HbA1c should be based on individualised assessment of risk for complications from diabetes, comorbidity, life expectancy, and patient preferences. An HbA1c level less than 7% (53 mmol/mol) based on individualised assessment is a reasonable goal for many but not all patients. Metformin is more effective than other pharmacologic agents in reducing glycemic levels and is not associated with weight gain. In addition, metformin aids in decreasing weight and reduces LDL cholesterol and triglyceride levels. Metformin was also associated with slightly lower all-cause mortality and cardiovascular mortality compared with sulfonylureas. Finally, metformin is associated with fewer hypoglycemic episodes and is cheaper than most other pharmacologic agents. Metformin is contraindicated in patients with impaired kidney function, decreased tissue perfusion or hemodynamic instability, liver disease, alcohol abuse, heart failure, and any condition that might lead to lactic acidosis. (No quality of evidence reported) Recommendation 2: ACP recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy to treat most patients with type 2 diabetes. (Grade: strong recommendation; high-quality evidence). Recommendation 3: ACP recommends that clinicians add a second agent to metformin to treat patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia. (Grade: strong recommendation; high-quality evidence) No good evidence supports one combination therapy over another, even though some evidence shows that the combination of metformin with another agent generally tends to have better efficacy than any other monotherapy or combination therapy. However, combination therapies are also associated with an increased risk for adverse effects compared with monotherapy. Generic sulfonylureas are the cheapest second-line therapy; however, adverse effects are generally worse with combination therapies that include a sulfonylurea. Although this guideline addresses only oral pharmacological therapy, patients with persistent hyperglycemia despite oral agents and lifestyle interventions may need insulin therapy.

SIGN Scottish Intercollegiate Guidelines Network 2010	-An HbA1c target of 7.0% *(53 mmol/mol)* among people with type 2 diabetes is reasonable to reduce the risk of microvascular disease and macrovascular disease (A). A target of 6.5% *(48 mmol/mol)* may be appropriate at diagnosis. Targets should be set for individuals in order to balance benefits with harms, in particular hypoglycaemia and weight gain (A). - Metformin should be considered as the <u>first line</u> oral treatment option for overweight patients with type 2 diabetes (A). - Sulphonylureas should be considered as <u>first line</u> oral agents in patients who are not overweight, who are intolerant of, or have contraindications to, metformin (A). Metformin is no longer contraindicated in patients with heart failure and diabetes (1+) -Sulphonylurea are <u>second line</u> options when targets are not reached with metformin. - Pioglitazone can be a <u>second line</u> option when targets are not reached with metformin and hypos are a concern and there is no heart failure. Pioglitazone can be added as third line option to metformin and sulphonylurea therapy, or substituted for either in cases of intolerance (A). The risk of fracture should be considered in the long term care of female patients treated with pioglitazone (B). Patients prescribed pioglitazone should be made aware of the increased risk of peripheral oedema. -DPP-4 inhibitors may be used to improve blood glucose control in people with type 2 diabetes (A). They can be a <u>second line</u> option when targets are not reached with metformin and hypos are a concern or weight gain is a concern. They are also a <u>third line</u> option when targets are not reached and weight gain is a concern. - Alpha-glucosidase inhibitors can be used as monotherapy for the treatment of patients with type 2 diabetes if tolerated (B). -Insulin is a <u>third line</u> option for people who are willing to self inject. NPH insulin before bedtime should initially be started. - GLP-1 agonists *(exenatide or liraglutide)* may be used to improve glycaemic control in obese adults *(BMI ≥ 30 kg/m2)* with type 2 diabetes who are already prescribed metformin and/or sulphonylureas. A GLP-1 agonist will usually be added as a <u>third line</u> agent in those who do not reach target glycaemia on dual therapy with metformin and sulphonylurea *(as an alternative to adding insulin therapy)* (A). Liraglutide may be used as a third line agent to further improve glycaemic control in obese adults *(BMI ≥30kg/m2)* with type 2 diabetes who are already prescribed metformin and a thiazolidinedione and who do not reach target glycaemia (A). Careful clinical judgement must be applied in relation to people with long duration of type 2 diabetes on established oral glucose-lowering drugs with poor glycaemic control (>10 years, these individuals being poorly represented in published studies) to ensure insulin therapy is not delayed inappropriately for the perceived benefits of GLP-1 agonists (Good clinical practice). -Oral metformin and sulphonylurea therapy should be continued when insulin therapy is initiated to maintain or improve glycaemic control (A).

NICE The National Collaborating Centre for Chronic Conditions 2008, 2009, 2010	-Initial therapy: Start metformin treatment in a person whose blood glucose is inadequately controlled by lifestyle interventions alone (HbA1c ≥ 6.5%, 48 mmol/mol)(level 1++). Review the dose of metformin if the eGFR is below 45ml/minute/1.73m^2. Stop metformin if the serum creatinine is below 30ml/min/1.73m^2. Consider a sulfonylurea as an option for first-line glucose lowering-therapy if: -the person is not overweight -metformin is not tolerated or contraindicated -a rapid response to therapy is required because of hyperglycaemic symptoms. -Second-line therapy: Add a sulfonylurea as second-line therapy when blood glucose control remains, or becomes inadequate with metformin (HbA1c ≥ 6.5%, 48 mmol/mol) (level 1+/1++). Consider offering a rapid-acting insulin secretagogue to a person with non-routine daily lifestyle patterns. Consider substituting pioglitazone or a DDP-4 inhibitor for the sulfonylurea if there is a significant risk of hypoglycemia (or its consequences) or a sulfonylurea is contraindicated or not tolerated. -Third-line therapy: Add insulin as third-line therapy when blood glucose control remains, or becomes inadequate with metformin + sulfonylurea (HbA1c ≥ 7.5%, 58 mmol/mol) (level 1+/1++). Consider adding sitagliptin or pioglitazone instead of insulin if insulin is unacceptable (because of employment, social, recreational or other personal issues, or obesity). Consider adding a GLP-1 mimetic (exenatide, liraglutide) as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5% (58 mmol/mol), or other higher level agreed with the individual), and the person has: a body mass index (BMI) ≥ 35.0 kg/m2 in those of European descent and specific psychological or medical problems associated with high body weight, or a BMI < 35.0 kg/m2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities (no level of evidence).

American Diabetes Association 2012	-At the time of type 2 diabetes diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated. (A). - Metformin contra-indications: reduced kidney function (no level of evidence reported) - In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or A1C, consider insulin therapy, with or without additional agents, from the outset. (E) - If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the A1C target (<7%, 53 mmol/mol) over 3–6 months, add a

	second oral agent, a GLP-1 receptor agonist, or insulin. (E) Choice is based on patient and drug characteristics, with the overriding goal of improving glycaemic control while minimizing side effects.

Agencia de Evaluación de Tecnologías Sanitarias del País Vasco (OSTEBA) 2008	-Metformin is the drug selected for people overweight or suffering from obesity (BMI 25,0 kg/m²)(A). - In obese diabetics, the treatment with metformin, in comparison with conventional therapy (sulfonylureas or insulin), reduces the risk of any event related with diabetes (1+). -Metformin is also the first line option for people not overweight (B). - Glycemic control, achieved with metformin, measured as the HbA_1c, reduction in non-obese patients is similar to that of obese patients (2+). Metformin is contraindicated for patients with renal failure (serum creatinine over 1,5 mg/dl for men and 1,4 mg/dl for women).(C) -Metformin, second generation sulfonylureas, repaglinide and glitazones are similar in effectiveness as regards HbA_1c reduction (nateglinide and alpha-glucosidases inhibitors seem to be less effective) (1++). - Sulfonylureas should be considered as initial treatment when metformin is not tolerated or is contraindicated and it can be used on patients not overweight (A). - Glinides can play a role to improve glycemic control in patients with non-routine models (no regular meals or missed meals)(B). - Acarbose can be considered an alternative therapy when there is intolerance or contraindication to the rest of oral antidiabetic drugs (B). - Glitazones should not be used as first line drugs (B). - Therapy with incretins is effective in the improvement of glycemic control measured as a decrease of HbA_1c. GLP-1 analogues produce weight loss, while the DPP4-inhibitors have no effect on weight. The GLP-1 analogues have frequent gastrointestinal adverse effects. The DPP4 inhibitors have a higher infection risk (nasopharyngitis, urinary infection) and headaches. There are no data on long-term safety (1++). -Sulfonylureas should be added to metformin when glycemic control is not appropriate (A). -In case of intolerance to sulfonylureas or in patients with non-routine intake models, glinides can be used (B). -Glitazones are second line drugs within a combined therapy. Their use could be considered individually when there is poor glycemic control as well as intolerance or contraindication to other oral antidiabetic drugs. In this case, the use of pioglitazone is recommended (B). -The data on the comparisons of the different oral anti-diabetic drugs are not conclusive, due to the methodological diversity and the lack of sufficient RCTs (1+). -Should there be an inadequate control of glycaemia despite using a double optimized oral therapy, the use of treatment with insulin is recommended (A). -When an insulin treatment is started, it is recommended to maintain the metformin and / or sulfonylurea therapy (A). -Triple oral therapy can be recommended after an evaluation of the potential cardiovascular risks in specific patients with insulinization problems (B).

Domus Medica 2009	-In type 2 diabetic patients medical treatment starts with metformin (level of evidence 1). For most patients the HbA1c target should be lower than 7% (53mmol/mol). - Situations in which lactic acid production can be increased, or clearance could be impaired are a contra-indication for metformin. A decreased kidney function (creatinin ≥1.5mg/dl in men and ≥1.4mg/dl in women) is also a contra-indication for metformin (no level of evidence reported). -Sulfonylurea are a good second choice. -If despite maximal oral therapy (maximum 2 oral agents) treatment goals are not achieved, insulin should be started immediately (level of evidence 1).

3.3. Prediabetes

3.3.1. Selected guidelines

American Diabetes Association	Standards of Medical Care in Diabetes - 2012 Diabetes Care, vol 35, suppl 1, January 2012
Agencia de Evaluación de Tecnologías Sanitarias del País Vasco (OSTEBA)	Clinical Practice Guideline for type 2 Diabetes Grupo de trabajo de la Guía de Práctica Clínica sobre Diabetes tipo 2. Guía de Práctica Clínica sobre Diabetes tipo 2. Madrid: Plan Nacional para el SNS del MSC. Agencia de Evaluación de Tecnologías Sanitarias del País Vasco; 2008. Guías de Práctica Clínica en el SNS: OSTEBA Nº 2006/08
NICE The National Collaborating Centre for Chronic Conditions	Preventing type 2 diabetes: risk identification and interventions for individuals at high risk. Issued July 2012.

3.3.2. Levels of evidence / grades of recommendation

American Diabetes Association 2012	Levels of Evidence	
	A	Clear evidence from well-conducted, generalizable, RCTs that are adequately powered, including: • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Compelling non-experimental evidence e.g. “all or none” rule developed by Center for Evidence Based Medicine at Oxford Supportive evidence from well-conducted randomised controlled trials that are adequately powered, including: • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
	B	Supportive evidence from well-conducted cohort studies • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study
	C	Supportive evidence from poorly controlled or uncontrolled studies • Evidence from RCTs with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
	E	Expert consensus or clinical experience
	No grades of recommendation	

Agencia de Evaluación de Tecnologías Sanitarias del País Vasco (OSTEBA) 2008	Levels of evidence	
	1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
	1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
	1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
	2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
	2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
	2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
	3	Non-analytic studies e.g. case reports, case series
	4	Expert opinion
	Grades of Recommendation	
	A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
	B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
	C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
	D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2+
	Good Practice Points	
	Recommended best practice based on the clinical experience of the guideline development group	

NICE The National Collaborating Centre for Chronic Conditions 2012	Quality appraisal of the evidence. No grades of recommendation	
	++	All or most of the checklist criteria have been fulfilled. Where they have not been fulfilled, the conclusions are very unlikely to alter.
	+	Some of the checklist criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are unlikely to alter the conclusions.
	-	Few or no checklist criteria have been fulfilled. The conclusions of the study are likely or very likely to alter.
	List of checklist criteria available on www.nice.org.uk; methods for the development of NICE public health guidance (second edition).	

3.3.3. Definition of prediabetes – Interventions

American Diabetes Association 2012	-Prediabetes: 2-h values in the OGTT of 140mg/dl to 199 mg/dl (IGT: impaired glucose tolerance), FPG (fasting plasma glucose) of 100-125mg/dl or an HbA1C of 5.7 (38 mmol/mol) to 6.4% (46 mmol/mol)(E) -Diet, exercise and pharmacological treatment

Agencia de Evaluación de Tecnologías Sanitarias del País Vasco (OSTEBA) 2008	-Intermediate hyperglycemias or pre-diabetic stage: Fasting plasma glycemia 110-125 mg/dl (WHO and IDF) or impaired glucose tolerance: 140-200 mg/dl 2h after 75g glucose intake. -Diet, exercise and pharmacological treatment

NICE The National Collaborating Centre for Chronic Conditions 2012	-Prediabetes: Pre-diabetes refers to raised (but not in the diabetic range) blood glucose levels (also known as non-diabetic hyperglycemia, impaired glucose regulation). Guideline does not use the term prediabetes. After a risk assessment using a validated risk assessment tool and if indicated a blood test, patients are divided in 3 groups: moderate risk, high risk and possible type 2 diabetes. Moderate risk: fasting plasma glucose <99mg/dl or HbA1C < 6.0% (42mmol/mol) High risk: fasting plasma glucose 99-125 mg/dl or HbA1c 6.0-6.4% (42-47 mmol/mol) Possible type 2 diabetes: fasting plasma glucose ≥126 mg/dl or HbA1c ≥6.5% (≥48 mmol/mol) -Intensive lifestyle-change programmes, physical activity, weight management advice, dietary advice and pharmacological treatment.

3.3.4. Members of development group - Target population

American Diabetes Association 2012	- Health care professionals, scientists and lay people - Clinicians, patients, researchers, payers

Agencia de Evaluación de Tecnologías Sanitarias del País Vasco (OSTEBA) 2008	- Primary care (medicine, nursing, pharmacy), specialised care (endocrinologists and nursing educators on diabetes) and professionals experienced in the creation of a Clinical Practice Guideline - Diabetes educators, family physicians, primary care and specialised nursing professionals, endocrinologists and other professionals who attend these patients in outpatient visits (ophthalmologists, internists, cardiologists, nephrologists, chiropodists, general and vascular surgeons, etc.)

NICE The National Collaborating Centre for Chronic Conditions 2012	- Public health practitioners, clinicians, representatives of the public, academics and technical experts. - GPs, nurses and other health professionals, as well as commissioners and managers within the NHS, local authorities and the wider public, private, voluntary and community sectors, pharmacists, occupational health specialists, optical practitioners, those involved in the NHS Health Check Programme and all those who deliver dietary, physical activity and weight management services

3.3.5. Recommendations

American Diabetes Association 2012	-Patients with IGT (A), IFG (E), or an HbA1C of 5.7–6.4% (38-46 mmol/mol)(E) should be referred to an effective ongoing support program targeting weight loss of 7% of body weight and increasing physical activity to at least 150 min per week of moderate activity such as walking. -Metformin therapy for prevention of type 2 diabetes may be considered in those with IGT (A), IFG (E), or an A1C of 5.7–6.4% (38-46 mmol/mol) (E), especially for those with BMI > 35 kg/m2, age < 60 years, and women with prior GDM. (A) -At least annual monitoring for the development of diabetes in those with prediabetes is suggested. (E)

Agencia de Evaluación de Tecnologías Sanitarias del País Vasco (OSTEBA) 2008	-The structured interventions which enable physical exercise and diet reduce the risk to develop diabetes [RR 0.51 (95%CI: 0.44-0.60); NNT 6.4] in patients with pre-diabetes. (1++) -The interventions with anti-diabetic drugs (metformin and acarbose) reduce the risk to develop diabetes [RR 0.70 (95% CI: 0.62-0.79); NNT 11 (8 to 15)].(1++) -An intensive intervention on lifestyle – hypocaloric diet, low in fat, physical exercise (at least two hours per week) and a program of educational sessions – is more effective than metformin to prevent diabetes. (1++) Recommendations: Structured programs which foster physical exercise and diet are advised for patients with Impaired Glucose Tolerance or Altered Basal Glycemia (A). The use of pharmacological treatments in patients with Impaired Glucose Tolerance or Altered Basal Glycemia is not recommended (A).

NICE The National Collaborating Centre for Chronic Conditions 2012	-Patients with moderate risk: offer a brief intervention to discuss the risks of developing diabetes, help modifying individual risk factors and offer tailored support services -Patients with high risk: offer an intensive lifestyle-change program to increase physical activity, achieve and maintain weight loss and increase dietary fibre, reduce fat intake (particularly saturated fat). -Patients with possible type 2 diabetes: perform a blood test to confirm or reject the presence of type 2 diabetes. Use clinical judgement on whether to offer metformin: -In adults at high risk whose blood glucose measure (fasting plasma glucose or HbA1c) shows they are still progressing towards type 2 diabetes, despite their participation in an intensive lifestyle-change programme. - In adults at high risk who are unable to participate in lifestyle-change programmes because of a disability or for medical reasons. The HR (0.64, 95%BI 0.53-0.67) for oral diabetes drugs was based on twelve studies: three multi-country studies: all ++ Use clinical judgement on whether to offer Orlistat: - In Adults who have a BMI of 28.0 kg/m2 or more, whose blood glucose measure (fasting plasma glucose or HbA1c) shows they are still

	progressing towards type 2 diabetes. In particular, this includes those who are not benefiting from lifestyle-change programmes, or who are unable to participate in physical activity because of a disability or for medical reasons. For anti-obesity drugs, the HR (0.67, 95%BI 0.55-0.81) was based on two studies, both ++.

3.4. Conclusions from guidelines

Type 2 diabetes

Pharmacologic therapy in patients diagnosed with type 2 diabetes should be started when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia. Most guidelines recommend a HbA1c target of 7 % (53mmol/mol).
5/6 guidelines consider metformin as first choice for all patients, 1 guideline (SIGN) reserves it for overweight people. Sulfonylurea are second choice. When targets are not reached with monotherapy a second agent should be started. Most guidelines recommend sulfonylurea in addition to metformin. If sulfonylurea are not appropriate other anti-diabetic drugs (pioglitazone, meglitinides, DPP-4 inhibitors) can be used depending on patient characteristics and preferences. Most guidelines recommend insulin as first choice for third-line therapy. If insulin is not appropriate other anti-diabetic drugs (pioglitazone, DPP-4 inhibitors, GLP-1 analogues) can be used depending on patient characteristics and preferences.

Prediabetes

Prediabetes refers to raised (but not in the diabetic range) blood glucose levels. The selected guidelines use different diagnostic criteria. The emphasis is on lifestyle interventions with diet and exercise. Two (2/3) guidelines consider pharmacologic therapy with metformin in selected patients as an option, one guideline does not recommend metformin.

4. Evidence tables and conclusions: HbA1c target: intensive treatment vs standard/conventional treatment

4.1. UKPDS 33. Sulphonylurea or insulin (intensive treatment) vs diet (conventional treatment)

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
UK prospective diabetes study Group: UKPDS 33 1998 Design: RCT (PG) open label Setting: 23 hospitals in UK	n= 3867 prior R: 3m diet DMII duration: newly diagnosed Mean baseline HbA1c: 7.1% Mean FPG: 6.1-15.0 mmol/l Mean BMI: 27.2 kg/m^2 <u>Inclusion</u> - FPG >6mmol/l on two mornings, 1-3w apart - Non-obese (body weight <120% of ideal) - No symptoms of hyperglycemia Median age: 54y Mean FPG: 6.1-15.0 <u>Exclusion</u> - Ketonuria >3mmol/l - Serum creatinine >175µmol/l - Myocardial infarction in previous year - Current angina or heart failure - >1 vascular event - Retinopathy requiring laser treatment - Malignant hypertension - Uncorrected endocrine disorder - Occupation that precluded insulin therapy - Severe concurrent illness	median 10.0y	<u>Int</u>ensive treatment (sulfonylurea or insulin) target: FPG <6mmol/l vs <u>Con</u>ventional treatment (diet alone°) target: FPG <15mmol/l	Efficacy		- Jadad score o RANDO: 1/2 o BLINDING: 0/2 o ATTRITION: 1/1 - FU: 96% - ITT: yes - Sponsor: NHS (UK)
				Any diabetes-related endpoint* (PE) (per 1000person years)	Int: 40.9 vs con: 46.0 RR=0.88 (95%CI: 0.79-0.99) **SS, p=0.029 in favour of int group** **NNT=19.6 (treat 19.6 for 10 y patients to prevent one patient developing any of these events)**	
				Diabetes-related death (per 1000person years)	Int: 10.4vs con: 11.8 RR=0.90 NS, p=0.34	
				All-cause mortality (per 1000person years)	Int: 17.9vs con: 18.9 RR=0.94 (95%CI: 0.80-1.10) NS: p=0.44	
				Myocardial infarction (per 1000person years)	Int: 14.7 vs con: 17.4 RR=0.84 (95%CI: 0.71-1.00) NS: p=0.052	
				Stroke (per 1000person years)	Int: 5.6 vs con: 5.0 RR=1.11 (95%CI: 0.81-1.51) NS: p=0.52	
				Amutation or death from PVD (per 1000person years)	Int: 1.1 vs con: 1.6 RR=0.65 (95%CI: 0.36-1.18) NS: p=0.15	
				Microvascular disease** (per 1000person years)	Int: 8.6 vs con: 11.4 RR=0.75 (95%CI: 0.60-0.93) **SS, p=0.0099 in favour of int group** *NNT=42 (treat 42 for median 10y to prevent microvasc disease in 1 extra patient)*	
				HbA1c over 10y (median)	Int: 7.0% (95%CI: 6.2-8.2) vs con: 7.9% (95%CI: 6.9-8.8) p<0.001 **SS in favour of intensive treatment** (sulfonylurea or insulin)	

				Harms		
				Weight gain at 10y	Mean: 3.1kg higher in int group compared to con group **SS: p<0.0001 in favour of con group**	
				Major hypoglycemic episodes/y	Con vs int: 0.7% vs +/- 1.4% **SS: p<0.0001 in favour of con group**	

° in the conventional group, the aim was best achievable FPG with diet alone; drugs were added only if there were hyperglycemic symptoms or FPG>15mmol/l
In the intensive group, the aim was FPG<6mmol/l

* Any diabetes-related endpoint = sudden death, death from hypo/hyperglycemia, myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness, cataract extraction

**Microvascular complications (retinopathy requiring photocoagulation, vitreous haemorrhage, and or fatal or non-fatal renal failure).most ofmicrovascular complications were due to fewer cases of retinal photocoagulation

4.2. UKPDS 34. Metformin (intensive treatment) vs diet (conventional treatment)

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
UK prospective diabetes study Group: UKPDS 34 1998 Design: RCT (PG) open label Setting: 23 hospitals in UK	n= 753 Median age: 53y prior R: 3m diet DMII duration: newly diagnosed Mean baseline HbA1c: 7.2%* Mean FPG: 8.1 (7.1-9.7 mmol/l Mean BMI: 31.4 kg/m^2 <u>Inclusion</u> - FPG >6mmol/l on two mornings, 1-3w apart - obese (body weight >120% of ideal) - No symptoms of hyperglycemia <u>Exclusion</u> - Ketonuria >3mmol/l - Serum creatinine >175µmol/l - Myocardial infarction in previous year - Current angina or heart failure - >1 vascular event - Retinopathy requiring laser treatment - Malignant hypertension - Uncorrected endocrine disorder - Occupation that precluded insulin therapy - Severe concurrent illness	median 10.7y	<u>Int</u>ensive treatment (metformin 1700-2550mg/d) target: FPG <6mmol/l vs <u>con</u>ventional treatment (diet alone°) target: FPG <15mmol/l	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING: 0/2 ○ ATTRITION: 1/1 - FU: 96% - ITT: yes - Sponsor: NHS (UK)
				Any diabetes-related endpoint*(PE) (events/1000patient years)	Int: 29.8 vs con: 43.3 RR=0.68 (95%CI: 0.53-0.87) **SS, p=0.0023 in favour of int** *NNT: 10 (treat 10 patients for median 10.7y to prevent 1 extra patient having an event)*	
				Diabetes-related death (PE) (events/1000py)	Int: 7.5 vs con: 12.7 RR=0.58 (95%CI: 0.37-0.91) **SS, p=0.017 in favour of int** *NNT=19 (treat 19 patients for median 10.7y to prevent 1 extra death from diabetes)*	
				All-cause mortality (PE) (events/1000py)	Int: 13.5 vs con: 20.6 RR=0.64 (95%CI: 0.45-0.91) **SS, p=0.011 in favour of int** *NNT=14 (treat 14 patients for median 10.7y to prevent 1 extra death)*	
				Myocardial infarction (events/1000py)	Int: 11.0 vs con: 18.0 RR=0.61 (95%CI: 0.41-0.89) **SS, p=0.01 in favour of int** *NNT=16 (treat 16 for median 10.7y to avoid 1 extra MI*)	
				Stroke (events/1000py)	Int: 3.3 vs con: 5.5 RR=0.59 (95%CI: 0.29-1.18) NS: p=0.13	
				Amputation or death from PVD (events/1000py)	Int: 1.6 vs con: 2.1 RR=0.74 (95%CI: 0.26-2.09) NS: p=0.57	
				Microvascular disease (events/1000py)	Int: 6.7 vs con: 9.2 RR=0.71 (95%CI: 0.43-1.19) NS: p=0.19	
				HbA1c over 10y	Int: 7.% vs con: 8.0 % (median) NT	
				Harms		
				Weight gain at 10y	Similar in both groups: NT	
				Major hypoglycemic episodes/y	Int: 0 vs con: 0.7 : NT	

° in the conventional group, the aim was best achievable FPG with diet alone; drugs were added only if there were hyperglycemic symptoms or FPG>15mmol/l
In the intensive group, the aim was FPG<6mmol/l

* Any diabetes-related endpoint = sudden death, death from hypo/hyperglycemia, myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness, cataract extraction

**Microvascular complications (retinopathy requiring photocoagulation, vitreous haemorrhage, and or fatal or non-fatal renal failure).most ofmicrovascular complications were due to fewer cases of retinal photocoagulation

NNT reported from ACP journal club, 199 jan-feb; 130:3. NNT based on number of patients with clinical endpoint.

Supplementary RCT, also in UKPDS 34: Metformin + sulphonylurea vs sulphonylurea

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
UKPDS 34 1998 Design: RCT (PG) open label Setting: 23 hospitals in UK	n= 537 Mean age: 59y prior R: maximum doses sulfonylurea DMII duration: mean 7.1 y Mean baseline HbA1c: 7.5% Mean FPG: 9.1 (7.7-11.1 mmol/l Mean BMI: 29.6 kg/m^2 <u>Inclusion</u> - FPG 6.1-15mmol/l - obese and non-overweight patients - Treated with maximum doses of sulfonylurea - No symptoms of hyperglycemia - <u>Exclusion</u> - Ketonuria >3mmol/l - Serum creatinine >175µmol/l - Myocardial infarction in previous year - Current angina or heart failure - >1 vascular event - Retinopathy requiring laser treatment - Malignant hypertension - Uncorrected endocrine disorder - Occupation that precluded insulin therapy - Severe concurrent illness	Median 6.6y	Metformin + sulfonylurea (Met+SU) Vs Sulfonylurea alone (SU)	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING: 0/2 ○ ATTRITION: 1/1 - FU: 96% - ITT: yes - Sponsor: NHS (UK)
				Any diabetes-related endpoint*(PE) (per 1000patient years)	Met+SU: 60.5 vs SU: 58.4 RR=1.04(95%CI: 0.77-1.42) NS	
				Diabetes-related death (PE) (per 1000 patient-years)	Met+SU: 16.8 vs SU:8.6 RR=1.96 (95%CI: 1.02-3.75) **SS, p=0.039 in favour of SU alone** *NNH=22 (treat 22 for median 6.6y to cause one more death from diabetes)*	
				All-cause mortality (PE) (per 1000 patient-years)	Met+SU: 30.3 vs SU:19.1 RR=1.60 (95%CI 1.02-2.52) **SS, p=0.039 in favour of SU alone** *NNT=17(treat 17 for median 6.6y to cause one more death*	
				Myocardial infarction (events/1000py)	Met+SU 22.0 vs SU: 20.2 RR=1.09 (95%CI: 0.67-1.78) NS	
				Microvascular disease (events/1000py)	Met+SU: 10.1 vs SU:12.1 RR=0.84 (95%CI: 1.43-1.66) NS	
				Other clinical endpoints	NS	
				HbA1c over 4 years (median)	Met+SU: 7.7% vs SU:8.2% NT	
				Harms		
				NR		

4.3. ACCORD. Intensive treatment (HbA1c <6.0%) vs conventional treatment (HbA1c 7.0-7.9%)

Ref	n/Population	Duration	Comparison	Outcomes			Methodological
ACCORD study group 2008 *2011* Design: RCT (OL) (PG) Setting: clinical centers	n=10251 mean age: 62.2y 38% women 35% previous cardiovascular event Prior R: NR DMII duration: median 10y Median baseline HbA1c: 8.1% (mean: 8.3%) <u>Inclusion</u> - DM II - 40-79y And cardiovascular disease - 55-79y And Significant atherosclerosis, albuminuria, left ventricular hypertrophy or min.2 additional risk factors for cardiovascular disease	Mean follow-up: 3.5y *3.7y**	Accord 2008: Standard therapy Target: HbA1c 7.0-7.9% Vs Intensive therapy Target: HbA1c<6.0% *Accord 2011:* *Standard therapy* *Target: HbA1c 7.0-7.9%* *Vs* *Standard therapy* *Target: HbA1c 7.0-7.9%* Used medications: any marketed antihyperglycemic therapy Blood-pressure and lipid trials are continuing (double 2-by-2 factorial design)	Efficacy			- Jadad score o RANDO: 1/2 o BLINDING: 0/2 o ATTRITION: 1/1 - FU: 99.5 % - ITT: yes - Other important methodological remarks: study terminated 17m before scheduled end (patients from intensive treatment group were switched to standard group) - Multicenter: 77 centers in US and Canada - Sponsor: NHLBI (National Heart, Lung and Blood Institute)
				Nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes (PE) (%patients per year)	ACCORD 2008	Stand: 2.29% vs Intens: 2.11% HR=0.90 (95%CI: 0.78-1.04) NS: p=0.16	
					Accord 2011	*Stand: 2.2% vs Intens: 2.1%* *HR=0.91 (95%CI: 0.81-1.03)* *NS: p=0.12*	
				Nonfatal myocardial infarction (SE) (% patients per year)	ACCORD 2008	Stand: 1.45% vs Intens: 1.11% HR=0.76 (95%CI: 0.62-0.92) **SS: p=0.004 in favour of intensive treatment** *NNT= 104 (treat 104 intensively for study duration to prevent 1 extra nonfatal MI*	
					Accord 2011	*Stand: 1.4% vs Intens: 1.2%* *HR=0.82 (CI: 0.70-0.96)* ***SS: p=0.01 in favour of intensive treatment***	
				Nonfatal stroke (SE) (% patients per year)	ACCORD 2008	Stand: 0.37% vs Intens: 0.39% HR=1.06 (CI: 0.75-1.50) NS: p=0.74	
					Accord 2011	*Stand: 0.4% vs Intens: 0.3%* *HR=0.87 (CI: 0.65-1.17)* *NS: p=0.87*	
				Death from cardiovascular causes (SE) (%patients per year)	ACCORD 2008	Stand: 0.56% vs Intens: 0.79% HR=1.35 (CI: 1.04-1.76) **SS: p=0.02 in favour of standard treatment** *NNH=125 (treat 125 intensively for study duration to cause 1 extra CV death)*	

	Exclusion - Frequent or serious hypoglycemic events - BMI ≥45 - Creatinine level >1.5mg/dl - Other serious illness				*Accord 2011*	*Stand: 0.6% vs Intens: 0.7%* *HR=1.29 (CI: 1.04-1.60)* ***SS: p=0.02 in favour of standard***	
				Mortality (SE) (%patients per year)	ACCORD 2008	Stand: 1.14% vs Intens: 1.41 HR=1.22 (CI: 1.01-1.46) **SS: p=0.04 in favour of standard treatment** *NNH=95 (treat 95 intensively for study duration to cause 1 extra death)*	
					Accord 2011	*Stand: 1.3% vs Intens: 1.5%* *HR=1.19 (CI: 1.03-1.38)* ***SS: p=0.02 in favour of standard treatment***	
				HbA1c (%)median	ACCORD 2008	Stand: 7.5% vs Intens: 6.4% NT	
					Accord 2011	*Stand: 7.6% vs Intens: 7.2%* *NT*	
				Safety			
				Hypoglycemia requiring medical assistance	ACCORD 2008	Stand: 1.0% vs Intens: 3.1% **SS: P<0.001 in favour of standard treatment** *NNH=14 (treat 14 intensively for study duration to cause 1 extra severe hypoglycemia)*	
					Accord 2011	*Similar after transition*	
				Weight gain (>10kg)	ACCORD 2008	Stand: 14.1% vs Intens: 27.8% **SS: P<0.001 in favour of standard treatment**	
					Accord 2011	*Stand: 15.8% vs Intens: 10.1%* *NT*	

* Remark: Patients originally randomised to intensive therapy group were switched to standard glycemic therapy on February 5, 2008. The report "ACCORD 2008" is based on data that were submitted to the coordinating center through December 10. 2007.

** NNT and NNH calculated by Farmaka using 'crude' event rates (persons with an event) from original study

4.4. ADVANCE. Intensive treatment (HbA1c <6.5%) vs conventional treatment

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
ADVANCE collaborative group 2008 Design: RCT (OL) (PG) Setting: university of Sydney	n= 11140 mean age: Prior R: non or hypoglycemic drugs or insulin DMII duration: 8.0y Mean baseline HbA1c: 7.5% <u>Inclusion</u> - DM type 2 diagnosed at ≥30y - AND ≥55y - AND History of major macro- or microvascular disease or min. 1 risk factor for vascular disease <u>Exclusion</u> - Indication for or contra-indication to any of study treatments	Median follow-up: 5y	Standard glucose control Aim: local guidelines Vs Intensive glucose control Aim: ≤6.5% HbA1c Antidiabetics: gliclazide modified release 30-120mg/d plus other drugs as required (metformin, thiazolidinediones, acarbose or insulin) Both groups also received fixed combination perindopril + indapamide	Efficacy		- Jadad score ○ RANDO: 1/2 ○ BLINDING: 0/2 ○ ATTRITION: 1/1 - FU: 99.8% - ITT: yes - Multicenter: 215 centers in 20 countries from Asia, Australasia, Europe, N-America - Sponsor: Servier is major financial sponsor, also supported by National Health and Medical Research Council of Australia
				Macrovascular and microvascular events* (PE)(n° of patients(%))	Stand: 20.0% vs Intens: 18.1% HR=0.90 (CI: 0.82-0.98) **SS: p=0.01 in favour of intensive treatment** *NNT=52 (treat 52 intensively for median 5y to prevent one extra macro or microvasc event.*	
				Major microvascular events (PE) (n° of patients(%))	Stand: 10.9% vs Intens: 9.4% HR=0.86 (CI: 0.77-0.97) **SS: p=0.01 in favour of intensive treatment** *NNT= 70 (treat 70 for median 5y to prevent 1 extra microvasc event*	
				Major macrovascular events (PE) (n° of patients(%))	Stand: 10.6% vs Intens: 10.0% HR=0.94 (CI: 0.84-1.06) NS: p=0.32	
				Death from cardiovascular causes (SE) (n° of patients(%))	Stand: 5.2% vs Intens: 4.5% HR=0.88 (CI: 0.74-1.04) NS: p=0.12	
				Death from any cause (SE) (n° of patients(%))	Stand: 9.6% vs Intens: 8.9% HR=0.93 (CI: 0.83-1.06) NS: p=0.28	
				HbA1c (mean, %)	Stand: 7.3 vs Intens: 6.5 **SS: p<0.001 in favour of intensive treatment**	
				Safety		
				Severe hypoglycemia	Stand: 1.5% vs Intens: 2.7% HR=1.86 (CI: 1.42-2.40) P<0.001 *NNH=80 (treat 80 intensively for study duration to cause 1 extra severe hypoglycemia)*	

* Macrovascular events were defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
Microvascular events were defined as new or worsening nephropathy (i.e., development of macroalbuminuria, defined as a urinary albumin:creatinine ratio of more than 300 μ g of albumin per milligram of creatinine [33.9 mg per millimole], or doubling of the serum creatinine level to at least 200 μ mol per liter [2.26 mg per deciliter], the need for renal-replacementment therapy, or death due to renal disease) or retinopathy (i.e., development of proliferative retinopathy, macular edema or diabetes-related blindness or the use of retinal photocoagulation therapy)

4.5. VADT. Intensive treatment vs standard treatment (absolute reduction of 1.5% vs control)

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Duckworth 2009: VADT Design: RCT (OL) (PG) Setting: veterans affairs	n=1791 mean age: 60.4y predominantly men (veterans) Prior R: 52% insulin DMII duration: mean 11.5y Baseline HbA1c: mean 9.4% Mean BMI: 31.3 40% had cardiovascular event <u>Inclusion</u> - Poorly controlled DMII <u>Exclusion</u> - HbA1c <7.5% - Cardiovascular event in previous 6m - Advanced congestive heart failure - Severe angina - Life expectancy <7y - BMI >40 kg/m2 - Serum creatinine >1.6mg/dl - Alanine aminotransferase >3x upper limit normal range	Median follow-up: 5.6y	Intensive therapy (maximal doses oral antidiabetics and if necessary: insulin)* Vs Standard therapy (half of maximal doses of oral antidiabetics and if necessary: insulin) Goal intensive group: absolute reduction of 1.5% in HbA1c as compared to standard therapy	Efficacy		- Jadad score ○ RANDO: 1/2 ○ BLINDING: 0/2 ○ ATTRITION: 1/1 - FU: 95% - ITT: yes - Methodological remarks: the guidelines allowed for the use of any approved drug at the discretion of the investigator - Sponsor: Veterans Affairs Cooperative Studies Program, Sanofi-Aventis, GlaxoSmithKline, Novo Nordisk, Roche, Kos Pharmaceuticals, Amylin
				Time to first major cardiovascular event° (PE)°	HR=0.88 (CI: 0.74-1.05) NS: p=0.14	
				Major cardiovascular events° ('event rate')	Stand: 33.5% vs Intens: 29.5% RRR=11.9% NT	
				Death from cardiovascular causes (% of patients)	Stand: 3.7% vs Intens: 4.5% NS	
				Time to death from cardiovascular cause	NS: p=0.26	
				Sudden death (% of patients)	Stand: 1.2% vs Intens: 0.4% NS: p=0.08	
				Death from any cause (% of patients)	Stand: 10.6% vs Intens: 11.4% HR=1.07 (CI: 0.81-1.42) NS: p=0.62	
				Diabetic retinopathy (new onset) (% of patients)	Stand: 48.9% vs Intens: 42.2% (of patients that had evaluation at baseline = 135 vs 128) NS: p=0.27	
				Macro-albuminuria (% of patients)	Stand: 5.1% vs Intens: 2.9% **SS: p=0.04 in favour of intensive therapy**	
				New neuropathy (% of patients)	Stand: 43.8% vs Intens: 43.5% NS: p=0.94	
				BMI (kg/m^2)	Stand: 32.3 vs Intens: 33.8 **SS, p=0.01 in favour of standard therapy**	
				HbA1c (median, %)	Stand: 8.4 vs Intens: 6.9 Goal achieved: absolute between-group difference of 1.5%	
				Safety		
				Hypoglycemia	Stand: 383 vs Intens: 1333	

				(symptomatic, number of episodes/100 patient-years)	**SS: p<0.001 in favour of standard therapy**	
				Serious adverse event (patients with at least 1 event)	Stand: 17.6% vs Intens: 24.1% NS: p=0.05	
				Dyspnea	**SS: p=0.006 in favour of standard therapy**	

* Treatment protocol:
BMI ≥27: metformin + rosiglitazone
BMI<27: glimepiride + rosiglitazone
Insulin was added to two oral antidiabetics if participants did not achieve HbA1c<6% in intensive treatment group and <9% in standard treatment group.

° Major cardiovascular event: myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, amputation for ischemic gangrene

4.6. Meta-analyses intensive treatment vs conventional treatment

Several meta-analyses have been performed on trials comparing intensive vs conventional treatment.

Ref	N/n	Comparison	Outcomes	Early trials	Recent trials	All trials
Kelly 2009 Design: meta-analysis Search date: January 1950-April 2009	N= 5 n= 27802	Intensive treatment Vs Conventional treatment	Cardiovascular disease	RR=0.79 (95%CI: 0.57-1.09)	RR=0.94 (95%CI: 0.86-1.02)	**RR=0.90 (95%CI: 0.83-0.98)**
			Coronary heart disease	RR=0.78 (95%CI: 0.59-1.04)	RR=0.91 (95%CI: 0.83-1.01)	**RR=0.89 (95%CI: 0.81-0.96)**
			Stroke	RR=0.91 (95%CI:0.53-1.58)	RR=0.97 (95%CI: 0.84-1.12)	RR=0.98 (95%CI:0.86-1.11)
			Congestive heart failure	RR=0.89 (95%CI:0.63-1.26)	RR=1.03 (95%CI: 0.87-1.22)	RR=1.01 (95%CI 0.89- 1.14)
			Cardiovascular mortality	RR=0.75 (95%CI: 0.48-1.19)	RR=1.13 (95%CI: 0.79-1.63)	RR=0.97 (95%CI: 0.76-1.24)
			All-cause mortality	RR=0.83 (95%CI: 0.59-1.16)	RR=1.08 (95%CI: 0.88-1.32)	RR=0.98 (95%CI: 0.84-1.15)
			Severe hypoglycaemia	RR=1.37 (95%CI: 0.58-3.27)	**RR=2.48 (95%CI: 1.78-3.47)**	**RR=2.03 (95%CI: 1.46-2.81)**

Studies included (Kelly 2009)

Ref + design	n	Population	Duration (median, y)	Comparison	Methodology
Early trials					
UKPDS 33 1998	3867	Newly diagnosed diabetes mellitus type 2 Non-obese patients Mean age: 53.3y	10.0	Sulfonylurea or insulin vs diet	- Jadad score: 2/5 - FU: 96% - ITT: yes
UKPDS 34 1998	753	Newly diagnosed diabetes mellitus type 2 Obese patients Median age: 53y	10.7	Metformin vs diet	- Jadad score: 3/5 - FU: 96% - ITT: yes
Recent trials					
ACCORD study group 2008	10251	Diabetes mellitus type 2, median duration of 10y Mean BMI=32.2 Mean age: 62.2y	3.4	≥2 classes of hypoglycemic agents plus other drugs vs diet or pharmacological treatment or both	- Jadad score: 2/5 - FU: 99.5% - ITT: yes
ADVANCE collaborative group 2008	11140	Diabetes mellitus type 2, mean duration of 7.9y Mean BMI=28.3 Mean age: 66y	5.0	Gliclazide plus other drugs vs continuation of current treatment (substitute gliclazide with another sulfonylurea)	- Jadad score: 2/5 - FU: 99.8% - ITT: yes
Duckwordt 2009	1791	Diabetes mellitus type 2, mean duration of 11.5y Mean BMI=31.3 Mean age: 60.4y	5.6	Glimepiride or metformin, plus rosiglitazone, or insulin vs same treatment but other target	- Jadad score: 2/5 - FU: 95% - ITT: yes

Remarks

Important differences in therapeutic regimens and achieved HbA1c levels existed among the trials included in this meta-analysis. Each trial used different combinations of diet, sulfonylureas, thiazolidinediones, metformin or insulin therapies to achieve target levels of glucose control.

The meta-analysis for all trials (5 key trials) was also done by another author (Turnbull 2009), published around the same time, and found the same results (significant result for myocardial infarction and major cardiovascular events, but not for other hard endpoints).

Contrary to this, a Cochrane analysis by Hemmingsen that included 20 studies (5 key trials above + 15 other trials, small and/or short), found no significant difference for any of the hard endpoints.

Ref	N/n	Comparison	Outcomes		Reported Grade
Hemmingsen 2011 Design: meta-analysis Search date: up to dec 8 2010	N=20 n= 29986 (n per trial 20 to 11140), duration 3d to 12.5y)	Intensive treatment Vs Conventional treatment	Cardiovascular mortality	RR=1.06 (95%CI:0.9-1.26)	Moderate
			All-cause mortality	RR=1.01 (95%CI:0.9-1.13)	Moderate
			Non-fatal stroke	RR=0.96 (95%CI:0.8-1.16)	Moderate
			Non-fatal myocardial infarction	RR=0.87 (95%CI:0.76-1.00)	Moderate
			Severe hypoglycaemia	**RR=2.05 (95%CI:1.39-3.02)**	High

4.1.bis. Summary and conclusions: Sulphonylurea or insulin (intensive treatment) vs diet (conventional treatment)

Sulphonylurea or insulin vs diet (UKPDS group: UKPDS33)					
Ref	**Duration**	**Population**	**Therapy/Target**	**Results**	
UKPDS 33	median 10.0y	n= 3867 newly diagnosed type 2 diabetes median age: 54y	Sulfonylurea or insulin(intensive) vs diet (conventional) Target: int FPG<6mmol/l vs con FPG<15mmol/l	HbA1c	**Int: 7.0% (95%CI: 6.2-8.2)** **Con: 7.9% (95%CI: 6.9-8.8)** **p<0.001**
				Any DM-related endpoint (macrovascular and microvascular)(PE)	**Int: 40.9 events/1000py** **Con: 46.0 events/1000py** **RR=0.88 (95%CI: 0.79-0.99)** **SS, p=0.029** **NNT[2]=19.6 (treat 19.6 patients for 10y to prevent one patient developing any of these events)**
				Diabetes-related death (PE)	Int: 10.4 events/1000py Con: 11.8 events/1000py RR=0.90 NS, p=0.34
				Mortality(PE)	Int: 17.9 events/1000py Con: 18.9 events/1000py RR=0.94 (95%CI: 0.80-1.10) NS: p=0.44
				Myocardial infarction	Int: 14.7 events/1000py Con: 17.4 events/1000py RR=0.84 (95%CI: 0.71-1.00) NS: p=0.052
				Stroke	Int: 5.6 events/1000py Con: 5.0 events/1000py RR=1.11 (95%CI: 0.81-1.51) NS: p=0.52
				Microvascular disease	**Int: 8.6 events/1000py** **Con: 11.4 events/1000py** **RR=0.75 (95%CI: 0.60-0.93)** **SS, p=0.0099** *NNT[3]= 42 (treat 42 for median 10y to prevent 1 extra event)*
				Adverse event Major hypoglycemic episodes	**Con: 0.7% per year** **Int: +/- 1.4% per year** **SS: p<0.0001**

Quality	Consistency	Directness	Imprecision
-1 for low jadad, composite EP, (directness)	NA	OK	OK
Grade assessment: moderate quality of evidence			

UKPDS 33 (newly diagnosed type 2 diabetes, non-obese patients, comparison sulphonylurea or insulin vs diet) found a statistically significant risk reduction in any diabetes-related endpoint (primary endpoint: macrovascular and microvascular events) and in microvascular diseases with intensive therapy (FPG below 6mmol/l) versus conventional therapy.

[2] As reported in the original study

[3] Calculated by Farmaka, using 'crude' event rates (persons with an event) from original study

4.2.bis. Summary and conclusions. Metformin (intensive treatment) vs diet (conventional treatment)

Metformin vs diet (UKPDS Group: UKPDS 34)					
Ref	**Duration**	**Population**	**Therapy/Target**	**Results**	**Ref**
UKPDS 34	median 10.7y	n= 753 newly diagnosed diabetes type 2 median age: 53y	Metformin vs diet Target: int FPG<6mmol/l vs con FPG<15mmol/l	HbA1c	Int: 7.4% vs con: 8.0% NT
				Any DM-related endpoint (macrovascular and microvascular) (PE)	**Int: 29.8 events/1000py** **Con: 43.3 events/1000py** **RR=0.68 (95%CI: 0.53-0.87)** **SS, p=0.0023** *NNT[4]: 10 (treat 10 patients for median 10.7y to prevent 1 extra patient having an event)*
				Diabetes-related death (PE)	**Int: 7.5 events/1000py** **Con: 12.7 events/1000py** **RR=0.58 (95%CI: 0.37-0.91)** **SS, p=0.017 in favour of int** *NNT[3]=19 (treat 19 patients for median 10.7y to prevent 1 extra death from diabetes)*
				Mortality(PE)	**Int: 13.5 events/1000py** **Con: 20.6 events/1000py** **RR=0.64 (95%CI: 0.45-0.91)** **SS, p=0.011** **NNT=14***NNT[3]=14 (treat 14 patients for median 10.7y to prevent 1 extra death)*
				myocardial infarction	**Int: 11.0 events/1000py** **Con: 18.0 events/1000py** **RR=0.61 (95%CI: 0.41-0.89)** **SS, p=0.01** *NNT[3]=16 (treat 16 for median 10.7y to avoid 1 extra MI)*
				Stroke	Int: 3.3 events/1000py Con: 5.5 events/1000py RR=0.59 (95%CI: 0.29-1.18) NS: p=0.13
				Microvascular disease	Int: 6.7 vs con: 9.2 RR=0.71 (95%CI: 0.43-1.19) NS: p=0.19
				Adverse event	Major hypoglycemic episodes Int: 0% vs con: 0.7% per year NT

Quality -1 for low jadad, composite EP, (directness)	Consistency NA	Directness OK	Imprecision OK
Grade assessment: moderate quality of evidence			

UKPDS 34 (newly diagnosed type 2 diabetes, obese patients, metformin vs diet) also reported a significant risk reduction on this primary endpoint (any diabetes related endpoint) and on hard endpoints as myocardial infarction and mortality.

[4] NNT as reported by ACP journal club (calculated with 'crude' event rates (persons with an event) from original study). ACP Journal Club. 1999 Jan-Feb; 130:3.

Both trials (UKPDS33 and 34) were published in 1998 and intensive glucose control has become more stringent since: intensive glucose control in early trials resembles standard glucose control in recent trials.

4.3.bis. Summary and conclusions. Intensive treatment (HbA1c <6.0%) vs conventional treatment (HbA1c <7.0-7.9%)

Intensive target HbA1c (<6.0%) vs conventional target (7.0-7.9%) (ACCORD study group 2008)					
Ref	**Duration**	**Population**	**Therapy/Target**	**Results**	**Ref**
ACCORD study group	mean 3.5y	n= 10251 median duration DM: 10y cardiovascular high-risk patients mean age: 62y	≥2 classes of hypoglycemic agents plus other drugs vs diet or pharmacological treatment or both Target: int HbA1c<6.0% vs con HbA1c 7.0-7.9%	HbA1c	Stand: 7.5% vs Intens: 6.4% NT
				Nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes (PE)	Stand: 2.29% patients per year Intens: 2.11% patients per year HR=0.90 (95%CI: 0.78-1.04) NS: p=0.16
				Cv mortality	**Stand: 0.56%** patients per year **Intens: 0.79%** patients per year **HR=1.35 (95%CI: 1.04-1.76)** **SS: p=0.02** *NNH[5]=125 (treat 125 intensively for study duration to cause 1 extra CV death)*
				Mortality	**Stand: 1.14%** patients per year **Intens: 1.41%** patients per year **HR=1.22 (95%CI: 1.01-1.46)** **SS: p=0.04** *NNH[4]=95 (treat 95 intensively for mean 3.5y to cause 1 extra death)*
				Nonfatal myocardial infarction (SE) (% patients per year)	**Stand: 1.45% patients per year** **Intens: 1.11% patients per year** **HR=0.76 (95%CI: 0.62-0.92)** **SS: p=0.004 in favour of intensive treatment** *NNT[4]= 104 (treat 104 intensively for mean 3.5y to prevent 1 extra nonfatal MI*
				Adverse event (% per year)	Hypoglycemia requiring medical assistance **Stand: 1.0% episodes/y** **Intens: 3.1% episodes/y** **SS: P<0.001**

Ten years later, ACCORD (median diabetes duration 10 years, high cardiovascular risk, target HbA1c<6%) identified an increased risk for death associated with intensive glucose control and therefore decided to end this therapy group and switch all patients to standard glycemic therapy.

GRADE: see meta-analysis below

[5] Calculated by Farmaka, using 'crude' event rates (persons with an event) from original study

4.4.bis. Summary and conclusions. Intensive treatment (HbA1c <6.5%) vs conventional treatment (conventional target)

Intensive target HbA1c ≤6.5% vs conventional target (local guidelines) (ADVANCE collaborative group 2008)					
Ref	**Duration**	**Population**	**Therapy/Target**	**Results**	**Ref**
ADVANCE collaborative group	median 5.0y	n= 11140 median duration DM: 7.9y history of cardiovascular disease mean age: 66y	Gliclazide plus other drugs vs continuation of current treatment (substitute gliclazide with another sulfonylurea) Target: int HbA1c≤6.5% vs con ~local guidelines	HbA1c	**Stand: 7.3% vs Intens: 6.5%** **SS: p<0.001**
				Macrovascular and microvascular events (PE)	**Stand: 20.0% of patients** **Intens: 18.1% of patients** **HR=0.90 (95%CI: 0.82-0.98)** **SS: p=0.01** *NNT[6]=52 (treat 52 intensively for median 5y to prevent one extra macro or microvasc event)*
				Major microvascular events (PE)	**Stand: 10.9% of patients** **Intens: 9.4% of patients** **HR=0.86 (95%CI: 0.77-0.97)** **SS: p=0.01 in favour of intensive treatment** *NNT[5]= 70 (treat 70 for median 5.0y to prevent 1 extra microvasc event)*
				Cv mortality	Stand: 5.2% of patients Intens: 4.5% of patients HR=0.88 (95%CI: 0.74-1.04) NS: p=0.12
				Mortality	Stand: 9.6% vs Intens: 8.9% HR=0.93 (95%CI: 0.83-1.06) NS: p=0.28
				Adverse event	Severe hypoglycemia **Stand: 1.5% of patients** **Intens: 2.7% of patients** **HR=1.86 (95%CI: 1.42-2.40)** **P<0.001**

The ADVANCE-trial (median diabetes duration 8 years, cardiovascular risk patients, target HbA1c≤6.5%) reported a risk reduction on the primary endpoint macrovascular and microvascular events and on the secondary endpoint microvascular events but found no effect of intensive glucose control on major cardiovascular events.

GRADE: see meta-analysis below

[6] Calculated by Farmaka, using 'crude' event rates(persons with an event) from original study

4.5.bis. Summary and conclusions. Intensive treatment vs standard treatment (absolute reduction of 1.5% vs control)

Intensive target vs standard target (absolute reduction of 1.5% vs control) (VADT 2009)					
Ref	**Duration**	**Population**	**Therapy/Target**	**Results**	**Ref**
Duckworth 2009	median 5.6y	n= 1791 median duration of DM: 11.5y predominantly men (veterans) mean age: 60.4y 40% had cv event	Glimepiride or metformin, plus rosiglitazone, or insulin vs same treatment but other target Target: absolute reduction of 1.5% in HbA1c int compared to con	HbA1c	Stand: 8.4% vs Intens: 6.9% Goal achieved: absolute between-group difference of 1.5%
				Time to first major cardiovascular event° (PE)	HR=0.88 (95%CI: 0.74-1.05) NS: p=0.14
				Cv events (event rate)	Stand: 33.5% vs Intens: 29.5% RRR=11.9% NT
				Cv mortality (% of patients)	Stand: 3.7% vs Intens: 4.5% NS
				Mortality (% of patients)	Stand: 10.6% vs Intens: 11.4% HR=1.07 (95%CI: 0.81-1.42) NS: p=0.62
				Adverse event	**Stand: 383 episodes vs Intens: 1333 episodes/100 patient years** **SS: p<0.001**

Finally, VADT (median duration diabetes 11.5 years, veterans, target absolute between group-difference HbA1cs of 1.5%) concluded there was no significant difference in cardiovascular events, cardiovascular mortality or all-cause mortality between the two therapy groups.

GRADE: see meta-analysis below

4.6.bis. Summary and conclusions. Meta-analyses intensive treatment vs conventional treatment

Meta-analysis intensive vs conventional treatment (Kelly 2009: UKPDS 33, UKPDS 34, ACCORD, ADVANCE, VADT)						
N/n	**Duration**	**Population**	**Results**			
N=5, n=27802	Median: 6.9y	* Early trials (UKPDS 33 and 34): newly diagnosed DMII, mean age: 53y	Cardiovascular disease		RR=0.79 (95%CI: 0.57-1.09)	
			Coronary heart disease		RR=0.78 (95%CI: 0.59-1.04)	
			Stroke		RR=0.91 (95%CI:0.53-1.58)	
			Cardiovascular mortality		RR=0.75 (95%CI: 0.48-1.19)	
			Quality OK	Consistency OK	Directness -1 for indirect comparison	Imprecision -1 for wide CI
			Grade assessment: *low quality of evidence*			
			All-cause mortality		RR=0.83 (95%CI: 0.59-1.16)	
			Quality OK	Consistency OK	Directness -1	Imprecision -1
			Grade assessment: *low quality of evidence*			
			Severe hypoglycaemia		RR=1.37 (95%CI: 0.58-3.27)	
			Quality OK	Consistency OK	Directness OK	Imprecision -1
			Grade assessment: *moderate quality of evidence*			
		* Recent trials (ACCORD, ADVANCE, VADT): DMII during 10y, mean age: 63y	Cardiovascular disease		RR=0.94 (95%CI: 0.86-1.02)	
			Coronary heart disease		RR=0.91 (95%CI: 0.83-1.01)	
			Stroke		RR=0.97 (95%CI: 0.84-1.12)	
			Cardiovascular mortality		RR=1.13 (95%CI: 0.79-1.63)	
			Quality OK	Consistency -1	Directness OK	Imprecision OK
			Grade assessment: *moderate quality of evidence*			
			All-cause mortality		RR=1.08 (95%CI: 0.88-1.32)	
			Quality OK	Consistency -1	Directness OK	Imprecision OK
			Grade assessment: *moderate quality of evidence*			
			Severe hypoglycaemia		**RR=2.48 (95%CI: 1.78-3.47)**	
			Quality OK	Consistency OK	Directness OK	Imprecision OK
			Grade assessment:*high quality of evidence*			
		* All trials (UKPDS 33, UKPDS 34, ACCORD, ADVANCE, VADT)	Cardiovascular disease		**RR=0.90 (95%CI: 0.83-0.98)**	
			Coronary heart disease		**RR=0.89 (95%CI: 0.81-0.96)**	
			Stroke		RR=0.98 (95%CI:0.86-1.11)	
			Cardiovascular mortality		RR=0.97 (95%CI: 0.76-1.24)	
			Quality OK	Consistency -1	Directness -1 for non uniform targets	Imprecision OK
			Grade assessment: *low quality of evidence*			
			All-cause mortality		RR=0.98 (95%CI: 0.84-1.15)	
			Quality OK	Consistency -1	Directness -1	Imprecision OK
			Grade assessment: *low quality of evidence*			
			Severe hypoglycaemia		**RR=2.03 (95%CI: 1.46-2.81)**	

			Quality OK	Consistency OK	Directness -1	Imprecision OK
			Grade assessment: *moderate quality of evidence*			

Meta-analysis intensive vs conventional treatment (Hemmingsen 2011: UKPDS 33, UKPDS 34, ACCORD, ADVANCE, VADT and 15 other trials)						
N/n	**Duration**	**Population**	**Results**			
N=20 n= 29986	3d to 12.5y	Type 2 diabetes (newly diagnosed to 15y duration)	Non-fatal stroke	RR=0.96 (95%CI:0.8-1.16)		
			Non-fatal myocardial infarction	RR=0.87 (95%CI:0.76-1.00)		
			Cardiovascular mortality	RR=1.06 (95%CI:0.9-1.26)		
			Quality OK	Consistency OK	Directness -1 for non-uniform targets	Imprecision -1 *
			Grade assessment: *low quality of evidence*			
			All-cause mortality	RR=1.01 (95%CI:0.9-1.13)		
			Quality OK	Consistency OK	Directness -1	Imprecision -1 *
			Grade assessment: *low quality of evidence*			
			Severe hypoglycaemia	RR=2.05 (95%CI:1.39-3.02)		
			Quality OK	Consistency OK	Directness -1	Imprecision OK
			Grade assessment: *moderate quality of evidence*			

** A sensitivity analysis revealed that more data were needed (insufficient power)*

Conducting meta-analyses on the basis of the above trials is a delicate issue, because the study populations and targets are heterogeneous, as well as the manner in which the target is reached.

The meta-analysis of Kelly et al. (2009) that compared intensive treatment with conventional treatment, distinguishes between early (UKPDS) and new trials and finds no significant differences between treatments for any of the hard endpoints.

GRADE: *low quality of evidence for older trials*
Moderate quality of evidence for recent trials

When all trials are analysed together, the overall risk of cardiovascular events and risk of coronary heart disease is significantly decreased through intensive glucose control but this is not the case for all cause mortality or cardiovascular mortality.
A more recent meta-analysis (Hemmingsen 2011) had wider inclusion criteria and analyses data from 20 trials. No significant differences between intensive and conventional therapy were found for any of the hard endpoints.

GRADE: *low quality of evidence*

- Intensive glucose control was associated with a (more than) 2-fold increase in severe hypoglycemia.

GRADE: *moderate quality of evidence*

5. Evidence tables and conclusions:Type 2 diabetes: monotherapy

5.1. Monotherapy versus placebo/control

5.1.1. Metformin versus placebo/control

5.1.1.1. Hard endpoints: UKPDS34: Metformin versus conventional treatment (diet alone)

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
UKPDS 34 1998 Design: RCT (PG) open label Setting: 23 hospitals in UK	n= 753 Median age: 53y prior R: 3m diet DMII duration: newly diagnosed Mean baseline HbA1c: 7.2%* Mean FPG: 8.1 (7.1-9.7 mmol/l Mean BMI: 31.4 kg/m^2 <u>Inclusion</u> - FPG >6mmol/l on two mornings, 1-3w apart - obese (body weight >120% of ideal) - No symptoms of hyperglycemia <u>Exclusion</u> - Ketonuria >3mmol/l - Serum creatinine >175µmol/l - Myocardial infarction in previous year - Current angina or heart failure - >1 vascular event - Retinopathy requiring laser treatment - Malignant hypertension - Uncorrected endocrine disorder - Occupation that precluded insulin therapy - Severe concurrent illness	median 10.7y	<u>Int</u>ensive treatment (metformin 1700-2550mg/d) target: FPG <6mmol/l vs <u>con</u>ventional treatment (diet alone°) target: FPG <15mmol/l	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING: 0/2 ○ ATTRITION: 1/1 - FU: 96% - ITT: yes - Sponsor: NHS (UK)
				Any diabetes-related endpoint*(PE) (events/1000patient years)	Int: 29.8 vs con: 43.3 RR=0.68 (95%CI: 0.53-0.87) **SS, p=0.0023 in favour of int** *NNT: 10 (treat 10 patients for median 10.7y to prevent 1 extra patient having an event)*	
				Diabetes-related death (PE) (events/1000py)	Int: 7.5 vs con: 12.7 RR=0.58 (95%CI: 0.37-0.91) **SS, p=0.017 in favour of int** *NNT=19 (treat 19 patients for median 10.7y to prevent 1 extra death from diabetes)*	
				All-cause mortality (PE) (events/1000py)	Int: 13.5 vs con: 20.6 RR=0.64 (95%CI: 0.45-0.91) **SS, p=0.011 in favour of int** *NNT=14 (treat 14 patients for median 10.7y to prevent 1 extra death)*	
				Myocardial infarction (events/1000py)	Int: 11.0 vs con: 18.0 RR=0.61 (95%CI: 0.41-0.89) **SS, p=0.01 in favour of int** *NNT=16 (treat 16 for median 10.7y to avoid 1 extra MI*)	
				Stroke (events/1000py)	Int: 3.3 vs con: 5.5 RR=0.59 (95%CI: 0.29-1.18) NS: p=0.13	
				Amputation or death from PVD (events/1000py)	Int: 1.6 vs con: 2.1 RR=0.74 (95%CI: 0.26-2.09) NS: p=0.57	
				Microvascular disease (events/1000py)	Int: 6.7 vs con: 9.2 RR=0.71 (95%CI: 0.43-1.19) NS: p=0.19	
				HbA1c over 10y	Int: 7.% vs con: 8.0 % (median) NT	
				Harms		
				Weight gain at 10y	Similar in both groups: NT	
				Major hypoglycemic episodes/y	Int: 0 vs con: 0.7 : NT	

° in the conventional group, the aim was best achievable FPG with diet alone; drugs were added only if there were hyperglycemic symptoms or FPG>15mmol/l
In the intensive group, the aim was FPG<6mmol/l

* Any diabetes-related endpoint = sudden death, death from hypo/hyperglycemia, myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness, cataract extraction

**Microvascular complications (retinopathy requiring photocoagulation, vitreous haemorrhage, and or fatal or non-fatal renal failure).most ofmicrovascular complications were due to fewer cases of retinal photocoagulation

NNT reported from ACP journal club, 199 jan-feb; 130:3. NNT based on number of patients with clinical endpoint.

5.1.1.1.bis. Summary and conclusions. Hard endpoints: UKPDS34: Metformin versus conventional treatment (diet alone)

Metformin vs diet (UKPDS 34)					
Ref	**Duration**	**Population**	**Therapy/Target**	**Results**	**Ref**
UKPDS 34	median 10.7y	n= 753 newly diagnosed diabetes type 2 median age: 53y	Metformin vs diet Target: int FPG<6mmol/l vs con FPG<15mmol/l	HbA1c	Int: 7.4% vs con: 8.0% NT
				Any DM-related endpoint (macrovascular and microvascular) (PE)	**Int: 29.8 events/1000py** **Con: 43.3 events/1000py** **RR=0.68 (95%CI: 0.53-0.87)** **SS, p=0.0023** *NNT[7]: 10 (treat 10 patients for median 10.7y to prevent 1 extra patient having an event)*
				Diabetes-related death (PE)	**Int: 7.5 events/1000py** **Con: 12.7 events/1000py** **RR=0.58 (CI: 0.37-0.91)** **SS, p=0.017 in favour of int** *NNT[3]=19 (treat 19 patients for median 10.7y to prevent 1 extra death from diabetes)*
				Mortality(PE)	**Int: 13.5 events/1000py** **Con: 20.6 events/1000py** **RR=0.64 (95%CI: 0.45-0.91)** **SS, p=0.011** **NNT=14***NNT[3]=14 (treat 14 patients for median 10.7y to prevent 1 extra death)*
				myocardial infarction	**Int: 11.0 events/1000py** **Con: 18.0 events/1000py** **RR=0.61 (95%CI: 0.41-0.89)** **SS, p=0.01** *NNT[3]=16 (treat 16 for median 10.7y to avoid 1 extra MI)*
				Stroke	Int: 3.3 events/1000py Con: 5.5 events/1000py RR=0.59 (95%CI: 0.29-1.18) NS: p=0.13
				Microvascular disease	Int: 6.7 vs con: 9.2 RR=0.71 (95%CI: 0.43-1.19) NS: p=0.19
				Adverse event	Major hypoglycemic episodes Int: 0% vs con: 0.7% per year NT

Quality	Consistency	Directness	Imprecision
-1 for low jadad, composite EP, (directness)	NA	OK	OK
Grade assessment: moderate quality of evidence			

UKPDS 34 (newly diagnosed type 2 diabetes, obese patients, metformin vs diet) also reported a significant risk reduction on this primary endpoint (any diabetes related endpoint) and on hard endpoints as myocardial infarction and mortality.

[7] NNT as reported by ACP journal club (calculated with 'crude' event rates (persons with an event) from original study). ACP Journal Club. 1999 Jan-Feb; 130:3.

5.1.2. Sulphonylurea versus placebo/control

No trials met our inclusion criteria.

5.1.2.1. Hard endpoints: UKPDS33: Sulphonylurea or insulin vs conventional treatment (diet alone)

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
UKPDS 33 1998 Design: RCT (PG) open label Setting: 23 hospitals in UK	n= 3867 prior R: 3m diet DMII duration: newly diagnosed Mean baseline HbA1c: 7.1% Mean FPG: 6.1-15.0 mmol/l Mean BMI: 27.2 kg/m^2 <u>Inclusion</u> - FPG >6mmol/l on two mornings, 1-3w apart - Non-obese (body weight <120% of ideal) - No symptoms of hyperglycemia Median age: 54y Mean FPG: 6.1-15.0 <u>Exclusion</u> - Ketonuria >3mmol/l - Serum creatinine >175µmol/l - Myocardial infarction in previous year - Current angina or heart failure - >1 vascular event - Retinopathy requiring laser treatment - Malignant hypertension - Uncorrected endocrine disorder - Occupation that precluded insulin therapy - Severe concurrent illness	median 10.0y	<u>Int</u>ensive treatment (sulfonylurea or insulin) target: FPG <6mmol/l vs <u>con</u>ventional treatment (diet alone°) target: FPG <15mmol/l	Efficacy		- Jadad score o RANDO: 1/2 o BLINDING: 0/2 o ATTRITION: 1/1 - FU: 96% - ITT: yes - Sponsor: NHS (UK)
				Any diabetes-related endpoint* (PE) (per 1000person years)	Int: 40.9 vs con: 46.0 RR=0.88 (95%CI: 0.79-0.99) **SS, p=0.029 in favour of int group** **NNT=19.6 (treat 19.6 for 10 y patients to prevent one patient developing any of these events)**	
				Diabetes-related death (per 1000person years)	Int: 10.4vs con: 11.8 RR=0.90 NS, p=0.34	
				All-cause mortality (per 1000person years)	Int: 17.9vs con: 18.9 RR=0.94 (95%CI: 0.80-1.10) NS: p=0.44	
				Myocardial infarction (per 1000person years)	Int: 14.7 vs con: 17.4 RR=0.84 (95%CI: 0.71-1.00) NS: p=0.052	
				Stroke (per 1000person years)	Int: 5.6 vs con: 5.0 RR=1.11 (95%CI: 0.81-1.51) NS: p=0.52	
				Amutation or death from PVD (per 1000person years)	Int: 1.1 vs con: 1.6 RR=0.65 (95%CI: 0.36-1.18) NS: p=0.15	
				Microvascular disease** (per 1000person years)	Int: 8.6 vs con: 11.4 RR=0.75 (95%CI: 0.60-0.93) **SS, p=0.0099 in favour of int group** *NNT=42 (treat 42 for median 10y to prevent microvasc disease in 1 extra patient)*	
				HbA1c over 10y (median)	Int: 7.0% (95%CI: 6.2-8.2) vs con: 7.9% (95%CI: 6.9-8.8) p<0.001 **SS in favour of intensive treatment** (sulfonylurea or insulin)	

				Harms		
				Weight gain at 10y	Mean: 3.1kg higher in int group compared to con group **SS: p<0.0001 in favour of con group**	
				Major hypoglycemic episodes/y	Con vs int: 0.7% vs +/- 1.4% **SS: p<0.0001 in favour of con group**	

° in the conventional group, the aim was best achievable FPG with diet alone; drugs were added only if there were hyperglycemic symptoms or FPG>15mmol/l
In the intensive group, the aim was FPG<6mmol/l

* Any diabetes-related endpoint = sudden death, death from hypo/hyperglycemia, myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness, cataract extraction

**Microvascular complications (retinopathy requiring photocoagulation, vitreous haemorrhage, and or fatal or non-fatal renal failure).most ofmicrovascular complications were due to fewer cases of retinal photocoagulation

5.1.2.1.bis. Summary and conclusions. Hard endpoints: UKPDS33: Sulphonylurea or insulin vs conventional treatment (diet alone)

Sulphonylurea or insulin vs diet (UKPDS33)					
Ref	**Duration**	**Population**	**Therapy/Target**	**Results**	
UKPDS 33	median 10.0y	n= 3867 newly diagnosed type 2 diabetes median age: 54y	Sulfonylurea or insulin(intensive) vs diet (conventional) Target: int FPG<6mmol/l vs con FPG<15mmol/l	HbA1c	**Int: 7.0% (95%CI: 6.2-8.2)** **Con: 7.9% (95%CI: 6.9-8.8)** **p<0.001**
				Any DM-related endpoint (macrovascular and microvascular)(PE)	**Int: 40.9 events/1000py** **Con: 46.0 events/1000py** **RR=0.88 (95%CI: 0.79-0.99)** **SS, p=0.029** **NNT[8]=19.6 (treat 19.6 patients for 10y to prevent one patient developing any of these events)**
				Diabetes-related death (PE)	Int: 10.4 events/1000py Con: 11.8 events/1000py RR=0.90 NS, p=0.34
				Mortality(PE)	Int: 17.9 events/1000py Con: 18.9 events/1000py RR=0.94 (95%CI: 0.80-1.10) NS: p=0.44
				Myocardial infarction	Int: 14.7 events/1000py Con: 17.4 events/1000py RR=0.84 (95%CI: 0.71-1.00) NS: p=0.052
				Stroke	Int: 5.6 events/1000py Con: 5.0 events/1000py RR=1.11 (95%CI: 0.81-1.51) NS: p=0.52
				Microvascular disease	**Int: 8.6 events/1000py** **Con: 11.4 events/1000py** **RR=0.75 (95%CI: 0.60-0.93)** **SS, p=0.0099** *NNT[9]= 42 (treat 42 for median 10y to prevent 1 extra event)*
				Adverse event Major hypoglycemic episodes	**Con: 0.7% per year** **Int: +/- 1.4% per year** **SS: p<0.0001**

Quality	Consistency	Directness	Imprecision
-1 for low jadad, composite EP, (directness)	NA	OK	OK
Grade assessment: moderate quality of evidence			

UKPDS 33 (newly diagnosed type 2 diabetes, non-obese patients, comparison sulphonylurea or insulin vs diet) found a statistically significant risk reduction in any diabetes-related endpoint (primary endpoint: macrovascular and microvascular events) and in microvascular diseases with intensive therapy (FPG below 6mmol/l) versus conventional therapy.

[8] As reported in the original study

[9] Calculated by Farmaka, using 'crude' event rates (persons with an event) from original study

5.1.3. Repaglinide versus placebo

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Jovanovic 2000 Design: DB RCT (PG) Setting: medical centers	n=361 mean age: 58y Prior R: OHA naive 26%; sulfonylurea 61% Combination 13% Other 4% DMII duration: Mean 6.6y Baseline HbA1c: mean 8.7% <u>Inclusion</u> 40-75y; DM at least 6 months; using OHA or diet and exercise program; if no OHA (naive) HbA1c >6.5%; if OHA HbA1c<12%; if previous OHA FPG had to increase by at least 25mg/dL in the 2 weeks following discontinuation of previous treatment <u>Exclusion</u> History of chronic insulin treatment; severe uncontrolled hypertension, cardiac disorders; elevated serum creatinine or liver transaminase level; previous exposure to repaglinide; concurrent therapy with systemic corticosteroids	24w	Repaglinide 1mg vs repaglinide 4mg vs placebo 2w wash-out period	Efficacy		- Jadad score o RANDO: 1/2 o BLINDING: 2/2 o ATTRITION: 1/1 - FU: repa 1mg 77% repa 4mg 69% placebo 40% - ITT: yes (LOCF) - Other important methodological remarks: - Randomisation described as 'in blocks of five', not specified - **High dropout rate in placebo group (60%!)** => median duration of exposure to study medication was significantly less in placebo group (92d) than in repaglinide groups (169d) - Multicenter: 20 centers in the US - Sponsor: Novo Nordisk Pharmaceuticals
				Change in FPG (baseline-24w)	Repaglinide 1mg: -47mg/dL Repaglinide 4mg: -49 mg/dL Placebo: +19mg/dL Difference and CI: NR **SS vs placebo**, p<0.001	
				Mean HbA1c at 24w	Repaglinide 1mg: 8.2% Repaglinide 4mg: 8.2% Placebo: 10% **SS vs placebo**, p<0.001	
				Patients with HbA1c<8% at 24w	Repaglinide 1mg: 50.4% Repaglinide 4mg: 52.3% Placebo: approx. 20% (figure) TNR	
				Patients with HbA1c<7% at 24w	Repaglinide 1mg: 31.8% Repaglinide 4mg: 32.3% Placebo: approx. 3% (figure) TNR	
				Safety		
				Patients with cardiovascular AE (chest pain, heart murmur, hypertension, ECG abnormalities, edema)	Repaglinide 1mg: 9% Repaglinide 4mg: 14% Placebo: 8% Repa 1mg vs pla NS, p=0.807 Repa 4mg vs pla NS, p=0.273	
				Patients with hypoglycemic events	Repaglinide 1mg: 27% Repaglinide 4mg: 35% Placebo: 11%	
				Patients with confirmed hypoglycemic symptoms (blood glucose <45mg/dL	Repaglinide 1mg: 0 Repaglinide 4mg: 2 Placebo: 0	
				Patients with myocardial infarction	Repaglinide 1 mg:1 Repaglinide 4mg: 1 Placebo: 0	

5.1.3.bis. Summary and conclusions: Repaglinide versus placebo

<table>
<tr><td colspan="6">Repaglinide 1-4mg/d vs placebo (Jovanovic 2000)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="6">N=1
n=
361</td><td rowspan="6">24w</td><td rowspan="6">Inadequately controlled type 2 diabetes (baseline HbA1c: 8.7%)

Using OAD (65%) or diet and exercise (26%)

Main exclusion: cardiac disorders, elevated serum creatinine or transaminase levels</td><td>Mean HbA1c at 24w</td><td colspan="3">Repaglinide 1mg: 8.2%
Repaglinide 4mg: 8.2%
Placebo: 10.0%
P<0.001, SS vs placebo</td></tr>
<tr><td><u>Quality</u>
-1 high drop-out rate</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td>Cardio-vascular AE
(% patients)</td><td colspan="3">Repaglinide 1mg: 9%
Repaglinide 4mg: 14%
Placebo: 8%
NS vs placebo (p=0.807 for repa 1mg vs pla, p=0.273 for repa 4mg vs pla)</td></tr>
<tr><td><u>Quality</u>
-1 high drop-out rate</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
-1 for short duration</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="2">Hypoglycaemic events
(% patients)</td><td colspan="3">Repaglinide 1mg: 27%
Repaglinide 4mg: 35%
Placebo: 11%
NT</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
</table>

- Patients having inadequately controlled type 2 diabetes received daily treatment with placebo, repaglinide 1mg or repaglinide 4mg. After 24 weeks, active treatments decreased the mean HbA1c significantly in comparison to placebo treatment.

GRADE: moderate quality of evidence

- No significant difference in cardiovascular adverse events was observed between repaglinide and placebo.

GRADE: low quality of evidence

- The number of patients with hypoglycemic events was not statistically tested. Change in body weight between treatment groups was not reported in this study.

GRADE: NA

5.1.4. Pioglitazone versus placebo

This comparison was not included in our literature search.

5.1.5. Linagliptin versus placebo

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Del Prato 2011 Design: DB RCT (PG) Setting: "Centres"	n= 503 mean age: 55y Prior R: NR DMII duration: NR Baseline HbA1c: NR <u>Inclusion</u> 18-80y; BMI<=40; treatment naive or previously received one OAD; HbA1c 7-10% <u>Exclusion</u> Myocardial infarction; stroke; TIA; impaired hepatic function; receiving rosiglitazone, pioglitazone, GLP-1 analogues, insulin or anti-obesity drugs; systemic steroids	24w	Linagliptin 5mg Vs Placebo Placebo run-in period of 2 weeks	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING:1/2 ○ ATTRITION: 1/1 - FU: 99% - ITT: yes, LOCF - Multicenter: 66 centres, 11 countries - Sponsor: Boehringer Ingelheim
				Change in HbA1c (PE)	Linagliptin: -0.44 Placebo: +0.25 **Mean diff= -0.69% (-0.85, -0.53)** P<0.0001 SS	
				% of patients that attained HbA1c <7%	Linagliptin 25.2% Placebo 11.6% **OR =2.9, p=0.0006** **SS**	
				Safety		
				Change in body weight	'NS' (no data reported)	
				% of patients with serious AE	Linagliptin: 3.0% Placebo:4.2% TNR	
				hypoglycaemia	Linagliptin: 0.3% Placebo: 0.6% TNR	

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
F123 Haak 2012 Design: RCT (DB) (PG) Setting: phase III clinical trial	n= 791 mean age: 55.3y Prior R: 47.5% treatment-naïve DMII duration: 37.4% had <1y DMII, 36.9% had DMII for 1-5y, 25.7% had DMII >5y Baseline HbA1c: mean 8.7% <u>Inclusion</u> - Type 2 diabetes - Aged 18-80y - BMI≤40 - Treatment-naïve or max. 1 OAD - HbA1c≥7%-≤10.5% for patients undergoing washout of previous OAD, HbA1c≥7%-<11% for treatment-naïve patients <u>Exclusion</u> - Previous treatment with rosiglitazone, GLP-1 a, insulin or anti-obesity drugs in previous 3m - Systemic steroids or change in dosage of thyroid hormones in previous 6w; Undergone gastric bypass - Myocardial infarction, stroke or TIA in previous 6m; Unstable or acute congestive heart failure - Renal failure or impairment - Impaired hepatic function - Known hypersensitivity or allergy to linagliptin, metformin or placebo - History of alcohol or drug abuse in previous 3m; Acute or chronic metabolic acidosis	24w	Linagliptin 5mg/d Vs Placebo 6 treatment arms	Efficacy		- Jadad score o RANDO: 1/2 o BLINDING: 1/2 o ATTRITION: 1/1 - FU: 791 patients were randomised for entire trial, 687 (87%) patients completed treatment period - ITT: full analysis set - Other important methodological remarks: °There are six treatment arms in the original study but in this report we only consider linagliptin versus placebo. °Rescue therapy was permitted for patients whose glycemia was not adequately controlled during the study. - Multicenter: 133 centers in 14 countries - Sponsor: Boehringer Ingelheim
				Change from baseline in HbA1c (PE)	lina -0.5% vs pla +0.1% difference: 0.6% (95% CI: -0.9% to -0.3%) p<0.0001, **SS in favour of linagliptin**	
				Change from baseline in FPG (SE)	lina -0.5mmol/l vs pla +0.6mmol/l difference: 1.0mmol/l (95% CI: -1.7 to -0.3) p<0.0001, **SS in favour of linagliptin**	
				Safety		
				Change from baseline in body weight	"No clinically meaningful change in body weight was noted in any of the treatment groups."	
				Any adverse event	lina 56.3% vs pla 54.2% NT	
				Hypoglycemic events	lina 0% vs pla 1.4% NT	
				Gastrointestinal AEs	lina 12.0% vs pla 13.9% NT	
				Infection and infestation AEs	lina 18.3% vs pla 22.2% NT	
				Nervous system AEs	lina 7.7% vs pla 4.2% NT	

5.1.5.bis. Summary and conclusions: linagliptin versus placebo

<table>
<tr><td colspan="6">Linagliptin 5 mg/d vs placebo (Haak 2012, Delprato 2011)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td>Results</td><td colspan="3"></td></tr>
<tr><td rowspan="6">N=2,
n= 717</td><td rowspan="6">Mean:
24w</td><td rowspan="6">- Type 2 diabetes
- Aged 18-80y
- BMI≤40
- Treatment-naïve or max. 1 OAD
- HbA1c≥7%-≤10à11%</td><td rowspan="2">Change in HbA1c (PE)</td><td colspan="3">Reported in 1/2 studies:
Mean between-groups difference= 0.60 à 0.69%
P<0.0001, SS in favour of linagliptin</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: high quality of evidence</td></tr>
<tr><td>Change in body weight (safety)</td><td colspan="4">NR</td></tr>
<tr><td>Any AE</td><td colspan="4">Reported in 1/2 studies:
linagliptin 56.3% vs placebo 54.2%
NT</td></tr>
<tr><td>Serious AE</td><td colspan="4">Reported in 1/2 studies:
linagliptin 3% vs placebo 4.2%
NT</td></tr>
<tr><td>Hypoglycemia</td><td colspan="4">linagliptin 0-0.3% vs placebo 0.6-1.4%
NT</td></tr>
<tr><td></td><td></td><td></td><td></td><td colspan="4">Grade assessment: NA</td></tr>
</table>

- Linagliptin 5mg qd was studied in two placebo-controlled trials. These trials are similar in design, population and duration. Change in HbA1c from baseline to end of study is the primary endpoint and proved to be significantly greater in favour of the active treatment.

GRADE: high quality of evidence

- Increase or decrease in body weight is not reported in these trials. However, the authors do not note any difference in treatment groups regarding this safety endpoint. No statistical test was mentioned.

GRADE: NA

The number of adverse events is small in both groups, though no adverse event is statistically tested.

5.1.6. Saxagliptin versus placebo

Ref	n/Population	Duration	Comparison	Outcomes			Methodological
Rosenstock 2009 Design: RCT (DB) (PG) Setting: phase III clinical trial	n= 403 mean age: 53.5y mostly white patients Prior R: diet and exercise DMII duration: mean 2.6y (median: 1.3y) Baseline HbA1c: mean 7.9% Baseline FPG: mean 175mg/dl (9.7mmol/l) Baseline body weight: 89.5kg mean Baseline BMI mean: 32 <u>Inclusion</u> - Type 2 diabetes - Age: 18-77y - Treatment naïve for diabetes (only diet and exercise) - HbA1c≥7% - Fasting C-peptide≥1ng/ml - BMI≤40 All inclusion criteria must be met to be eligible <u>Exclusion</u> - Symptoms of poorly controlled DMII - Diabetic ketoacidosis or hyperosmolar nonketotic coma - Cardiovascular event within 6m - Congestive heart failure or left ventricular ejection fraction	24w	saxa 2.5mg/d Vs saxa 5mg/d Vs saxa 10mg/d Vs placebo	Efficacy			- Jadad score ○ RANDO: 1/2 ○ BLINDING: 1/2 ○ ATTRITION: 1/1 - FU: 66% - ITT: randomised patients who received at least 1 dose of study medication and who had a baseline and at least 1 post-baseline measurement - Other important methodological remarks: in case of lack of adequate glucose control*, OL metformin was added as rescue therapy; efficacy and safety measurements obtained after rescue were not included in analyses - Multicenter: yes, in Mexico and USA - Sponsor: Bristol-Myers Squibb and AstraZeneca
				Change from baseline in HbA1c, mean (PE)	saxa 2.5 vs pla	-0.43% vs +0.19% P<0.0001 **SS in favour of saxagliptin**	
					saxa 5 vs pla	-0.46% vs +0.19% P<0.0001 **SS in favour of saxagliptin**	
					saxa 10 vs pla	-0.54% vs +0.19% P<0.0001 **SS in favour of saxagliptin**	
				Change from baseline in FPG, mean (SE)	saxa 2.5 vs pla	-15mg/dl vs +6mg/dl P=0.0002 **SS in favour of saxagliptin**	
					saxa 5 vs pla	-9mg/dl vs +6mg/dl P=0.0074 **SS in favour of saxagliptin**	
					saxa 10 vs pla	-17mg/dl vs +6mg/dl P<0.0001 **SS in favour of saxagliptin**	
				Change from baseline in body weight, mean	saxa 2.5 vs pla	-1.2kg vs -1.4kg NT	
					saxa 5 vs pla	-0.1kg vs -1.4kg NT	
					saxa 10 vs pla	-0.1kg vs -1.4kg NT	
				Safety			
				At least one adverse event		saxa 75.5% vs placebo 71.6% NT	
				Upper respiratory tract AE		saxa 8.8% vs placebo 11.6% NT	
				Headache		saxa 8.2% vs placebo 7.4% NT	

	≤40% - Renal, liver or psychiatric history - Alcohol or drug abuse in previous year - Immunocompromised - Clinically significant abnormalities in hepatic, renal, endocrine, metabolic or hematologic function			Urinary tract AE	saxa 6.9% vs placebo 4.2% NT	
				Nasopharyngitis	saxa 5.9% vs placebo 6.3% NT	
				Sinusitis	saxa 5.6% vs placebo 3.2% NT	
				Hypoglycemic events	saxa 5.2% vs placebo 6.3% NT	

*Glycemic rescue criteria:
FPG>240mg/dl (13.3mmol/l) at weeks 4 and 6, FPG>220mg/dl (12.2mmol/l) at week 8 or FPG>200mg/dl (11.1mmol/l) at weeks 12, 16, 20 and 24.

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Pan 2012 Design: DB RCT (PG) Setting: "centres"	n= 568 mean age: 51.4y Asian patients Prior R: drug-naive DMII duration: mean 1y Baseline HbA1c: 8.2% <u>Inclusion</u> ≥18y; drug-naive; HbA1c 7-10% <u>Exclusion</u> DMI; heart failure or recent CV history; unstable or rapidly progressing renal disease; GI surgery; …	24w	Saxagliptin 5mg Vs Placebo	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING: 2/2 ○ ATTRITION: 1/1 - FU: 90% - ITT: yes, LOCF - Multicenter: 40 centers, 4 countries (China, India, Philippines, South Korea) - Sponsor: AstraZenica & Bristol-Myers Squibb
				Change in HbA1c (PE)	Saxagliptin: -0.84% Placebo:- 0.34% **mean diff= -0.50% (-0.65, -0.34)** **SS, p<0.0001**	
				Weight reduction	Saxagliptin: -0.32 kg Placebo: -1.14 kg TNR	
				Safety		
				Myocardial infarction	Saxagliptin: n=1; placebo n=0 TNR	
				Serious adverse events	Saxa 8.1%; placebo 3.9%; TNR	
				Pancreatitis	None	
				Deaths	Saxa n=1; placebo n=0	
				Hypoglycaemic event	Saxa 1.8%; placebo 0.7% TNR "few patients (<=4 for each AE) experienced lymphopenia, thrombocytopenia, skin disorders, localized oedema, hypersensitivity, fractures or CV adverse events"	

5.1.6.bis. Summary and conclusions. Saxagliptin versus placebo

<table>
<tr><td colspan="6">Saxagliptin 2.5-5-10mg/d vs placebo (Rosenstock 2009, Pan 2012)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="13">N=2,
n= 971</td><td rowspan="13">24w</td><td rowspan="13">- Type 2 diabetes
- Age ≥18y
- Treatment naïve for diabetes (only diet and exercise)
- HbA1c≥7%

- Asians (1 study)
- Americans + Mexicans (1 study)</td><td rowspan="6">Change in HbA1c (PE)</td><td colspan="2">saxa 2.5mg vs placebo</td><td>-0.43% vs +0.19%
P<0.0001
SS in favour of saxagliptin</td></tr>
<tr><td colspan="2">saxa 10mg vs placebo</td><td>-0.54% vs +0.19%
P<0.0001
SS in favour of saxagliptin</td></tr>
<tr><td><u>Quality</u>
-1
large number of drop-outs</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="3">Grade assessment: moderate quality of evidence</td></tr>
<tr><td colspan="2">saxa 5mg vs placebo</td><td>Reported in 1/2 studies
Difference: 0.50-0.65%
P<0.0001
SS in favour of saxagliptin</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="3">Grade assessment: high quality of evidence</td></tr>
<tr><td rowspan="5">Change in body weight</td><td colspan="2">saxa 2.5mg vs placebo</td><td>-1.2kg vs -1.4kg
NT</td></tr>
<tr><td colspan="2">saxa 10mg vs placebo</td><td>-0.1kg vs -1.4kg
NT</td></tr>
<tr><td colspan="3">Grade assessment: NA</td></tr>
<tr><td colspan="2">saxa 5mg vs placebo</td><td>Reported in 1/2 studies:
-0.1kg vs -1.4kg in one study,
-0.32kg vs -1.14kg in other study
NT</td></tr>
<tr><td colspan="3">Grade assessment: NA</td></tr>
<tr><td rowspan="2">Hypoglycemic events</td><td colspan="3">Reported in 2/2 studies:
saxa 5.6% vs placebo 3.2% in one study,
saxa 1.8% vs placebo 0.7% in other study
NT</td></tr>
<tr><td colspan="3">Grade assessment: NA</td></tr>
</table>

- Two studies compared saxagliptin to placebo. A Mexican-American study examined different doses of saxagliptin: 2.5mg, 5mg or 10 mg daily, while an Asian study only investigated the 5mg/d dose. All participants were treatment-naïve patients with type 2 diabetes inadequately controlled with diet and exercise.
All doses of saxagliptin led to statistically significant reductions in HbA1c versus placebo.

GRADE: moderate quality of evidence (2.5mg and 10mg daily doses)
GRADE: high quality of evidence (5mg/d dose)

Weight change was reported but not statistically tested.

GRADE: NA

- Hypoglycemic events were reported not statistically tested.

GRADE: NA

5.1.7. Sitagliptin versus placebo

Ref	N/n	Comparison	Outcomes	
Richter 2009* Part of MA Design: meta-analysis (MA) Search date: 30 Jan 2008	N= 6 n= 1714	Sitagliptin vs placebo	Change in HbA1c from baseline to endpoint	Mean difference: -0.75 (95% CI: -0.86 to -0.63) **SS in favour of sitagliptin**
	N= 3 n= 1109	Sitagliptin vs placebo	Change in body weight from baseline to endpoint	Mean difference: 0.69 (95% CI: 0.32 to 1.06) **SS in favour of placebo**
			Adverse events: all-cause infections (data from 8 studies, 3589 participants, sitagliptin vs placebo or sitagliptin vs another single hypoglycaemic agent)	Risk ratio: 1.29 (95% CI: 1.09-1.52) **SS in favour of control**

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Aschner 2006	741	Inadequately controlled type 2 diabetes On and not on OAD main exclusion - Unstable cardiac disease - Creat clear <50ml/min - Elevated liver enzymes	24w	sita 100 or 200mg/d vs pla	- Jadad score: 3/5 - completed: 639 (86%) - ITT: no, all-patients-treated population
Goldstein 2007	1091	Inadequately controlled type 2 diabetes On and not on OAD main exclusion - Unstable cardiac disease - Creat clear <60ml/min - Elevated liver enzymes	24w	sita 100mg/d vs pla	- Jadad score: 2/5 - completed: 906 (83%) - ITT: no, all-patients-treated population
Hanefeld 2007	555	Inadequately controlled type 2 diabetes On and not on OAD main exclusion - Unstable cardiac disease - Elevated liver enzymes	12w	sita 25 or 50 or 100mg/d vs pla	- Jadad score: 2/5 - completed: 472 (85%) - ITT: no, all-patients-treated population
Nonaka 2008	152	Inadequately controlled type 2 diabetes On and not on OAD main exclusion - Unstable cardiac disease - Serum creat >1.2-1.3mg/dl - Elevated liver enzymes	12w	sita 100mg/d vs pla	- Jadad score: 4/5 - completed: 140 (92%) - ITT: no, all-patients-treated population
Raz 2006	521	Inadequately controlled type 2 diabetes On and not on OAD main exclusion - Unstable cardiac disease - Significant renal disease - Elevated liver enzymes, significant hepatic disease	18w	sita 100 or 200mg/d vs pla	- Jadad score: 2/5 - completed: 463 (89%) - ITT: no, all-patients-treated population
Scott 2007a	743	Inadequately controlled type 2 diabetes On and not on OAD main exclusion - Unstable cardiac disease - Creat clear <60ml/min - Elevated liver enzymes, active liver disease	12w	sita 10 or 25 or 50 or 100mg/d vs pla	- Jadad score: 2/5 - completed: 651 (88%) - ITT: no, all-patients-treated population

5.1.7.bis. Summary and conclusions: Sitagliptin versus placebo

<table>
<tr><td colspan="6">Sitagliptin 10-200mg/d vs placebo (Richter 2009)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td>Results</td><td colspan="3"></td></tr>
<tr><td rowspan="9">6/1714</td><td rowspan="9">12-24w</td><td rowspan="9">Inadequately controlled type 2 diabetes

On and not on OAD

Main exclusion criteria: unstable cardiac disease, creat clear <50ml/min, elevated liver enzymes</td><td rowspan="3">Change in HbA1c (baseline-endpoint)</td><td colspan="3">Mean difference: -0.75 (95% CI: -0.86 to -0.63)
SS in favour of sitagliptin</td></tr>
<tr><td><u>Quality</u>
-1 low
Jadad</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Change in weight (baseline-endpoint)</td><td colspan="3">Mean difference: 0.69 (95% CI: 0.32 to 1.06)
SS in favour of placebo</td></tr>
<tr><td><u>Quality</u>
-1 low
Jadad</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">AE: all-cause infections (sitagliptin vs placebo or sitagliptin vs another single hypoglycaemic agent)</td><td colspan="3">Risk ratio: 1.29 (95% CI: 1.09-1.52)
SS in favour of control</td></tr>
<tr><td><u>Quality</u>
-1 low
Jadad</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
-1 not reported separately for sita vs pla</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
</table>

-Sitagliptin at different doses (10-200mg qd) was compared to placebo amongst others in a Cochrane review. All included studies had participants with inadequately controlled type 2 diabetes who were either on or not on oral therapy with antidiabetics. Patients with unstable cardiac disease or dysfunction of liver or kidneys were excluded from all trials.

- Sitagliptin in comparison with placebo resulted in a statistically significant HbA1c reduction of approximately 0.7%.

GRADE: *moderate quality of evidence*

- Sitagliptin therapy did not result in weight gain but weight loss was significantly more pronounced following placebo interventions.

GRADE: *moderate quality of evidence*

- All-cause infections increased significantly after sitagliptin treatment compared with either placebo or another single hypoglycemic agent. Data on comparisons with placebo alone on adverse events are not reported.

GRADE: *low quality of evidence*

5.1.8. Vildagliptin versus placebo

Ref	N/n	Comparison	Outcomes	
SIGN278 Richter 2009* Part of MA Design: meta-analysis (MA) Search date: 30 Jan 2008	N= 6 n= 1139	Vildagliptin vs placebo	Change in HbA1c from baseline to endpoint	Mean difference: -0.32 (95% CI: -0.34 to -0.30) **SS in favour of vildagliptin**
	N= 3 n= 484	Vildagliptin vs placebo	Change in body weight from baseline to endpoint	Mean difference: 0.76 (95% CI: 0.19 to 1.32) **SS in favour of placebo**
			Adverse events: all-cause infections (data from 10 studies, 3573 participants, vildagliptin vs placebo or vildagliptin vs another single hypoglycaemic agent)	Risk ratio: 1.04 (95% CI: 0.87-1.24) NS

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR)
Dejager 2007	632	Inadequately controlled type 2 diabetes Drug-naive patients Main exclusion - Ischaemic heart disease - Heart failure NYHA III-IV - Serum creat >2.5mg/dl - Liver disease or elevated liver enzymes	24w	vilda 50 or 100mg/d vs pla	- Jadad score: 2/5 - completed: 632 (81%) - ITT: yes (primary ITT)
Mimori 2006	291	Inadequately controlled type 2 diabetes Drug-naive patients -- Japanese Main exclusion NR	12w	vilda 20 or 50 or 100mg/d vs pla	- Jadad score: 3/5 - completed: NR (abstract only) - ITT: NR (abstract only)
Pi-Sunyer 2007	354	Inadequately controlled type 2 diabetes Drug-naive patients Main exclusion - Ischaemic heart disease - Heart failure NYHA III-IV - Serum creat >220mmol/L - Liver disease or elevated liver enzymes	24w	vilda 50 or 100mg/d vs pla	- Jadad score: 2/5 - completed: 273 (77%) - ITT: yes
Pratley 2006	100	Inadequately controlled type 2 diabetes Drug-naive patients, diet only Main exclusion - Significant cardiovascular abnormalities - Serum creat >220mmol/L - Liver disease or elevated liver enzymes	12w	vilda 50mg/d vs pla	- Jadad score: 3/5 - completed: 91 (91%) - ITT: yes
Ristic 2005	279	Inadequately controlled type 2 diabetes Drug-naive patients, Main exclusion - Significant cardiovascular abnormalities - Liver disease	12w	vilda 25 or 50 or 100mg/d vs pla	- Jadad score: 2/5 - completed: NR - ITT: yes
Scherbaum 2008	306	Type 2 diabetes, HbA1c 6.2-7.5% Drug-naive patients Main exclusion - Significant cardiac arrhythmia - Heart failure NYHA III-IV - Liver disease - Significant laboratory abnormalities	52w	vilda 50mg/d vs pla	- Jadad score: 4/5 - completed: 264 (86%) - ITT: yes

5.1.8.bis. Summary and conclusions: Vildagliptin versus placebo

<table>
<tr><td colspan="6">Vildagliptin 20-100mg/d vs placebo (Richter 2009)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td>Results</td><td colspan="2"></td><td></td></tr>
<tr><td rowspan="8">6/1139</td><td rowspan="8">12-52w</td><td rowspan="8">Inadequately controlled type 2 diabetes

Drug-naïve patients

Main exclusion criteria: significant cardiovascular abnormalities, creat clear <50ml/min, elevated liver enzymes</td><td rowspan="2">Change in HbA1c (baseline-endpoint)</td><td colspan="3">Mean difference: -0.32 (95% CI: -0.34 to -0.30)
SS in favour of vildagliptin</td><td></td></tr>
<tr><td><u>Quality</u>
-1 low
Jadad</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Change in weight (baseline-endpoint)</td><td colspan="3">Mean difference: 0.76 (95% CI: 0.19 to 1.32)
SS in favour of placebo</td><td></td></tr>
<tr><td><u>Quality</u>
-1 low
Jadad</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">AE: all-cause infections (sitagliptin vs placebo or sitagliptin vs another single hypoglycaemic agent)</td><td colspan="3">Risk ratio: 1.04 (95% CI: 0.87-1.24)
NS</td><td></td></tr>
<tr><td><u>Quality</u>
-1 low
Jadad</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
-1 not reported separately for vilda vs pla</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
</table>

-Vildagliptin at different doses (20-100mg qd) was compared to placebo amongst others in a Cochrane review. All included studies had participants with inadequately controlled type 2 diabetes who did not take any oral antidiabetics. Patients with cardiavascular diseases or dysfunction of liver or kidneys were excluded from all trials.

- Vildagliptin in comparison to placebo resulted in a statistically significant HbA1c reduction.

GRADE: *moderate quality of evidence*

- Vildagliptin therapy did not result in weight gain but weight loss was significantly more pronounced following placebo interventions.

GRADE: *moderate quality of evidence*

- All-cause infections did not increase significantly with vildagliptin treatment compared to either placebo or another single hypoglycemic agent. Data on comparisons to placebo alone on adverse events are not reported.

GRADE: *low quality of evidence*

5.1.9. GLP-1 agonists versus placebo

This comparison was not included in our review.
GLP-1 agonists are not registered as monotherapy.

5.1.10. Insulin versus placebo

This comparison was not included in our review.

5.2. Monotherapy versus monotherapy

These comparisons are not included in our literature review.
We have included the findings of the AHRQ document(Bennett 2011) involving all monotherapy comparisons to provide this information.

AHRQ Key findings and strength of the evidence: intermediate outcomes for monotherapy

Comparison	HbA1c	Weight/BMI
MONOTHERAPY COMPARISONS		
Metformin versus		
TZD	Neither Favoured; Mod	Favours Met; High
SU	Neither Favoured; High	Favours Met; High
DPP-4 inhibitor	Favours Met; Mod	Favours Met; Mod
Meglitinides	Neither Favoured; Low* Favours Met; Low†	Unclear; Low
GLP-1 agonist	Insufficient	Insufficient
TZD versus		
SU	Neither Favoured; Mod	Favours SU; Low
DPP-4 inhibitor	Insufficient	Insufficient
Meglitinides	Unclear; Low* Neither Favoured; Low†	Unclear; Low
GLP-1 agonist	Insufficient	Insufficient
SU versus		
DPP-4 inhibitor	Neither Favoured; Low	Unclear; Low
Meglitinides	Neither Favoured; High* Neither Favoured;Low†	Unclear; Low
GLP-1 agonist	Unclear; Low	Favours GLP-1; Mod
DPP-4 inhibitor versus		
Meglitinides	Insufficient	Insufficient
GLP-1 agonist	Insufficient	Insufficient

BMI = body mass index; HDL = high density lipoprotein; HbA1c = hemoglobin A1c; Meg = meglitinides; Met = metformin; LDL = low density lipoprotein; Pio = pioglitazone;
Rosi = rosiglitazone; Sita = sitagliptin; SU = sulfonylurea; TG = triglycerides; TZD = thiazolidinedione
* For comparisons with repaglinide
† For comparisons with nateglinide
‡ For comparisons with rosiglitazone
§ For comparisons with pioglitazone
The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Mod = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.
All other comparisons and intermediate outcomes were graded as insufficient since there were no studies.

AHRQ Key Points and Evidence Grades: Intermediate outcomes for monotherapy

HbA1c

• Most oral diabetes medications had similar efficacy in achieving reductions in HbA1c, with absolute reduction by around 1 percent compared with baseline values. The strength of evidence was graded high for metformin versus sulfonylurea with a pooled between group difference of 0.1 percent (95 percent confidence interval [CI] -0.1 percent to 0.3 percent). The strength of evidence was graded as moderate for the following comparisons: metformin versus thiazolidinediones, thiazolidinediones versus sulfonylureas, sulfonylureas versus repaglinide, and pioglitazone versus rosiglitazone.

• Metformin had a greater reduction in hemoglobin A1c (HbA1c) compared with dipeptidyl peptidase-4 (DPP-4) inhibitors, with a pooled between-group difference of -0.4 percent (95 percent CI -0.5 percent to -0.2 percent), with moderate strength of evidence.

Weight

• When compared with thiazolidinediones, metformin maintained or decreased weight with a pooled between-group difference of -2.6 kg (95 percent CI -4.1 kg to -1.2 kg). The strength of evidence was graded as high, favouring metformin.

• When compared with sulfonylureas, metformin maintained or decreased weight with a pooled between-group difference of -2.7 kg (95 percent CI -3.5 kg to -1.9 kg). The strength of evidence was graded as high, favouring metformin.

• Sulfonylureas had similar effects on body weight as the meglitinides when used as monotherapy, with a high evidence grade.

• When compared with sulfonylureas, GLP-1 agonists decreased weight (pooled betweengroup difference of -2.5 kg, 95 percent CI -3.8 kg to -1.1 kg). The strength of evidence was graded moderate favouring GLP-1 agonists.

• When compared with DPP-4 inhibitors, metformin had greater weight reduction (pooled between-group difference of -1.4 kg (95 percent CI -1.8 kg to -1.0 kg). The strength of evidence was graded as moderate, favouring metformin.

• Sulfonylureas caused slightly less weight gain when compared with thiazolidinediones (between-group difference of -1.2 kg, 95 percent CI -1.9 kg to -0.6 kg). While this was graded as low evidence for the monotherapy comparisons, it was strengthened by the combination comparisons (described below) which favour metformin plus sulfonylurea over metformin plus a thiazolidinedione (pooled between-group difference of -0.9 kg, 95 percent CI -1.3 kg to -0.4 kg) with a moderate grade of evidence.

AHRQ Key findings and strength of the evidence: Hard outcomes for monotherapy

Comparison	All-cause mortality	CVD mortality	CVD and cerebrovascular morbidity
MONOTHERAPY COMPARISONS			
Metformin versus			
TZD	Neither favoured; Low	Neither favoured;Low	Unclear; Low
SU	Favours Met; Low	Favours Met; Low	Unclear; Low
DPP-4 inhibitor	Unclear; Low	Insufficient	Insufficient
Meglitinide	Unclear; Low	Unclear; Low	Unclear; Low
GLP-1 agonist	Insufficient	Insufficient	Insufficient
TZD versus			
SU	Neither favoured; Low	Unclear; Low	Unclear; Low
DPP-4 inhibitor	Insufficient	Insufficient	Insufficient
Meglitinide	Insufficient	Insufficient	Insufficient
GLP-1 agonist	Unclear; Low	Insufficient	Unclear; Low
SU versus			
DPP-4 inhibitor	Insufficient	Insufficient	Insufficient
Meglitinide	Unclear; Low	Unclear; Low	Unclear; Low
GLP-1 agonist	Insufficient	Insufficient	Insufficient
DPP-4 inhibitor versus			
Meglitinide	Insufficient	Insufficient	Insufficient
GLP-1 agonist	Insufficient	Insufficient	Insufficient

CVD = cardiovascular disease; DPP-4 inhibitor = dipeptidyl peptidase-4 inhibitor; GLP-1 agonist = glucagon-like peptide 1 agonist; Met = metformin; Pio = pioglitazone; SU = sulfonylurea; TZD = thiazolidinedione

Data presented here are strength of the evidence and main conclusion. The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

AHRQ Key Points and Evidence Grades: Hard outcomes for monotherapy

All-Cause Mortality

• The majority of comparisons were graded with low strength of evidence because many RCTs had short duration (less than 1 year) and had few deaths, limiting the precision of results.

• Metformin was associated with lower risk of all-cause mortality compared with a sulfonylurea, with low strength of evidence because of moderate risk of bias from primarily observational studies, and inconsistent results when compared to a 4-year RCT.

• We found insufficient evidence for several comparisons, including: most DPP-4 inhibitor and GLP-1 agonist comparisons.

Cardiovascular Mortality

• Only one RCT, the RECORD trial, had cardiovascular disease mortality as its primary outcome, and the completeness of its outcome ascertainment has been a source of concern.

• The majority of studied comparisons were graded with low strength of evidence because many RCTs had short duration (less than 1 year) and had few deaths, limiting the precision of results.

• Metformin was associated with slightly lower risk of cardiovascular mortality compared with a sulfonylurea, with low strength of evidence because of high imprecision and moderate risk of bias, with the majority of studies being observational.

• Risk of cardiovascular mortality was similar between metformin and thiazolidinediones as monotherapy, with low strength of evidence because of high imprecision and moderate risk of bias.

• Metformin alone was slightly favoured over a combination of metformin and rosiglitazone for lower risk of fatal myocardial infarction, with consistent direction of results, but high imprecision.

• We found insufficient evidence for several comparisons, including: most DPP-4 inhibitor and GLP-1 agonist comparisons

Cardiovascular and Cerebrovascular Morbidity

• The majority of these comparisons were graded with low strength of evidence because many RCTs had short duration (less than 1 year) and had few cardiovascular or cerebrovascular events, limiting the precision of results.

• Risk of cardiovascular and cerebrovascular morbidity between metformin and thiazolidinedione as monotherapy was inconclusive, with low strength of evidence because of high imprecision and inconsistency in direction of findings.

• Metformin alone was slightly favoured over a combination of metformin and rosiglitazone for lower risk of combined fatal and non-fatal ischemic heart disease, with consistent direction of results but high imprecision, which did not reach the level of statistical significance. The pooled odds ratio (OR) for combined fatal and nonfatal ischemic heart disease events was 0.463, 95 percent CI 0.17 to 1.10.

• We found insufficient evidence for several comparisons, including: most DPP-4 inhibitor and GLP-1 agonist comparisons.

AHRQ Key findings and strength of the evidence: safety outcomes for monotherapy

Comparison	Hypoglycemia	GI adverse events	CHF	Pancreatitis and cholecystitis	Fractures
MONOTHERAPY COMPARISONS					
Metformin versus					
TZD	Neither favoured;Mod	Favours TZD; High	Neither favoured;Mod	Favours Met*; Low Insufficient†	Favours Met; High
SU	Favoured Met; High	Favours SU; Mod	Favours Met; Mod	Insufficient	Unclear; Low
DPP-4 inhibitor	Neither favoured; High	Favours DPP-4; Mod	Insufficient	Insufficient	Insufficient
Meglitinides	Favours Met; Mod	Favours Meg‡; Low	Insufficient	Insufficient	Insufficient
GLP-1 agonists	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
TZD versus					
SU	Favours TZD; High	Neither Favoured, Hight	Favours SU; Mod	Neither favoured*;Low Insufficient†	Favours SU; High
DPP-4 inhibitors	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Meglitinides	Favours TZD; Low	Unclear; Low	Insufficient	Insufficient	Insufficient
GLP-1 agonists	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
SU versus					
DPP-4 inhibitors	Favours DPP4; Mod	Insufficient	Insufficient	Insufficient	Insufficient
Meglitinides	Favours Meg; Low	Insufficient	Insufficient	Insufficient	Insufficient
GLP-1 agonist	Favours GLP1; High	Favours SU; Low	Insufficient	Insufficient	Insufficient
DPP-4 inhibitor versus					
Meglitinides	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
GLP-1 agonists	Insufficient	Insufficient	Insufficient	Insufficient* Neither favoured†;	Insufficient

CHF = congestive heart failure; GI = gastrointestinal; Met = metformin; Rosi = rosiglitazone; SU = sulfonylurea; TZD = thiazolidinedione

* Key finding and evidence grade for cholecystitis.

† Key finding and evidence grade for pancreatitis.

‡ For diarrhea only.

§ When lower dose of metformin.

¶ For dyspepsia.

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Mod = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

All other comparisons and intermediate outcomes were graded as insufficient since there were no studies.

AHRQ Key Points and Evidence Grades: safety outcomes for monotherapy

Hypoglycemia

• There was high strength of evidence to conclude that the risk of hypoglycemia with sulfonylureas exceeds the risk with metformin with a pooled OR for mild to moderate hypoglycemic events of 4.6 (95 percent CI 3.2 to 6.5) for sulfonylurea versus metformin.

• There was high strength of evidence to conclude that the risk of hypoglycemia with sulfonylureas exceeds the risk with thiazolidinediones with a pooled OR of 3.9, 95 percent CI 3.0 to 4.9 for mild to moderate hypoglycemia for sulfonylurea versus thiazolidinediones.

• Moderate grade evidence showed that the risk of hypoglycemia with metformin is comparable to the risk with thiazolidinediones.

• Moderate grade evidence showed that the risk of hypoglycemia with sulfonylurea exceeds the risk with DPP-4 inhibitors.

• Moderate grade evidence showed a modest increase (OR 3.0, 95 percent CI 1.8 to 5.2) in risk of hypoglycemia with meglitinides over metformin.

• The evidence on hypoglycemia for the other comparisons had low strength or was insufficient.

• No monotherapy or combination therapy convincingly demonstrated more occurrences of severe hypoglycemia than another.

Congestive Heart Failure

• Moderate evidence showed that thiazolidinediones increase the risk of heart failure when compared to sulfonylureas.

• There were no long-term trials that provide a robust assessment of the comparative safety of the DPP-4 inhibitors and GLP-1 agonists on the risk of heart failure.

Severe Lactic Acidosis

• Moderate strength of evidence indicated that there is no increased risk of lactic acidosis in metformin users compared to those using a sulfonylurea or a combination of metformin and a sulfonylurea.

Cancer

• The evidence had low strength and did not allow definitive conclusions about the risk of cancer with any of the antidiabetic medication comparisons.

Hip and Non-Hip Fractures

• High grade evidence showed that thiazolidinediones, either in combination with another medication or as monotherapy, are associated with a higher risk of bone fractures compared with metformin alone or in combination with sulfonylurea.

Pancreatitis

• The evidence had low strength and did not allow definitive conclusions about the comparative safety of oral antidiabetic agents on the outcome of acute pancreatitis.

Gastrointestinal (GI) Side Effects

• High grade evidence showed that metformin was associated with more frequent GIadverse events compared with thiazolidinediones.

• High strength of evidence demonstrated that the rates of GI adverse effects were similar between thiazolidinediones and sulfonylureas.

• Moderate strength of evidence showed that metformin was associated with more frequent GI adverse events compared with second-generation sulfonylureas.

• Moderate strength of evidence showed that metformin was associated with more frequent GI adverse events compared with DPP-4 inhibitors

6. Type 2 diabetes: dual therapy

6.1. Dual therapy versus monotherapy

6.1.1. Sulphonylurea + metformin versus placebo + metformin

Liraglutide+metformin vs glimepiride+metformin vs placebo+metformin

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Nauck 2009 LEAD-III study Design: DB RCT (PG) Setting: multicenter	n=1091 mean age: 57y Prior R: Monotherapy: 36% Combination therapy 64% DMII duration: 8y Baseline HbA1c: 8.4% <u>Inclusion</u> 18-80y; DMII; AbH1c 7-11% (previous OAD monotherapy >= 3 months) or 7-10% (previous OAD combination therapy >= 3 months); BMI <=40 <u>Exclusion</u> Use of insuline during previous 3m (except short treatment)	26w	Liraglutide 0.6mg or 1.2mg or 1.8mg (injection) + metformin 1g bid Vs Glimepiride 4mg+metformin 1g bid Vs Placebo+metformin 1g bid Metformin run-in period (6w)	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING:2/2 ○ ATTRITION: 0/1 - FU: 80.7% - ITT: yes - Other important methodological remarks: no information on dropout - Multicenter:170 centers, 21 countries - Sponsor: Novo Nordisk
				Change in HbA1c	Liraglutide 0.6mg: -0.7 Liraglutide 1.2mg: -1.0 Liraglutide 1.8mg: -1.0 Glimepiride 4mg: -1.0 Placebo: +0.1 Lira 0.6 vs plac: -0.8% (-1.0, -0.6)=>NS Lira 1.2 vs plac: -1.1% (-1.3, -0.9) =>NS Lira 1.8 vs plac: -1.1% (-1.3, -0.9) =>NS 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	
				HbA1c <7%	Liraglutide 0.6mg: 28.0% Liraglutide 1.2mg: 35.3% Liraglutide 1.8mg: 42.4% Glimepiride 4mg: 36.3% Placebo: 10.8% **Lira (all doses) vs plac p<0.02 =>SS** **Lira 1.2mg vs lira 1.8mg: 35.3% vs 42.4%, p=0.0265 =>SS** Lira vs glime "similar" TNR	
				Weight loss	Liraglutide 0.6mg: -1.8kg Liraglutide 1.2mg: -2.6kg Liraglutide 1.8mg: -2.8kg Glimepiride 4mg: +1.0kg Placebo: -1.5kg **Lira 1.2mg and 1.8mg vs plac p<=0.01 =>SS** **Lira (all doses) vs glime p<0.0001 =>SS**	

				Safety		
				Gastro-intestinal (nausea, vomiting, diarrhea)	Liraglutide 0.6mg: 35% Liraglutide 1.2mg: 40% Liraglutide 1.8mg: 44% Glimepride 4mg: 17% Placebo: 17% TNR	
				Deaths	No deaths after randomisation	
				Pancreatitis without prior history	Lira: n=1 Glime: n=1	
				Major hypoglycaemic events	None	
				Minor hypoglycaemic events	Liraglutide & placebo 3% Glimepiride 17% **Liraglutide vs glimepiride: p<0.001 =>SS**	

6.1.1.bis. Summary and conclusions. Sulphonylurea + metformin versus placebo + metformin

Glimepiride 4mg/d + Metformin 2000mg/d vs Placebo + Metformin 2000mg/d (Nauck 2009)				
N/n	**Duration**	**Population**	**Results**	
N=1, n= 1091 in total	Mean: 26w	Inadequately controlled type 2 diabetes Prior R: Monotherapy: 36% Combination therapy 64% Mean age: 57y DMII duration: 8y Baseline HbA1c: 8.4%	Change in HbA1c (PE)	Glimepiride 4mg: -1.0% Placebo: +0.1% Glim vs pla: NR
				Grade assessment: NA
			Change in body weight (SE)	Glimepiride 4mg: +1.0kg Placebo: -1.5kg Glim vs pla: NR
				Grade assessment: *NA*
			Hypoglycemic events (minor)	Glimepiride: 17.0% Placebo: 3.0% NT
			Gastro-intestinal AEs	Glimepride 4mg: 17% Placebo: 17% NT

This study consisted of 6 study-arms, in which liraglutide at different doses was compared to glimepiride and to placebo, all as add-on treatment to metformin, in type 2 diabetes patients with inadequate glycaemic control.

The comparison glimepiride + metformin versus placebo + metformin was not statistically tested.

GRADE: NA

No other studies met our inclusion criteria.

6.1.2. Repaglinide + metformin versus placebo + metformin

No studies met our inclusion criteria.

6.1.3. Pioglitazone + metformin versus placebo + metformin

No studies met our inclusion criteria.

6.1.4. Hard endpoints: PROactive. Pioglitazone versus placebo , in addition to existing treatment

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Dormandy 2005 PROactive study Design: RCT DB PG Setting: (primary care and hospital)	n= 5238 mean age: 61.7y - evidence of macrovascular disease - Prior R: Diet (4%) oral glucose-lowering agents with or without insulin (30% monotherapy) - DMII duration: mean 8y - Baseline HbA1c: median 7.8% <u>Inclusion</u> - 35-75Y - HBA1c>6.5% - MI or stroke ≥6 months - percutaneous coronary intervention or coronary artery bypass surgery ≥6 months - acute coronary syndrome ≥3 months - objective evidence of coronary artery disease or obstructive arterial disease in the leg. - <u>Exclusion</u> - type 1 diabetes - taking only insulin - planned coronary or	Mean 34.5 mo	Pioglitazone (titrated 15mg to 45mg) Vs Placebo In addition to other glucose-lowering drugs +increase all therapy to optimum (aim HbA1c<6.5%)	Efficacy		- Jadad score o RANDO: 2/2 o BLINDING: 2/2 o ATTRITION: 1/1 - FU: 99% - ITT: yes Other important methodological remarks - Time-to-event analysis planned but number of first events reported - Secondary composite endpoint SS but primary endpoint not SS - Secondary composite endpoint not prespecified? - Caution: Only first event is considered for composite endpoint (if second event (eg. death) occurs in 1 patient: not included in composite endpoint) - Multicenter: 321 centers, 19 countries - Sponsor: Takeda pharmaceutical company and Eli Lilly
				(Time to) first event: All-cause mortality, non-fatal myocardial infarction (including silent), stroke, acute coronary syndrome, endovascular or surgical intervention in coronary or leg arteries, amputation above the ankle (PE)	Pioglitazone: 514/2605 (19.7%) Placebo: 572/2633 (21.7%) HR 0.90 (95% CI 0.80–1.02) NS p=0.095	
				(Time to) first event: All-cause mortality, non-fatal myocardial infarction (excluding silent), stroke (SE)	**Pioglitazone: 301/2605 (11.6%)** **Placebo: 358/2633 (13.6%)** **HR=0.84 (95%CI 0.72–0·98)** **SS in favour of pio (p=0.027)** **NNT=48* (treat 48 patients over 3y to prevent 1 first major cardiovascular event)**	
				Cardiovascular death (SE)	Pioglitazone: 127/2605 (4.9%) Placebo: 136/2633 (5.2%) NT	
				All-cause mortality (SE)	Pioglitazone: 177/2605 (6.8%) Placebo: 186/2633 (7.1%) HR=0.96 (95%CI 0.78–1.18) = >NS	
				non-fatal myocardial infarction (including silent) (SE)	Pioglitazone: 119/2605 (4.6%) Placebo: 144/2633 (5.5%) HR= 0.83 (95%CI 0.65–1.06) =>NS	
				Stroke (SE)	Pioglitazone: 86/2605 (3.3%) Placebo: 107/2633 (4.1%) HR= 0.81 (95%CI 0.61–1.07) =>NS	

	peripheral revascularization - NYHA class ≥II heart failure - ischaemic ulcers, gangrene, or rest pain in leg - haemodialysis - > 2.5 times upper limit of normal concentrations of alanine aminotransferase					
				Safety		
				Any serious adverse event (n° of patients)	Pioglitazone: 1204/2605 (46%) Placebo: 1275/2633 (48%) NS, p=0.110	
				Hospital admissions for diabetes control (n° of patients)	**Pioglitazone: 2%** **Placebo: 3%** **SS, p=0.003**	
				Angina pectoris (n° of patients)	**Pioglitazone: 3%** **Placebo: 5%** **SS, p=0.025**	
				Any report of heart failure (n° of patients)	**Pioglitazone: 11%** **Placebo: 8%** **SS, p<0.0001**	
				Hospital admission for heart failure (n° of patients)	**Pioglitazone: 6%** **Placebo: 4%** **SS, p=0.007**	
				Neoplasms(n° of patients)	Pioglitazone: 4% Placebo: 4% NT	
				Malignant neoplasm bladder (n° of patients)	Pioglitazone: 1% Placebo: <1% NS, p=0.069 (p=0.309 cases remaining after blinded review)	

*As reported in the study

6.1.4.bis. Summary and conclusions. Hard endpoints: PROactive. Pioglitazone + existing treatment versus placebo + existing treatment

<table>
<tr><td colspan="5">Pioglitazone vs placebo (with other glucose-lowering drugs) (Dormandy 2005: PROactive)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td>Results</td><td></td></tr>
<tr><td rowspan="19">1/
5238</td><td rowspan="19">Mean
34.5 mo</td><td rowspan="19">mean age:
61.7y

evidence of macrovascular disease

DMII duration:
mean 8y
Baseline HbA1c:
median 7.8%</td><td rowspan="3">First event: All-cause mortality, non-fatal myocardial infarction (including silent), stroke, acute coronary syndrome, endovascular or surgical intervention coronary or leg arteries, amputation above ankle (PE)</td><td>Pio (19.7%) vs Placebo (21.7%)
HR 0.90 (95% CI 0.80–1.02)
NS p=0.095</td></tr>
<tr><td><table><tr><td><u>Quality</u>
-1 for endpoints</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr></table></td></tr>
<tr><td>Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">First event: All-cause mortality, non-fatal myocardial infarction (excluding silent), stroke (SE)</td><td>Pio (11.6%) vs placebo (13.6%)
HR=0.84 (95%CI 0.72–0·98)
SS in favour of pio (p=0.027)
NNT=48 (treat 48 patients over 3y to prevent 1 first major cardiovascular event)</td></tr>
<tr><td><table><tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1 sec endpoint</td></tr></table></td></tr>
<tr><td>Grade assessment: low quality of evidence</td></tr>
<tr><td>Cardiovascular death (SE)</td><td>Pio (4.9%) vs Placebo (5.2%)
NT</td></tr>
<tr><td>All-cause mortality (SE)</td><td>Pio (6.8%) vs Placebo (7.1%)
HR=0.96 (95%CI 0.78–1.18) = >NS</td></tr>
<tr><td></td><td><table><tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr></table></td></tr>
<tr><td></td><td>Grade assessment: moderate quality of evidence</td></tr>
<tr><td>Any serious adverse event (n° of patients)</td><td>Pio (46%) vsPlacebo (48%)
NS, p=0.110</td></tr>
<tr><td></td><td><table><tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr></table></td></tr>
<tr><td></td><td>Grade assessment:moderate low quality of evidence</td></tr>
<tr><td>Any report of heart failure (n° of patients)</td><td>Pio 11% vs Placebo: 8%
SS, p<0.0001</td></tr>
<tr><td>Hospital admission for heart failure (n° of patients)</td><td>Pio 6% vs Placebo: 4%
SS, p=0.007</td></tr>
<tr><td></td><td><table><tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr></table></td></tr>
<tr><td></td><td>Grade assessment: moderate quality of evidence</td></tr>
<tr><td>Neoplasms(n° of patients)</td><td>Pioglitazone: 4% vs Placebo: 4%
NT</td></tr>
<tr><td>Malignant neoplasm bladder (n° of patients)</td><td>Pioglitazone: 1% vs Placebo: <1%
NS, p=0.069</td></tr>
<tr><td></td><td><table><tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1 for low event rates</td></tr></table></td></tr>
<tr><td></td><td>Grade assessment: low quality of evidence</td></tr>
</table>

This study compares pioglitazone versus placebo (added on to existing oral glucose-lowering agents) for a primary composite endpoint, in patients with type 2 diabetes and pre-existing macrovascular disease.
No significant difference is observed between pioglitazone and placebo for the composite of the following 'first events': all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention coronary or leg arteries and amputation above ankle.
There is also no significant difference observed for all-cause mortality considered seperately.

GRADE: *Moderate quality of evidence*

1 composite secondary endpoint (first event: all-cause mortality, non-fatal myocardial infarction (excluding silent), stroke) does show a significant difference in favour of pioglitazone (HR=0.84 (95%CI 0.72–0·98). Since the primary endpoint does not show a significant difference, this result should be considered as hypothesis-generating.

GRADE: *Low quality of evidence*

Significantly more patients with heart failure (11% vs 8%, $p<0.0001$) and hospitalization for heart failure (6% vs 4%, $p=0.007$) are reported with pioglitazone than with placebo.

GRADE: *Moderate quality of evidence*

No significant difference in malignant neoplasm of the bladder are observed.

GRADE: *Low quality of evidence*

6.1.5. Linagliptin + metformin versus placebo + metformin

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Taskinen 2011 Design: RCT (DB) (PG) Phase III study Setting: NR	n= 701 mean age: 56.5y Prior R: metformin and max. 1 other OAD(washed out before study) DMII duration: 55% had DMII >5 years Baseline HbA1c: mean 8.1% Baseline FPG: mean 9.4mmol/l <u>Inclusion</u> - Type 2 diabetes - Insufficient glycemic control: HbA1c 7.0-10.0% for patients on metformin or HbA1c 6.5-9.0% for patients also treated with additional OAD - Age: 18-80y - BMI≤40 <u>Exclusion</u> - Previous treatment with rosi-, pioglitazone, GLP-1 -a, insulin or antiobesity drug within ≤ 3m - Changed dosage of thyroid hormone drug ≤6w - Treatment with systemic steroids - Impaired hepatic function or renal failure - Myocardial infarction, stroke or TIA ≤ 6m History of acute or chronic metabolic acidosis, unstable or acute congestive heart failure, hereditary galactose intolerance or dehydration - Participation in other trial of investigational drug within previous 2m	24w (+4w washout +2w run-in +1w follow-up)	Linagliptin 5mg/d Vs Placebo Add-on to metformin ≥1500mg/d	Efficacy		- Jadad score o RANDO: 1/2 o BLINDING: 1/2 o ATTRITION: 1/1 - FU: 92.3% ITT: no, FAS (all randomised patients who were treated with at least 1 dose of study medication , had a baseline HbA1c measurement and had at least 1 on-treatment HbA1c measurement - Other important methodological remarks: °Rescue medication (sulphonylurea) could be initiated during randomised trial °Randomisation was in 3:1 ratio (523 patients received linagliptin vs 177 patients received placebo) - Multicenter: 82 centers in 10 countries - Sponsor: Boehringer Ingelheim
				Adjusted mean change from baseline HbA1c (PE)	Lina -0.49% Pla +0.15% Treatment difference: -0.64% (95% CI: -0.78 to -0.50) **p<0.0001** **SS in favour of linagliptin**	
				Adjusted mean change from baseline FPG (SE)	Lina -0.6mmol/l Pla +0.6mmol/l treatment difference:-1.2mmol/l **p<0.0001** **SS in favour of linagliptine**	
				Need for rescue medication	Lina 8% Pla 19% OR=0.28, p=0.0001 **SS in favour of linagliptin**	
				Change in mean body weight	Lina -0.4kg vs plac -0.5kg NT	
				Safety		
				Any adverse event	Lina 52.8% vs pla 55.4% NT	
				Hyperglycemia	Lina 5.2% vs pla 14.7% NT	
				Hypoglycemia	Lina 0.6% vs pla 2.8% NT	

6.1.5.bis. Summary and conclusions. Linagliptin + metformin versus placebo + metformin

<table>
<tr><td colspan="6">Linagliptin 5mg/d + Metformin ≥1500mg/d vs Placebo + Metformin ≥1500mg/d (Taskinen 2011)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="6">N=1,
n= 701</td><td rowspan="6">24w</td><td rowspan="6">Type 2 diabetes
Inadequately controlled

mean age: 56.5y

Prior R: metformin and max. 1 other OAD(washed out before study)
DMII duration: 55% had DMII >5 years
Baseline HbA1c: mean 8.1%</td><td rowspan="3">Change in HbA1c (PE)</td><td colspan="3">Lina+met: -0.49%
Met: +0.15%
Treatment difference:
-0.64% (95% ci: -0.78 to -0.50)
P<0.0001
SS in favour of linagliptin + metformin</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: high quality of evidence</td></tr>
<tr><td rowspan="2">Change in body weight</td><td colspan="3">Lina+met: -0.4kg
Met: -0.5kg
NT</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
<tr><td rowspan="2">Hypoglycemia</td><td colspan="3">Lina+met: 0.6%
Met: 2.8%
NT</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
</table>

- One RCT was carried out to investigate linagliptin 5mg/d as add-on therapy to metformin ≥1500mg/d. Linagliptin showed significant reductions in HbA1c versus placebo add-on (p<0.0001).

GRADE: high quality of evidence

- The difference in weight change between both groups was not statistically tested.

GRADE: NA

- The risk of hypoglycaemia was reported but not statistically tested.

GRADE: NA

6.1.6. Saxagliptin + metformin versus placebo + metformin

Ref	n/Population	Duration	Comparison	Outcomes					Methodological
De Fronzo 2009 Design: RCT (DB) (PG) Setting: university and specialised diabetes centers	n= 743 mean age: 54.6y Prior R: metformin 500-2550mg/d DMII duration: 6.5y Baseline HbA1c: mean 8.0% <u>Inclusion</u> - DMII, inadequetely controlled with metformin alone (≥1500mg/d,≤2550mg/d) HbA1c ≥7% and ≤10% - Age: 18-77y - BMI ≤40 <u>Exclusion</u> - Poorly controlled diabetes, diabetic ketoacidosis or hyperosmolar non-ketotic coma - Use of any other OAD ≤ 8w or insulin ≤1 year - Cardiovascular event ≤6m or congestive heart failure	24w (+2w placebo run-in period)	Saxagliptin 2.5mg/d added to metformin Vs Saxagliptin 5mg/d added to metformin Vs Saxagliptin 10mg/d added to metformin vs Placebo added to metformin	Efficacy					- Jadad score ○ RANDO: 2/2 ○ BLINDING: 2/2 ○ ATTRITION: 1/1 - FU: 73% - ITT: no, efficacy and safety analyses were based on the all-patients-treated population (randomly assigned patients who received at least 1 dose of study treatment and had both a baseline and at least 1 post-baseline measurement) - - Other important methodological remarks: differences in exposure time for the saxagliptin treatment groups versus the metformin plus placebo group
					Placebo + Met	Saxa 2.5mg + Met	Saxa 5mg + Met	Saxa 10mg + Met	
				Change from baseline HbA1c (adjusted mean) (PE)	+0.13%	-0.59%	-0.69%	-0.58%	
					Difference vs placebo + met:	-0.73% (95% CI: -0.92 to -0.53)	-0.83% (95% CI: -1.02 to -0.63)	-0.72% (95% CI: -0.91 to -0.52)	
					SS, p<0.0001 in favour of treatment with saxagliptin				
				Change from baseline FPG (adjusted mean) (SE)	+1.2mg/dl	-14.3mg/dl	-22.0mg/dl	-20.5mg/dl	
					Difference vs placebo + met:	-15.6mg/dl (95% CI: -22.5 to -8.5)	-23.3mg/dl (95% CI: -30.3 to -16.3)	-21.7mg/dl (95% CI: 28.8 to -14.7)	
					SS, p<0.0001 in favour of treatment with saxagliptin				
				Safety					
					Placebo + Met	Saxa 2.5mg + Met	Saxa 5mg + Met	Saxa 10mg + Met	
				Any adverse event	64.8%	79.7%	70.2%	72.9%	
				Serious adverse event	2.8%	2.6%	4.2%	2.8%	
				Mortality	0.6%	0	0	0	
				Discontinuation due to adverse event	1.1%	2.6%	3.1%	2.8%	
				Hypoglycemia	5.0%	7.8%	5.2%	3.9%	

	and/or left ventricular ejection fraction ≤40% - Chronic or repeated corticosteroid therapy - Alcohol or drug abuse ≤1y - Abnormalities in renal, hepatic, endocrine, metabolic or hematologic function - Immunocompromised patients - Pregnant or breastfeeding								- Multicenter: NR - - Sponsor: Bristol-Myers Squibb and AstraZeneca

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Yang 2011 Design: DB RCT (PG) Setting: multicenter study (not specified)	n= 570 mean age: 54y Asian patients Prior R: Metformin ≥1500 mg DMII duration: 5.1y Baseline HbA1c: 7.9% Mean BMI:26.2 <u>Inclusion</u> Adults; HbA1c 7-10%; stable dose metformin >=1500mg <u>Exclusion</u> DMI; poorly controlled diabetes; heart failure or recent CV history; unstable or rapidly progressing renal disease; GI surgery; …	24w	Saxagliptin 5mg + metformin Vs Placebo + metformin	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING: 2/2 ○ ATTRITION: 1/1 - FU: 88% - ITT: yes, LOCF - Multicenter: 40 centers, 3 countries (China, India, South Korea - Sponsor: AstraZenica & Bristol-Myers Squibb
				Change in HbA1c (PE)	Saxa + metformin: -0.78% Placebo + metformin: -0.37% **Mean diff= -0.42% (95%CI: -0.55, -0.29) SS, P<0.0001**	
				Safety		
				≥1 serious adverse events	Saxa 2.8%; placebo 1.0%	
				Localised edema	Saxa 0.7%; placebo 0%	
				Deaths Cerebral infarction	None Saxa n=1; placebo n=1	
				Hypoglycemic events	Saxa 1.4%; placebo 1.4%	
				Upper respiratory tract infection	Saxa 6.7%; placebo 4.5% TNR	

6.1.6.bis. Summary and conclusions. Saxagliptin + metformin versus placebo + metformin

<table>
<tr><td colspan="7">Saxagliptin 2.5 – 5 – 10 mg/d vs Placebo, added to ongoing metformin therapy (DeFronzo 2009, Yang 2011)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="4">Results</td></tr>
<tr><td rowspan="11">N=2,
n=
1313</td><td rowspan="11">24w</td><td rowspan="11">mean age 54y

DMII inadequately controlled on metformin
DMII duration: 5.1-6.5y
Baseline HbA1c: 7.9%

1 study: all Asians</td><td rowspan="4">Change from baseline HbA1c (PE)</td><td>Saxa 2.5mg</td><td colspan="3">Reported in 1/2 studies
Saxa 2.5mg + Met : -0.59%
Placebo +Met: +0.13%
Mean difference: -0.73% (95% CI: -0.92 to -0.53)
SS</td></tr>
<tr><td>Saxa 10mg</td><td colspan="3">Reported in 1/2 studies
Saxa 2.5mg + Met : -0.58%
Placebo +Met: +0.13%
Mean difference: -0.72% (95% CI: -0.91 to -0.52)</td></tr>
<tr><td><u>Quality</u>
-1 low FU and no ITT</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Change from baseline HbA1c (PE)</td><td>Saxa 5 mg</td><td colspan="3">Reported in 2/2 studies
Mean difference:
-0.83% (95% CI: -1.02 to -0.63) and
-0.42% (-0.55, -0.29)
SS, P<0.0001</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: high quality of evidence</td></tr>
<tr><td>BMI (kg/m^2)</td><td colspan="4">not reported</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
<tr><td rowspan="2">Upper respiratory tract infections</td><td colspan="4">Reported in 1/2 trials
Saxa 5mg + met: 6.7%
Placebo + met: 4.5%
TNR</td></tr>
<tr><td colspan="4">Grade assessment:NA</td></tr>
<tr><td rowspan="2">Hypo-glycaemia</td><td colspan="4">Reported in 2/2 trials
NT</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
</table>

-Saxagliptin (at different doses) was compared to placebo, when added to ongoing metformin therapy in type 2 diabetes patients with inadequate glycaemic control with metformin.

Decrease in HbA1c with saxagliptin (all doses) is significantly different from placebo, when added to ongoing metformin therapy.

GRADE: moderate to high quality of evidence

Weight change was not reported in these studies

Adverse events, such as upper respiratory tract infections and hypoglycaemia were reported but not statistically tested.

GRADE: NA

6.1.7. Sitagliptin + metformin versus placebo + metformin

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Charbonnel 2006 Design: RCT (DB) (PG) Setting: NR	n= 701 mean age: 54.6y Prior R: metformin ≥1500mg/d DMII duration: 6.2y Baseline HbA1c: mean 8.0% Baseline BMI: mean 31.2 Baseline mean body weight: 88.2kg <u>Inclusion</u> - Type 2 diabetes - Inadequetely controlled with metformin alone HbA1c ≥7% and ≤10% - Age: 18-78y - Not taking other OAD <u>Exclusion</u> - Type 1 diabetes - Insulin use ≤8w - Renal function impairment - FPG >14.4mmol/l (260mg/dl)	24w (+2w placebo run-in period)	Sitagliptin 100mg/d added to metformin vs Placebo added to metformin Rescue medication: pioglitazone (if patients exceeded specific glycemic limits*)	Efficacy		- Jadad score ○ RANDO: 1/2 ○ BLINDING: 1/2 ○ ATTRITION: 1/1 - FU: 87% - ITT: no, efficacy and safety analyses were based on the all-patients-treated population (randomly assigned patients who received at least 1 dose of study treatment and had both a baseline and at least 1 post-baseline measurement) - Other important methodological remarks: data obtained after initiation of rescue therapy were treated as missing data to avoid confounding influence - Multicenter: multinational - Sponsor: Merck Research Laboratories
				Change from baseline HbA1c (least-squares) (PE)	sita+met -0.67% vs met -0.02% between-group difference: 0.65% (95% CI: -0.77 to -0.53) p<0.001, **SS in favour of sitagliptin plus metformin**	
				Change from baseline FPG (least-squares) (SE)	sita+met -0.9mmol/l vs met 0.5mmol/l between-group difference: 1.4mmol/l (95% CI: -1.7 to -1.1) p<0.001, **SS in favour of sitagliptin plus metformin**	
				Safety		
				Any adverse event	sita+met 56.5% vs met 54.0% 'similar' - NT	
				Serious adverse event	sita+met 2.8% vs met 3.0% 'similar' - NT	
				Hypoglycemia	sita+met 1.3% vs met 2.1% 'NS' - TNR	
				Change from baseline mean body weight	between-group difference: NR (p=0.835) NS	

* Patients exceeding specific glycemic limits during the 24-week treatment period were provided rescue therapy: pioglitazone. Rescue therapy was initiated if FPG was >15.0mmol/l (270mg/dl) from baseline through week 6, >13.3mmol/l (240mg/dl) after week 6 through week 12 and >11.1mmol/l (200mg/dl) after week 12 until the end of the study period.

6.1.7.bis. Summary and conclusions. Sitagliptin + metformin versus placebo + metformin

<table>
<tr><td colspan="6">Sitagliptin 100mg/d + Metformin ≥1500mg/d vs Placebo + Metformin ≥1500mg/d (Charbonnel 2006)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td>Results</td><td colspan="2"></td><td></td></tr>
<tr><td rowspan="6">N=1,
n= 701</td><td rowspan="6">24w</td><td rowspan="6">Inadequately controlled type 2 diabetes

mean age: 54.6y

Prior R: metformin ≥1500mg/d
DMII duration: 6.2y
Baseline HbA1c: mean 8.0%
Baseline BMI: mean 31.2</td><td rowspan="2">Change in HbA1c (PE)</td><td colspan="3">Sita+met -0.67%
Met -0.02%
Between-group difference:
0.65% (95% CI: -0.77 to -0.53)
p<0.001, SS in favour of sitagliptin plus metformin</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: high quality of evidence</td></tr>
<tr><td rowspan="2">Hypoglycemia</td><td colspan="3">Sita+met 1.3%
Met 2.1%
‘NS’ – TNR</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
<tr><td rowspan="2">Change in body weight (safety)</td><td colspan="3">between-group difference: NR (p=0.835) NS</td></tr>
<tr><td><u>Quality</u>
-1 for unclear evaluating and reporting</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
</table>

This trial compared the DPP-4 inhibitor sitagliptin to placebo, both added to ongoing metformin therapy, in patients with type 2 diabetes inadequately controlled with metformin alone.

- At week 24 (end of trial), sitagliptin treatment led to a significantly larger decrease in HbA1c compared to metformin monotherapy.

GRADE: high quality of evidence

- The authors reported that there was no increased risk of hypoglycemia with sitagliptin in comparison to metformin alone. The statistical test was not reported.

GRADE:NA

- There was no significant difference in weight change between both treatment groups.

GRADE: moderate quality of evidence

6.1.8. Vildagliptin + metformin versus placebo + metformin

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Bosi 2007 Design: DB RCT (PG) Setting: multicenter	n=544 mean age:54y Prior R: metformin (average 17m) DMII duration: 6.2y Baseline HbA1c: 8.4% <u>Inclusion</u> DMII; metformin monotherapy ≥3m; stable dose ≥1500mg min 4 w before visit 1 >=3m; HbA1c 7.5-11%; 18-78y; BMI 22-45; FPG<15 <u>Exclusion</u> DMI;secondary diabetes; heart failure; myocardial infarction;unstable angina; coronary artery bypass surgery within 6m; liver disease; renal disease/dysfunction	24w	Vildagliptin 50mg + metformin Vs Vildagliptin 100 mg + metformin Vs Placebo + metformin	Efficacy		- Jadad score o RANDO: 1/2 o BLINDING:1/2 o ATTRITION: 0/1 - FU: >83% - ITT: yes, LOCF - Multicenter: .109 centers, 4 countries - Sponsor: Novartis
				Change in HbA1c (PE)	Vildagliptin 50mg: -0.5 Vildagliptin 100mg: -0.9 Placebo: +0.2 **Vilda 50mg vs plac: -0.7, p<0.001; SS** **Vilda 100mg vs plac: -1.1, p<0.001; SS**	
				HbA1c<7% TNR)	Patients with baseline <=7.9% Vildagliptin 50mg: 50% Vildagliptin 100mg: 54.4% Placebo: 14% Patients with baseline >7.9 but <=8.5% Vildagliptin 50mg: 22.2% Vildagliptin 100mg: 31.4% Placebo: 12.5% Patients with baseline >8.5% Vildagliptin 50mg: 7.5% Vildagliptin 100mg: 16.3% Placebo: 2.1%	
				Body weight	Vildagliptin 50mg: -0.4kg Vildagliptin 100mg: +0.2kg Placebo: -1.0 kg Vilda50 vs plac NS **Diff. vilda 100mg vs plac: 1.2kg SS**	
				Safety		
				Gastrointestinal AE	**Vildagliptin 50mg vs placebo ;P=0.022; SS**	
				Serious AE	Vildagliptin 50mg: 2.3% Vildagliptin 100mg: 2.7% Placebo: 4.4% TNR	
				deaths	None	
				Serious hypoglycaemia	None	

Ref	n/Population	Duration	Comparison	Outcomes			Methodological
Goodman 2009 Design: RCT (DB) (PG) Superiority trial Setting: NR	n= 370 mean age: 54y Prior R: metformin DMII duration: NR Baseline HbA1c: 8.6% <u>Inclusion</u> - Type 2 diabetes - HbA1c 7.5-11% - Treated with metformin only at stable dose of ≥1500mg/d for at least 3m - Age 18-78y - BMI 22-40 <u>Exclusion</u> - Pregnant or lactating - Type 1 diabetes or secondary forms of diabetes - Acute metabolic diabetic complications in previous 6m - Significant diabetic complications - Liver disease - Significant renal dysfunction - Treatment with OAD (except for metformin) within 3m - Chronic insulin treatment in past 6m - Significant laboratory abnormalities	24w	Vildagliptin 100mg AM Vs Vildagliptin 100mg PM Vs Placebo Added to metformin	Efficacy			- Jadad score o RANDO: 1/2 o BLINDING: 1/2 o ATTRITION: 0/1 - FU: 78% 287 patients completed study - ITT: all randomised patients who received at least one dose of study drug and had at least one post-baseline primary efficacy variable assessment - Multicenter: 67 centers in Europe and USA - Sponsor: Novartis
				Change from baseline to study endpoint, adjusted mean HbA1c (PE)	vilda AM vs placebo	-0.66% vs 0.17% Difference: 0.83% P<0.001 **SS in favour of vildagliptin AM**	
					vilda PM vs placebo	-0.53% vs 0.17% Difference: 0.70% P<0.001 **SS in favour of vildagliptin PM**	
					vilda AM vs vilda PM	-0.66% vs -0.53% Difference: 0.13% P=0.38; NS	
				Change from baseline to study endpoint, adjusted mean FPG	vilda AM vs placebo	-1.02mmol/l vs 0.08mmol/l Difference: 1.10mmol/l P<0.001 **SS in favour of vildagliptin AM**	
					vilda PM vs placebo	-1.21mmol/l vs 0.08mmol/l Difference: 1.29mmol/l P<0.001 **SS in favour of vildagliptin PM**	
					vilda AM vs vilda PM	NR	
				Change from baseline to study endpoint, adjusted mean body weight	vilda AM or vilda PM vs placebo	+0.06kg vs -0.69kg Difference: 0.75kg P=0.017 **SS in favour of placebo**	
					vilda AM vs vilda PM	-0.19kg vs +0.32kg NT	

				Safety			
					vilda AM	vilda PM	placebo
				Any adverse event	30.4%	39.0%	34.4%
				Fatigue	2.4%	2.4%	0.8%
				Tremor	2.4%	2.4%	0%
				Diarrhea	2.4%	0.8%	4.9%
				Dizziness	1.6%	4.1%	0.8%
				Hypoglycemic event	0.8%	0.8%	0%
				Safety endpoints NT			

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Filozof 2010 Design: RCT (DB) (PG) non-inferiority/ superiority trial Setting: NR	n= 914 mean age: 57y Prior R: metformin 850-1000mg/d DMII duration: 4.7y Baseline HbA1c: 7.3% Baseline FPG: 8.6mmol/l Baseline mean BMI: 31.1 <u>Inclusion</u> - Type 2 diabetes - HbA1c 6.5%-9.0% - FPG <270mg/dl - BMI 22-45 - Received metformin 850-1000mg/d for at least 2m prior to screening <u>Exclusion</u> - Type 1 diabetes or secondary forms - Diabetic complications - Acute infections - Myocardial infarction, unstable angina or coronary artery bypass surgery in previous 6m - Congestive heart failure - Malignancy - Liver disease - ECG abnormalities - Laboratory abnormalities	24w (=2w titration + 22w maintenance)	Vildagliptin 100mg/d (blinded) added to OL metformin 1000mg/d Vs Metformin 500mg/d for 2w and then 1000mg/d (blinded) added to OL metformin 1000mg/d	Efficacy		- Jadad score o RANDO: 1/2 o BLINDING: 1/2 o ATTRITION: 1/1 - FU: 87.3% (914 patients were randomised, 798 completed study) - ITT: no Author:"yes", randomised patients received at least one dose of each study drug and had at least one post-baseline HbA1c assessment - Other important methodological remarks: discontinuation was higher in metformin than in vilda+met group (14.4% vs 11.0%), most frequent reason was withdrawal of consent - Sponsor: Novartis Pharmaceuticals Corporation
				Change from baseline HbA1c (adjusted mean) (PE)	vilda+met -0.51% met -0.37% mean difference: -0.14% (95% CI: -0.24 to -0.05) non-inferiority achieved (margin: 0.4%) **SS superiority of combination vilda + met over monotherapy met (p=0.002)**	
				Change from baseline FPG (adjusted mean) (SE)	vilda+met -0.77mmol/l met -0.59mmol/l mean difference: -0.18mmol/l (95% CI: -0.38 to 0.02) NS, p=0.07	
				Change from baseline body weight (adjusted mean)	vilda+met -1.35kg vs met -0.62kg **SS, p<0.001**	
				Safety		
				Any adverse event	vilda+met 48.2% vs met 51.7% NT	
				Gastrointestinal adverse events	vilda+met 15.4% vs met 21.0% **SS, p=0.032**	
				Diarrhea	vilda+met 4.6% vs met 8.5% NT	
				Headache	vilda+met 3.9% vs met 6.1% NT	
				Hypoglycemia	1 patient in each Group had 1 event NT	

	- Chronic insulin treatment in previous 6m and/or any OAD in previous 3m - Treatment with growth hormones, cytostatic drugs, anti-arrhythmics - Contraindications for metformin - History of active drug abuse (incl. alcohol) within past 2y - Participation in previous vildagliptin studies					

Ref	n/Population	Duration	Comparison	Outcomes				Methodological
Pan 2012 Design: DB RCT (PG) Setting: diabetes ambulatory hospital setting	n=438 Chinese patients mean age: 54y Prior R: monotherapy with metformin DMII duration: 5y Baseline HbA1c: 8% <u>Inclusion</u> Age 18-78; HbA1c 7-10% Stable dose of metformin >=1500mg; BMI 20-40; FPG <15 mmol/l <u>Exclusion</u> DMI, secondary diabetes, diabetic complications, myocardial infarction; unstable angina, coronary bypass surgery; congestive heart failure; liver disease	24w	Vildagliptin 50 mg bid + metformin Vs Vildagliptin 50 mg qd + metformin Vs Placebo + metformin	Efficacy				- Jadad score ○ RANDO: 1/2 ○ BLINDING:1/2 ○ ATTRITION:1/1 - FU: 92% - ITT: yes, LOCF - Multicenter: 20 centers, 1 country - Sponsor: Novartis Beijing
				Change in HbA1c (PE)	Vilda 50 bid: -1.05 Vilda 50 qd: -0.92 Placebo: -0.54 **Vilda 50 bid vs plac: -0.51, SS, p<0.001**			
				% with HbA1c <7%	Vilda 50 bid: 53.7% Vilda 50 qd: 48.9% Placebo: 34.8% **Vilda 50 bid vs placebo: SS, p=0.002** **Vilda 50 qd vs placebo: SS, p=0.018**			
				Safety				
					Vilda 50 bid	vilda 50 qd	placebo	
				Diabetic nephropathy	0.7%	2.7%	2.8%	
				diarrhea	4.1%	3.4%	2.1%	
				nausea	0.7%	1.4%	3.5%	
				abdominal discomfort	0.7%	0.0%	2.1%	
				Oedema peripheral	2.1%	0.7%	0.0%	
				Death	None			
				Hypoglycaemic event	One patient in vilda 50 mg bid			

6.1.8.bis. Summary and conclusions. Vildagliptin + metformin versus placebo + metformin

<table>
<tr><td colspan="5">Vildagliptin 50-100mg/d + Metformin 1000-≥1500mg/d vs Placebo + Metformin ≥1500-2000mg/d (Bosi 2007, Goodman 2009, Filozof 2010, Pan 2012)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="2">Results</td></tr>
<tr><td rowspan="6">N=4,
n=
2266</td><td rowspan="6">24w</td><td rowspan="6">Type 2 diabetes
Inadequately controlled with metformin monotherapy (1000mg/d in 1 trial, ≥1500mg/d in other trials)

mean age 54-57y
Mean baseline HbA1c 7.3-8.6%
mean DMII duration: 4.7y-6.2y (NR in 1 trial)

Including 1 Chinese trial (438 patients)</td><td>Change in HbA1c (PE), between-group difference</td><td>Reported in 4/4 studies:
Vilda 50mg/d vs Pla (add-on to met 1500mg/d)
-0.70% SS
Vilda 100mg/d vs Pla (add-on to met 1500mg/d)
-0.51% to -1.10% SS
Vilda 100mg/d AM vs Pla (add-on to met 1500mg/d)
-0.83% SS
Vilda100mg/d PM vs Pla (add-on to met 1500mg/d)
-0.70% SS

Vilda 100mg/d + met 1000mg/d vs met 2000mg/d)
-0.14% SS

All vildagliptin + metformin groups SS better than metformin monotherapy groups.
<table>
<tr><td><u>Quality</u>
-1 due to high drop-out rates</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
</table></td></tr>
<tr><td>Change in body weight</td><td>Reported in 2/4 studies:
Vilda 100mg/d vs pla (add-on to met 1500mg/d)
+0.06kg vs -0.69kg in one study
+0.2kg vs -1.0kg in other study
(SS in favour of metformin monotherapy)

Reported in 1/4 studies:
Vilda 50mg/d vs pla (add-on to met 1500mg/d)
-0.4kg vs -1.0kg
(SS in favour of metformin monotherapy)
Metformin monotherapy ≥1500mg/d SS better than all vildagliptin + metformin groups.

Reported in 1/4 studies:
Vilda100mg/d + met 1000mg/d vs met 2000mg/d:
-1.35kg vs -0.62kg
(SS in favour of vilda + met)
Vildagliptin in combination with metformin 1000mg/d SS better than metformin monotherapy 2000mg/d.
<table>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
-1</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
</table></td></tr>
<tr><td>Hypoglycemic events</td><td>Reported in 4/4 studies but NT
Vildagliptin 50mg/d: 0%
Vildagliptin 100mg/d: 0.1-0.8%
Metformin mono: 0-0.1%</td></tr>
<tr><td>Mortality</td><td>Reported in 3/4 studies
Vildagliptin 50mg/d: 0%
Vildagliptin 100mg/d: 0%
Metformin mono: 0%</td></tr>
<tr><td></td><td>Grade assessment: NA</td></tr>
</table>

- Three trials compared metformin monotherapy ≥1500mg/d to combination therapy of metformin ≥1500mg/d and vildagliptin 50mg or 100mg daily dose in inadequately controlled type 2 diabetes patients. One of these trials only included Chinese patients. Another of these trials investigated whether there was a difference between administering vildagliptin 100mg daily dose in the morning or evening.
- One trial compared metformin monotherapy in 2000mg daily dose to combination therapy of metformin 1000mg/d and vildagliptin 100mg/d.
All vildagliptin combination therapies reported a significantly greater reduction in HbA1c in comparison to metformin monotherapy.

GRADE: moderate quality of evidence

Results on weight change were not consistent. 3 comparisons are in favour of metformin monotherapy, 1 comparison is in favour of vildagliptin + metformin. Although these differences are statistically significant, they have little clinical relevance (mean difference +/- 0.5 to 1.2 kg).

GRADE: low quality of evidence

- The adverse events were not statistically tested. No deaths occurred in any of the trials. However, one study did not report mortality.

GRADE: NA

6.1.9. Exenatide + metformin versus placebo + metformin

Ref	n/Population	Duration	Comparison	Outcomes				Methodological
DeFronzo 2005 Design: RCT (TB) (PG) Setting: NR	n= 336 mean age: 53±10y Prior R: metformin DMII duration: 5.9y Baseline HbA1c: 8.2±1.1% Baseline BMI: 34 Baseline body weight: 100kg <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-glucosidase inhibitors, exogenous insulin therapy, weight loss drugs, corticosteroids, transplantation medications, drugs affecting gastrointestinal motility or any study drug for 3m before screening	30w (=4w acclimation period* + 26w full dose treatment)	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 - FU: 67.6% - ITT: no - Author:"yes", all randomised subjects who received at least one injection of medication starting from the evening of day 1 - Multicenter: 82 centers in USA - Sponsor: Amylin Pharmaceuticals and Eli Lily
					Placebo	Exenatide 5	Exenatide 10	
				Change from baseline HbA1c (PE)	+0.08%	-0.40%	-0.78%	
					SS, p<0.002			
				% patients achieving HbA1c≤7% (SE)	13%	32%	46%	
					SS, p<0.01 vs placebo			
				Change from baseline body weight (SE)	0	-1.6kg	-2.8kg	
					SS, p<0.001 vs placebo			
				Safety				
				Serious adverse events	3.5%	4.5%	2.7%	
				Nausea	23%	36%	45%	
				Hypoglycemia (mild-moderate)	5.3%	4.5%	5.3%	

6.1.9.bis. Summary and conclusions. Exenatide + metformin versus placebo + metformin

<table>
<tr><td colspan="6">Exenatide 5µg bid or Exenatide 10µg bid vs placebo, added to existing metformin treatment (DeFronzo 2005)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="11">N=1,
n= 336</td><td rowspan="11">30w</td><td rowspan="11">mean age: 53±10y

Prior R: metformin
DMII duration: 5.9y
Baseline HbA1c: 8.2±1.1%
Baseline BMI: 34</td><td rowspan="3">Change from baseline HbA1c (PE)</td><td colspan="3">Exenatide 5µg bid: -0.40%
Exenatide 10µg bid: -0.78%
Placebo: +0.08%
SS, p<0.002</td></tr>
<tr><td><u>Quality</u>
-1 low FU, no ITT</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Change from baseline body weight</td><td colspan="4">Exenatide 5µg bid: -1.6kg
Exenatide 10µg bid: -2.8kg
Placebo: 0
SS, p<0.001 vs placebo</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td>Serious adverse events</td><td colspan="4">Exenatide 5µg bid: 4.5%
Exenatide 10µg bid: 2.7%
Placebo: 3.5%
NT</td></tr>
<tr><td>Nausea</td><td colspan="4">Exenatide 5µg bid: 36%
Exenatide 10µg bid: 45%
Placebo: 23%
NT</td></tr>
<tr><td>Hypoglycemia (mild-moderate)</td><td colspan="4">Exenatide 5µg bid: 4.5%
Exenatide 10µg bid: 5.3%
Placebo: 5.3%
NT</td></tr>
<tr><td></td><td colspan="4">Grade assessment:NA</td></tr>
</table>

This study compares exenatide (5 or 10µg bid) with placebo, when added to an existing treatment with metformin, in patients with type 2 diabetes and inadequate glycaemic control.

A significant decrease in HbA1c is observed with exenatide when compared to placebo.

GRADE: moderate quality of evidence

Exenatide is associated with a significant weight decrease, compared to placebo

GRADE: moderate quality of evidence

Adverse events were reported but not statistically tested.

GRADE: NA

6.1.10. Liraglutide + metformin versus placebo + metformin

Liraglutide+metformin vs glimepiride+metformin vs placebo+metformin

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Nauck 2009 LEAD-III study Design: DB RCT (PG) Setting: multicenter	n=1091 mean age: 57y Prior R: Monotherapy: 36% Combination therapy 64% DMII duration: 8y Baseline HbA1c: 8.4% <u>Inclusion</u> 18-80y; DMII; AbH1c 7-11% (previous OAD monotherapy >= 3 months) or 7-10% (previous OAD combination therapy >= 3 months); BMI <=40 <u>Exclusion</u> Use of insuline during previous 3m (except short treatment)	26w	Liraglutide 0.6mg or 1.2mg or 1.8mg (injection) + metformin 1g bid Vs Glimepiride 4mg+metformin 1g bid Vs Placebo+metformin 1g bid Metformin run-in period (6w)	Efficacy		- Jadad score o RANDO: 2/2 o BLINDING:2/2 o ATTRITION: 0/1 - FU: 80.7% - ITT: yes - Other important methodological remarks: no information on dropout - Multicenter:170 centers, 21 countries - Sponsor: Novo Nordisk
				Change in HbA1c	Liraglutide 0.6mg: -0.7 Liraglutide 1.2mg: -1.0 Liraglutide 1.8mg: -1.0 Glimepiride 4mg: -1.0 Placebo: +0.1 **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** 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	
				HbA1c <7%	Liraglutide 0.6mg: 28.0% Liraglutide 1.2mg: 35.3% Liraglutide 1.8mg: 42.4% Glimepiride 4mg: 36.3% Placebo: 10.8% **Lira (all doses) vs plac p<0.02 =>SS** **Lira 1.2mg vs lira 1.8mg: 35.3% vs 42.4%, p=0.0265 =>SS** Lira vs glime "similar" TNR	
				Weight loss	Liraglutide 0.6mg: -1.8kg Liraglutide 1.2mg: -2.6kg Liraglutide 1.8mg: -2.8kg Glimepiride 4mg: +1.0kg Placebo: -1.5kg **Lira 1.2mg and 1.8mg vs plac p<=0.01 =>SS** **Lira (all doses) vs glime p<0.0001 =>SS**	

				Safety		
				Gastro-intestinal (nausea, vomiting, diarrhea)	Liraglutide 0.6mg: 35% Liraglutide 1.2mg: 40% Liraglutide 1.8mg: 44% Glimepride 4mg: 17% Placebo: 17% TNR	
				Deaths	No deaths after randomisation	
				Pancreatitis without prior history	Lira: n=1 Glime: n=1	
				Major hypoglycaemic events	None	
				Minor hypoglycaemic events	Liraglutide & placebo 3% Glimepiride 17% **Liraglutide vs glimepiride: p<0.001 =>SS**	

6.1.10.bis. Summary and conclusions. Liraglutide + metformin versus placebo + metformin

<table>
<tr><td colspan="6">Liraglutide 0.6-1.2-1.8mg/d + Metformin 2000mg/d vs Metformin 2000mg/d (Nauck 2009)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="8">N=1, n= 1091 in total</td><td rowspan="8">Mean: 26w</td><td rowspan="8">Inadequately controlled type 2 diabetes

Prestudy OAD therapy

All treatments are in combination with metformin!</td><td rowspan="3">Change in HbA1c (PE)</td><td colspan="3">Liraglutide 0.6mg: -0.7%
Liraglutide 1.2mg: -1.0%
Liraglutide 1.8mg: -1.0%
Placebo: +0.1%

Lira 0.6 vs plac: -0.8% (95%CI: -1.0, -0.6) =>SS
Lira 1.2 vs plac: -1.1% (95%CI: -1.3, -0.9) =>SS
Lira 1.8 vs plac: -1.1% (95%CI: -1.3, -0.9) =>SS</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: high quality of evidence</td></tr>
<tr><td rowspan="3">Change in body weight (SE)</td><td colspan="3">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</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: high quality of evidence</td></tr>
<tr><td>Hypoglycemic events (minor)</td><td colspan="3">Liraglutide (all doses): 3.0%
Placebo: 3.0%
NT</td></tr>
<tr><td>Gastro-intestinal AEs</td><td colspan="3">Liraglutide 0.6mg: 35%
Liraglutide 1.2mg: 40%
Liraglutide 1.8mg: 44%
Placebo: 17%
NT</td></tr>
<tr><td></td><td colspan="3">Grade assessment: NA</td></tr>
</table>

In this 26-week study, inadequately controlled type 2 diabetes patients were randomly assigned to once-daily liraglutide (either 0.6, 1.2 or 1.8mg/day injected subcutaneously) or to placebo. All treatments were in combination with metformin treatment(1g twice daily).

- There was a significant difference in HbA1c–decrease between the treatment groups (active or placebo).

GRADE: high quality of evidence

- Body weight decreased significantly in the liraglutide 1.2 and 1.8mg/d treatment groups compared to placebo (p≤0.01).

GRADE: high quality of evidence

- The incidence of adverse events was not statistically tested.

GRADE: NA

6.1.11. Insulin + metformin versus placebo + metformin

No studies met our inclusion criteria.

6.1.12. Hard endpoints: Origin trial: Insulin glargin in addition to existing glycaemic control regimen verus standard care

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
ORIGIN trial investigators 2012 Design: RCT (OL) (PG) Setting: cardiology, diabetes and other clinical sites	n=12537 mean age: 63.5y Prior R: 59% oral glucose-lowering agent Duration diabetes: mean 5.4y Baseline median HbA1c: 6.4% 6% new diabetes[1], 82% prior diabetes, 12% IGT 35% female <u>Inclusion</u> - ≥50y and IGT, impaired FPG [2] or DMII (stable on 0 GLA, HbA1c<9% or 1 OAD, HbA1c <8%) and other cardiovascular risk factors[3] - <u>Exclusion</u> - inability to inject insulin, intolerance to insulin - heart failure - coronary artery bypass surgery in prior 4y - cancer affecting survival	Median follow-up: 6.2y	Insulin glargine (add ins glargine to glycemic control regimen and increase dose)(target FPG 95mg/dl)[4] Vs Standard care (investigator's best judgment and local guidelines[5])	Efficacy		- Jadad score o RANDO: 1/2 o BLINDING: 0/2 o ATTRITION: 1/1 - FU: 99% - ITT: no (intention reported but not executed) - Multicenter: 573 centers in 40 countries - Important methodological remarks: - This study also compared n- fatty acids vs placebo in a 2-by-2 design - 10 day placebo run-in - Definition of 'new diabetes' in this trial differs from standard ADA/WHO definition - No specific target defined in standard care group - Sponsor: Sanofi
				Nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes (per 100 person-years) (PE)	Insulin: 2.94 vs Standard: 2.85 HR=1.02 (95%CI: 0.94-1.11) NS: p=0.63	
				Nonfatal myocardial infarction, nonfatal stroke, death from cardiovascular causes, revascularization or hospitalization for heart failure (per 100 person-years)(PE)	Insulin: 5.52 vs Standard: 5.28 HR=1.04 (95%CI: 0.97-1.11) NS: p=0.27	
				All-cause mortality	Insulin: 2.57 vs Standard: 2.60 HR=0.98 (95%CI: 0.90-1.08) NS: p=0.70	
				Composite microvascular outcomes	Insulin: 3.87 vs Standard: 3.99 HR=0.97 (95%CI: 0.90-1.05) NS: p=0.43	
				New onset diabetes[6](among 1456 participants without baseline diabetes)	Insulin: 30% vs Standard: 35% OR=0.80 (95%CI: 0.64-1.00) NS: p=0.05	
				HbA1c (%) at 7y	Insulin: 6.2 vs Standard: 6.5 NT	
				Safety		
				Severe hypoglycemia (per 100 person-years)	Insulin: 1.00 vs Standard: 0.31 **SS: p<0.001 in favour of standard**	
				Weight (median change)	Insulin: +1.6kg vs Standard: -0.5kg NT	
				Cancers	HR=1.00 (CI: 0.88-1.13) NS: p=0.97	

1. Definition of newly detected diabetes in this trial based on either a FPG ≥ 6.1 mmol/L [110 mg/dL] or a 2 hour plasma glucose ≥ 7.8 mmol/L [140 mg/dL] after a 75 g oral glucose load.
2. FPG ≥ 6.1 mmol/L [110 mg/dL]
3. prior CV event (myocardial infarction, stroke or revascularization), angina with documented ischaemia, albuminuria, left ventricular hypertrophy, stenosis of coronary, carotid or leg artery
4. If target FPG levels could not be achieved without symptomatic hypoglycemia, investigators were permitted to: replace glyburide used at baseline with a comparable dose of glimepiride; to reduce or stop any other glucose-lowering drugs; and/or to add metformin. If participants developed uncontrolled hyperglycemia, investigators were permitted to add rapid-acting insulin.
5. investigators were advised to avoid insulin until maximal doses of 2 different oral glucose-lowering agents were required in the standard care group.
6. New diabetes was diagnosed during the trial if 2 consecutive FPG levels within a 4-month period were > 7 mM (126 mg/dL); or if a diagnosis of diabetes was made by a physician, and the participant was taking a pharmacologic glucose lowering agent and there was documentation of either a FPG > 7 mM (126 mg/dL) or any glucose value > 11.1 mM (200 mg/dL). New diabetes was diagnosed during down-titration of glargine insulin (i.e. before the last visit) if at least 1 capillary glucose level was ≥ 11.1 mM (200 mg/dl) with a FPG ≥ 7 mmol/l (126 mg/dl); or a random plasma glucose was ≥ 11.1 mM (200mg/dl). New diabetes was diagnosed after the last visit if any FPG was ≥ 7 mM (126 mg/dl) or 2 hour plasma glucose was > 11.1 mM (200 mg/dl) during the first OGTT (3-4 w after), and durability of the effect was assessed by the second test (10-12 w after).

6.1.12.bis. Summary and conclusions. Hard endpoints: Origin trial: Insulin glargin in addition to existing glycaemic control regimen verus standard care

<table>
<tr><td colspan="5">Insulin Glargine (added to existing regimen) Vs Standard care (ORIGIN trial investigators 2012)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td>Results</td><td></td></tr>
<tr><td rowspan="10">1/
12537</td><td rowspan="10">Median follow-up: 6.2y</td><td rowspan="10">DMII or IGT or IFG and cardiovascular disease

Prior R: 59% oral glucose-lowering agent
Duration diabetes: mean 5.4y
Baseline median HbA1c: 6.4%

6% new diabetes[1], 82% prior diabetes, 12% IGT</td><td rowspan="3">Nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes (per 100 person-years) (PE)</td><td>Insulin: 2.94 vs Standard: 2.85(per 100 person-years)
HR=1.02 (CI: 0.94-1.11)
NS: p=0.63</td></tr>
<tr><td><table><tr><td><u>Quality</u>
-1 for low JADAD and no ITT</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr></table></td></tr>
<tr><td>Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Nonfatal myocardial infarction, nonfatal stroke, death from cardiovascular causes, revascularization or hospitalization for heart failure (per 100 person-years)(PE)</td><td>Insulin: 5.52 vs Standard: 5.28
HR=1.04 (CI: 0.97-1.11)
NS: p=0.27</td></tr>
<tr><td><table><tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr></table></td></tr>
<tr><td>Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">New onset diabetes during or after trial (among 1456 participants without baseline diabetes)</td><td>Insulin: 30% vs Standard: 35%
OR=0.80 (CI: 0.64-1.00)
NS: p=0.05</td></tr>
<tr><td><table><tr><td><u>Quality</u>
- 1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
-1different diabetes definition</td><td><u>Imprecision</u>
OK</td></tr></table></td></tr>
<tr><td>Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Severe hypoglycemia (per 100 person-years)</td><td>Insulin: 1.00 vs Standard: 0.31
SS: p<0.001 in favour of standard</td></tr>
<tr><td><table><tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr></table></td></tr>
<tr><td>Grade assessment: moderate quality of evidence</td></tr>
<tr><td>Weight (median change)</td><td>Insulin: +1.6kg vs Standard: -0.5kg
NT</td></tr>
</table>

In this study, patients with a documented cardiovascular disease and type 2 diabetes or IFG or IGT were randomised between adding insulin glargine to existing therapy or standard care. After a median follow-up of 6.2 years there is no significant difference for a composite endpoint of non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality (HR=1.02, 95%CI: 0.94-1.11).

GRADE: *moderate quality of evidence*

In the group treated with insulin glargine there are significantly more cases of severe hypoglycemia than in the standard care group (1.00/100py vs 0.31/100py, $p<0.001$).

GRADE: *moderate quality of evidence*

In a predefined subgroup analysis in patients without baseline diabetes, there is no significant difference between treatment arms in developing diabetes (OR=0.80 (CI: 0.64-1.00)).

GRADE: *low quality of evidence*

6.1.13. Hard endpoints: UKPDS 34bis. Sulphonylurea + metformin versus sulphonylurea

Supplementary RCT in UKPDS 34

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
UKPDS 34 1998 Design: RCT (PG) open label Setting: 23 hospitals in UK	n= 537 Mean age: 59y prior R: maximum doses sulfonylurea DMII duration: mean 7.1 y Mean baseline HbA1c: 7.5% Mean FPG: 9.1 (7.7-11.1 mmol/l Mean BMI: 29.6 kg/m^2 <u>Inclusion</u> - FPG 6.1-15mmol/l - obese and non-overweight patients - Treated with maximum doses of sulfonylurea - No symptoms of hyperglycemia - <u>Exclusion</u> - Ketonuria >3mmol/l - Serum creatinine >175µmol/l - Myocardial infarction in previous year - Current angina or heart failure - >1 vascular event - Retinopathy requiring laser treatment - Malignant hypertension - Uncorrected endocrine disorder - Occupation that precluded insulin therapy - Severe concurrent illness	Median 6.6y	Metformin + sulfonylurea (Met+SU) Vs Sulfonylurea alone (SU)	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING: 0/2 ○ ATTRITION: 1/1 - FU: 96% - ITT: yes - Sponsor: NHS (UK)
				Any diabetes-related endpoint*(PE) (per 1000patient years)	Met+SU: 60.5 vs SU: 58.4 RR=1.04(95%CI: 0.77-1.42) NS	
				Diabetes-related death (PE) (per 1000 patient-years)	Met+SU: 16.8 vs SU:8.6 RR=1.96 (95%CI: 1.02-3.75) **SS, p=0.039 in favour of SU alone** *NNH=22 (treat 22 for median 6.6y to cause one more death from diabetes)*	
				All-cause mortality (PE) (per 1000 patient-years)	Met+SU: 30.3 vs SU:19.1 RR=1.60 (95%CI 1.02-2.52) **SS, p=0.039 in favour of SU alone** *NNT=17(treat 17 for median 6.6y to cause one more death*	
				Myocardial infarction (events/1000py)	Met+SU 22.0 vs SU: 20.2 RR=1.09 (95%CI: 0.67-1.78) NS	
				Microvascular disease (events/1000py)	Met+SU: 10.1 vs SU:12.1 RR=0.84 (95%CI: 1.43-1.66) NS	
				Other clinical endpoints	NS	
				HbA1c over 4 years (median)	Met+SU: 7.7% vs SU:8.2% NT	
				Harms		
				NR		

* Any diabetes-related endpoint = sudden death, death from hypo/hyperglycemia, myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness, cataract extraction

**Microvascular complications (retinopathy requiring photocoagulation, vitreous haemorrhage, and or fatal or non-fatal renal failure).most ofmicrovascular complications were due to fewer cases of retinal photocoagulation

6.1.13.bis. Summary and conclusions. Hard endpoints: UKPDS 34bis. Sulphonylurea + metformin versus sulphonylurea

<table>
<tr><td colspan="6">Metformin + sulphonylurea vs sulphonylurea (UKPDS34 1998)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="15">N=1
N=537</td><td rowspan="15">mean
6.6y</td><td rowspan="15">Mean age: 59y

prior R: maximum doses sulfonylurea DMII duration: mean 7.1y

Mean baseline HbA1c: 7.5%
Mean BMI: 29.6 kg/m^2</td><td rowspan="3">Any diabetes-related endpoint*(PE)</td><td colspan="3">Met+SU: 60.5 /1000 patient years
SU: 58.4/1000 patient years
RR=1.04(95%CI: 0.77-1.42)
NS</td></tr>
<tr><td><u>Quality</u>
-1 (power NR)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment:moderate quality of evidence</td></tr>
<tr><td>Diabetes-related death (PE)</td><td colspan="3">Met+SU: 16.8 /1000 patient years
SU:8.6/1000 patient years
RR=1.96 (95%CI: 1.02-3.75)
SS, p=0.039 in favour of SU alone
NNT=22 (treat 22 for median 6.6y to cause one more death from diabetes)</td></tr>
<tr><td>All-cause mortality (PE)</td><td colspan="3">Met+SU: 30.3/1000 patient years
vs SU:19.1/1000 patient years
RR=1.60 (95%CI: 1.02-2.52)
NS, p=0.039 in favour of SU alone
NNT=17(treat 22 for median 6.6y to cause one more death</td></tr>
<tr><td rowspan="2"></td><td><u>Quality</u>
-1</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u></td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td>Microvascular disease</td><td colspan="3">Met+SU: 10.1 /1000 patient years
vs SU:12.1/1000 patient years
RR=0.84 (95%CI: 1.43-1.66)
NS</td></tr>
<tr><td>Other clinical endpoints</td><td colspan="3">NS</td></tr>
<tr><td rowspan="2"></td><td><u>Quality</u>
-1</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td>HbA1c over 4y (median)</td><td colspan="3">Met+SU: 7.7% vs SU:8.2%
NT</td></tr>
</table>

This additional study within UKPDS compared the addition of metformin in patients inadequately controlled on sulphonylurea versus the continuation of sulphonylurea monotherapy.

No significant difference was found for 'any diabetes-related endpoint'.

Patients treated with metformin + sulphonylurea had a higher risk of diabetes-related death (RR=1.96 (CI: 1.02-3.75). All cause mortality was also higher in patients treated with metformin + sulphonylurea than with sulphonylurea monotherapy (RR= 1.60 (CI 1.02-2.52)).

GRADE: *Moderate quality of evidence*

6.1.14. Linagliptin + sulphonylurea versus placebo + sulphonylurea

No studies met our inclusion criteria.

6.2. Dual therapy versus dual therapy

6.2.1. Pioglitazone + metformin versus sulphonylurea + metformin

6.2.1.1. Pioglitazone + metformin versus gliclazide+ metformin

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Matthews 2005 *Charbonnel 2005** Design: RCT (DB) (PG) Setting: GPs and specialists in internal medicine/ endocrinology	n= 630 mean age: 56.5y Prior R: metformin DMII duration: 5.7y Baseline HbA1c: 8.62% Baseline FPG: 11.6mmol/l <u>Inclusion</u> - Type 2 diabetes (poorly controlled) - HbA1c ≥7.5% to ≤11.0% - Taking only metformin at ≥50% of max recommended dose or at max tolerated dose for ≥3m - Age: 35-65y <u>Exclusion</u> - Type 1 diabetes - Ketoacidosis - Myocardial infarction - TIA or stroke in previous 6m - Symptomatic heart failure - Acute malabsorption or chronic pancreatitis - Familial polyposis coli - Malignant disease in previous 10y - Substance abuse - Pregnant or breastfeeding - Previous treatment with insulin, study drug or other SU or TZD	52w=1y (=16w forced titration + 36w maintenance) *104w=2y (16w forced titration + 88w maintenance)*	Pioglitazone (15-45mg/d) Vs Gliclazide (80-320mg/d) In addition to metformin at pre-study dose (+/-1700mg) (dietary advice was given at baseline)	Efficacy		- Jadad score ○ RANDO: 1/2 ○ BLINDING: 2/2 ○ ATTRITION: 1/1 - FU: 97% - *75%* - ITT: no (modified ITT) - Multicenter: 75 centers in 10 countries - Sponsor: Takeda Europe R&D, Eli Lily & Company
				HbA1c, change from baseline to week 52 (PE)	pioglitazone -0.99% vs gliclazide -1.01% between-group difference: 0.02% (95%CI: -0.15 to 0.19), p=0.837 => NS *pioglitazone -0.89% vs gliclazide -0.77%* *between-group difference: 0.12%, p=0.200 => NS*	
				FPG, adjusted mean change from baseline (SE)	pioglitazone -1.9mmol/l vs gliclazide -1.7mmol/l between-group difference: 0.2mmol/l (95%CI: -0.6 to 0.3), p=0.506 => NS *pioglitazone -1.8mmol/l vs gliclazide -1.1mmol/l* ***between-group difference: 0.7mmol/l, p<0.001 => SS***	
				Mean albumin /creatinine ratio	**pioglitazone -10% vs gliclazide +6%** **p=0.027**	
				Safety (1y)		
				Adverse events	pioglitazone 55.5% vs gliclazide 58.1% NT	
				Serious adverse events	Pioglitazone: 15 patientsvs gliclazide: 20 patients NT	
				Mortality	pioglitazone 0% vs gliclazide 0.6% NT	
				Hypoglycaemia	pioglitazone 1.3% vs gliclazide 11.2% NT	
				Oedema	pioglitazone 6.3% vs gliclazide 2.2% NT	
				Body weight (change from baseline)	pioglitazone +1.5kg vs gliclazide +1.2kg NT	
				Liver enzymes (AST, ALT, GGT, AP)	" smaller mean changes in metformin plus gliclazide group"; NT	

*Matthews 2005 was published online on 15 June 2004 and the trial duration was 1 year.
Charbonnel 2005 was published online on 12 May 2005 and was a follow-up study of the former trial during 2 years.

6.2.1.1.bis. Summary and conclusions. Pioglitazone + metformin versus gliclazide + metformin

<table>
<tr><td colspan="6">Pioglitazone 15-45mg/d vs Gliclazide 80-320mg/d; in addition to ongoing metformin therapy (Matthews 2005(1y), Charbonnel 2005 (2y,FU study))</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="11">N=1,
n= 630</td><td rowspan="11">1 and 2y</td><td rowspan="11">mean age:
56.5y

Prior R:
metformin
2*850mg/d

DMII duration:
5.7y

Baseline
HbA1c: 8.62%</td><td rowspan="4">HbA1c (PE)
1y</td><td colspan="3">Pioglitazone: -0.99%
Gliclazide: -1.01%
between-group difference: 0.02%, p=0.837 => NS</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: high quality of evidence</td></tr>
<tr><td rowspan="3">HbA1c (PE)
2y</td><td colspan="3">Pioglitazone: -0.89%
Gliclazide: -0.77%
between-group difference: 0.12%, p=0.200 => NS</td></tr>
<tr><td><u>Quality</u>
-1 low FU and not ITT</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="2">Adverse events
1y</td><td colspan="3">Pioglitazone 55.5% vs gliclazide 58.1%
NT</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
<tr><td rowspan="2">Hypoglycaemia
1y</td><td colspan="3">Pioglitazone 1.3% vs gliclazide 11.2%
NT</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
<tr><td rowspan="2">Oedema
1y</td><td colspan="3">Pioglitazone 6.3% vs gliclazide 2.2%
NT</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
</table>

In patients with inadequate controlled type 2 diabetes (HbA1c ≥7.5%) on metformin monotherapy, pioglitazone in addition to metformin results in equal reduction of HbA1c after 1 and 2 years compared to gliclazide in addition to metformin. Patients with cardiovascular morbidity were excluded.

GRADE: high quality of evidence

There is no statistical test reported on adverse events

GRADE: NA

6.2.1.2. Pioglitazone + metformin versus glimepiride + metformin

Ref	n/Population	Duration	Comparison	Outcomes			Methodological
Pfutzner 2011 PIOfix-study Design: DB RCT (PG) Setting: NR	n=305 mean age: 59y Prior R: metformin DMII duration: 6y Baseline HbA1c: 7.3% <u>Inclusion</u> DMII; 18-75y; pretreated with metformin as monotherapy <u>Exclusion</u> DMI; history of significant CV, repiratory, GI, hepatic, renal, neurological; psychiatric, and/or hematological disease	6m	Fixed pioglitazone 15mg + metformin 850mg combination twice daily Vs Glimepiride 2mg in the morning + metformin 850mg twice daily	Efficacy			- Jadad score ○ RANDO: 1/2 ○ BLINDING:1/2 ○ ATTRITION: 1/1 - FU: 80% - ITT: yes, LOCF - Other important methodological remarks: Primary outcome was HDL cholesterol - Multicenter:? Centers, 1 country (Germany) - Sponsor: Takeda Pharma?
				Change in HbA1c	Pio+metf: Glime+metf: NS, TNR	-0.8% -1.0%	
				Change in weight	Pio+metf: Glime+metf NS, TNR	+0.7kg +0.7kg	
				Safety (TNR)			
				Serious adverse events:	Pio+metf (n)	Glime+metf (n)	
				Benign breast neoplasm	1	0	
				Chest pain	1	0	
				Lactic acidosis	1	0	
				Acute renal failure	1	0	
				Hepatic failure	1	0	
				Hyponatreamia	1	0	
				hyperkalemia	1	0	
				leukocytosis	1	0	
				thrombocytopenia	1	0	
				tumor marker increased	1	0	
				cardiac failure	2	0	
				cardiomegaly	1	0	
				tachycardia	1	0	
				coronary artery disease	0	1	
				carotid artery stenosis	0	1	
				peripheral artery occlusive dis.	0	1	
				Hypertensive crisis	0	1	
				Prostatic cancer	0	1	
				hypoglycemia	Pio+metf: Glime+metf:	n=2 n=5	
				Peripherical edema	Pio+metf: Glime+metf:	n=8 n=4	

6.2.1.2.bis. Summary and conclusions. Pioglitazone + metformin versus glimepiride + metformin

<table>
<tr><td colspan="6">Pioglitazon 15mg/d vs Glimepiride 2mg/d, in addition to ongoing metformin therapy (Pfutzner 2011)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="10">N=1,
n= 305</td><td rowspan="10">6 mo</td><td rowspan="10">mean age: 59y

Inadequately controlled DMII
Prior R: metformin 2*850mg

DMII duration: 6y

Baseline HbA1c: 7.3%</td><td rowspan="3">HbA1c</td><td colspan="3">Pio+metf: -0.8%
Glime+metf: -1.0%
“NS”, TNR</td></tr>
<tr><td><u>Quality</u>
-1 low jadad and FU</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
-1 for primary outcome cholesterol</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Low quality of evidence</td></tr>
<tr><td rowspan="3">Weight</td><td colspan="3">Pio+metf: +0.7kg
Glime+metf +0.7kg
“NS”, TNR</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
-1</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Low quality of evidence</td></tr>
<tr><td rowspan="2">Hypoglycemia</td><td colspan="3">Pio+metf: n=2
Glime+metf: n=5
NT</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
<tr><td rowspan="2">Peripheral edema</td><td colspan="3">Pio+metf: n=8
Glime+metf: n=4
NT</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
</table>

In patients with type 2 diabetes pioglitazone in addition to metformin results in equal reduction of HbA1c compared to glimepiride in addition to metformin. There is no difference in effect on weight.

GRADE: Low quality of evidence

There is no statistical test reported on adverse events.

GRADE: NA

6.2.2. DPP-4 inhibitors + metformin versus sulphonylurea + metformin

6.2.2.1. Linagliptin + metformin versus glimepiride + metformin

Ref	n/Population	Duration	Comparison	Outcomes			Methodological
Gallwitz 2012 Design: RCT (DB-) (PG) non-inferiority Setting: outpatients	n= 1552 (FAS: 1519, PPS: 905)* mean age: 60y Prior R: metformin alone or with 1 additional OAD (washed out during screening) DMII duration: 53% of patients had DM II for ≥5 years Baseline HbA1c: 7.7% 40% female, 60% male 85% white, 12% Asian, 3% black <u>Inclusion</u> - Type 2 diabetes - HbA1c 6.5-10% - Taking metformin at stable dose of ≥1500mg/d or 1 additional OAD - Age: 18-80y - BMI ≤40 irrespective of ethnicity <u>Exclusion</u> - Myocardial infarction, stroke or	2y=104w	Linagliptin 5mg/d vs Glimepiride 1-4mg/d Added to metformin (93% ≥1500mg/d)	Efficacy			- Jadad score ○ RANDO: 2/2 ○ BLINDING: 2/2 ○ ATTRITION: 1/1 - FU: 77% 1552 randomised, 360 discontinued treatment - ITT: no FAS and PPS data were reported - Multicenter: 209 centers 16 countries - Sponsor: Boehringer Ingelheim
					FAS*	PPS*	
				Change in HbA1c from baseline to week 104 (adjusted mean)(PE)	linagliptin -0.16% vs glimepiride -0.36% Between-group difference: 0.20% (95% CI: 0.09-0.30) p=0.0004 Non-inferiority criterion: 0.35% **Linagliptin is non-inferior to glimepiride**	linagliptin -0.35% vs glimepiride -0.53% Between-group difference: 0.17% (95% CI: 0.07-0.28) p=0.0001 Non-inferiority criterion: 0.35% **Linagliptin is non-inferior to glimepiride**	
				Change in body weight vs baseline	linagliptin (−1.4 [SE 0.2] kg) vs glimepiride (1.3 [0.2] kg) treatment difference −2.7 kg (97.5% CI −3.2 to−2.2), p<0.0001 **SS in favour of linagliptin**		
				Safety			
				Any adverse event	linagliptin 85% vs glimepiride 91% NT		
				Serious adverse event	linagliptin 17% vs glimepiride 21% NT		
				Mortality	linagliptin 1% vs glimepiride 1% NT		

	TIA in previous 6m - Impaired hepatic function - Treatment with rosiglitazone, pioglitazone, GLP-1 analogue or agonist, insulin or antiobesity drug during previous 3m			Adjudicated major cardiovascular events (n° of patients with at least one event)	Linagliptin 12(2%) vs glimepiride 26(3%) **RR= 0·46 (0·23–0·91) p=0.02** **SS in favour of linagliptin**	
				Cardiovascular death	Linagliptin 2 vs glimepiride 2 RR=1·00 (0·14–7·07) NS	
				Non-fatal myocardial infarction	Linagliptin 6 vs glimepiride 10 RR=0·60 (0·22–1·64) NS	
				Non-fatal stroke	Linagliptin 3 vs glimepiride 11 0·27 (0·08–0·97) P=0.03 SS in favour of linagliptin	
				Hypoglycemia	**linagliptin 7% vs glimepiride 36%** **SS in favour of linagliptin p<0.0001**	
				Neoplasms	linagliptin 5% vs glimepiride 6% NT	
				Pancreatitis	linagliptin <1% vs glimepiride 0% NT	

* FAS (functional analysis set) included randomised patients who received at least one dose of treatment, had a baseline HbA1c measurement and at least one on-treatment HbA1c measurement. PPS (per protocol set) completers included patients in FAS who did not have important protocol violations, completed at least 684 days of treatment and had HbA1c measured at week 104.

6.2.2.1.bis. Summary and conclusions. Linagliptin + metformin versus glimepiride + metformin

<table>
<tr><td colspan="6">Linagliptin 5mg/d + Metformin ≥1500mg/d vs Glimepiride max 4mg/d + Metformin ≥1500mg/d (Gallwitz 2012)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="11">N= 1
n=
1552</td><td rowspan="11">2y</td><td rowspan="11">mean age: 60y

Prior R: metformin* alone or with 1 additional OAD (washed out during screening)

DMII duration: 53% of patients had DM II for ≥5 years

Baseline HbA1c: 7.7% (6.5-10%)</td><td rowspan="3">Change in HbA1c (PE)</td><td colspan="4">lina+met -0.16% vs glim+met -0.36%
Between-group difference: 0.20% (95% CI: 0.09-0.30) p=0.0004
Non-inferiority criterion: 0.35%
Linagliptin combi is non-inferior to glimepiride combi</td></tr>
<tr><td><u>Quality</u>
-1 due to high drop-out rate</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Change in body weight</td><td colspan="4">lina+met −1.4 kg vs glim+met +1.3 kg
treatment difference −2.7 kg (97.5% CI −3.2 to−2.2), p<0.0001
SS in favour of linagliptin combination therapy</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Adjudicated major cardiovascular events (number of patients with at least one event)</td><td colspan="4">lina+met 12(2%) vs glim+met 26(3%)
RR= 0·46 (0·23–0·91) p=0.02
SS in favour of linagliptin combination therapy</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
-1 for low event rates</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Hypoglycemia</td><td colspan="4">lina+met 7% vs glim+met 36%
p<0.0001
SS in favour of linagliptin combination therapy</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
</table>

- In this 2-year non-inferiority trial, patients with type 2 diabetes and HbA1c 6.5-10% on stable dose of metformin alone or with one additional oral antidiabetic drug (washed out during screening) were randomly assigned to linagliptin 5mg or glimepiride 1-4mg once daily.
Reductions in mean HbA1c were similar in both groups (difference: 0.20%) meeting the predefined non-inferiority criterion of 0.35%.

GRADE: moderate quality of evidence

- Body weight decreased with linagliptin but increased with glimepiride. The treatment difference was -2.7kg (p<0.0001).

GRADE: moderate quality of evidence

- The overall incidence of hypoglycemic events was significantly, about 5 times lower with linagliptin than with glimepiride.

GRADE: moderate quality of evidence

- Linagliptin was also associated with significantly fewer cardiovascular events compared with glimepiride.

GRADE: low quality of evidence

6.2.2.2. Saxagliptin + metformin versus glipizide + metformin

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Göke 2010 Design: DB RCT (PG) Setting: 'multicenter'	n=858 mean age: 57.6y Prior R: metformin mean dose 1910 mg DMII duration: 5.4y Baseline HbA1c: 7.7% <u>Inclusion</u> Age >= 18y, DMII, HbA1c >6.5-10%, stable dose of metformin >=1500mg/d <u>Exclusion</u> DMI; congestive heart failure; significant CV history in past 6m; history of haemoglobinopathies; alcohol or drug abuse; liver disease; history of ketoacidosis or hyperosmolar non-ketotic coma; previous insulin therapy; treatment with systemic glucocorticoids, treatment with thiazolidinedione	52 w	Saxagliptin 5mg/d + metformin Vs Glipizide titrated to max 20 mg/d (mean final dose 14.7mg) + metformin 2 week placebo run-in	Efficacy		- Jadad score o RANDO: 2/2 o BLINDING: 2/2 o ATTRITION: 1/1 - FU: 73.8% - ITT: yes, "to confirm PP results" , results not reported - Other important methodological remarks : results of ITT analysis not reported - Multicenter: ? centers, ? countries - Sponsor: AstraZenica
				Change in HbA1c PP analysis (PE)	Saxa + metform: -0.74% Glipi + metform: -0.80% Mean diff= 0.06% (-0.05, 0.16) NS	
				Change in HbA1c ITT analysis	Saxa + metform: -0.57% Glipi + metform: -0.66% "consistent results", TNR	
				% of patients with HbA1c<7% in patients with baseline HbA1c>= 7%	Saxa + metform: 42.6% Glipi + metform: 47.8% Mean diff= 1-5.2 (-12.9, 2.5) NS	
				Body weight	Saxa + metform: -1.1kg Glipi + metform: +1.1kg **Mean diff= -2.2kg (-2.7, -1.7)** **SS, p<0.0001**	
				Safety		
				Serious adverse events	Saxa + metform: 9.1% Glipi + metform: 7.4% TNR	
				Deaths	Saxa + metform: 2/428 patients Glipi + metform: 2/430 patients	
				Hypoglycaemia	Saxa + metform: 3.0% Glipi + metform: 36.3% **Mean diff= -33.2% (-38.1, -28.5)** **SS, p<0.0001**	
				Lymphopaenia, thrombocytopaenia, Skin disorders, Localised oedema	≤ 2 patients in each treatment group	

				CV Adverse Events	Saxa + metform: 1.9% Glipi + metform: 0.9% TNR	
				Pancreatitis	Saxa + metform: 0% Glipi + metform: 0.2% TNR	
				Diarrhoea	Saxa + metform: 5.1% Glipi + metform: 3.7% TNR	

6.2.2.2.bis. Summary and conclusions. Saxagliptin + metformin versus glipizide + metformin

<table>
<tr><td colspan="5">Saxagliptin 5mg/d vs Glipizide max 20mg/d, in addition to ongoing metformin (Göke 2010)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="2">Results</td></tr>
<tr><td rowspan="11">N= 1
n= 858</td><td rowspan="11">52w</td><td rowspan="11">mean age:
57.6y

Prior R:
metformin
mean dose
1910 mg

DMII duration:
5.4y

Baseline
HbA1c: 7.7%</td><td>HbA1c (PE)</td><td>Per protocol:
Saxa + metform: -0.74%
Glipi + metform: -0.80%
Mean diff= 0.06% (-0.05, 0.16)
NS
ITT (no statistical analysis)
Saxa + metform: -0.57%
Glipi + metform: -0.66%</td></tr>
<tr><td colspan="2"><table><tr><td><u>Quality</u>
-1 for low FU and no reporting ITT</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr></table></td></tr>
<tr><td colspan="2">Grade assessment: Moderate quality of evidence</td></tr>
<tr><td>Body weight</td><td>Saxa + metform: -1.1kg
Glipi + metform: +1.1kg
Mean diff= -2.2kg (-2.7, -1.7)
SS, p<0.0001</td></tr>
<tr><td colspan="2"><table><tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr></table></td></tr>
<tr><td colspan="2">Grade assessment: Moderate quality of evidence</td></tr>
<tr><td>Serious adverse events</td><td>Saxa + metform: 9.1%
Glipi + metform: 7.4%
NT</td></tr>
<tr><td colspan="2">Grade assessment: NA</td></tr>
<tr><td>Hypo-glycaemia</td><td>Saxa + metform: 3.0%
Glipi + metform: 36.3%
Mean diff= -33.2% (-38.1, -28.5)
SS, p<0.0001</td></tr>
<tr><td colspan="2"><table><tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr></table></td></tr>
<tr><td colspan="2">Grade assessment: Moderate quality of evidence</td></tr>
</table>

In patients with type 2 diabetes and inadequate glycaemic control on metformin (HbA1c ≥6.5%), saxagliptin in addition to metformin is non-inferior to glipizide plus metformin in reducing HbA1c after 52 weeks.

GRADE: Moderate quality of evidence

Weight increased with glipizide and decreased with saxagliptin. The mean difference of -2.2kg between treatment arms is statistically significant (p<0.0001).

GRADE: Moderate quality of evidence

Saxagliptin has a lower risk of hypoglycaemia compared to glipizide.

GRADE: Moderate quality of evidence

6.2.2.3. Sitagliptin + metformin versus glimepiride + metformin

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Arechavaleta 2011 Design: DB RCT (PG) Non-inferiority Setting: 'multicenter'	n= 1035 mean age: 56y Prior R: metformin DMII duration: 6.8y Baseline HbA1c: 7.5% <u>Inclusion</u> DMII, >=18y, HbA1c 6.5-9.0%; stable dose metformin >=1500mg/d <u>Exclusion</u> DMI, renal function impairment	30 w	Sitagliptin 100mg/d + metformin Vs Glimepiride titrated to max 6mg/d + metformin Mean dose achieved with glimepiride 2.1mg/d 2w placebo run-in	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING:2/2 ○ ATTRITION: 1/1 - FU: 90.4% - ITT: yes, to assess the robustness of the primary PP analysis - Multicenter: ? centers, ? countries - Sponsor: Merck
				Change in HbA1c PP analysis (PE)	Sita + metform: -0.47% Glime + metform: -0.54% Mean diff= 0.07% (95%CI -0.03, 0.16) NS	
				Change in HbA1c ITT analysis	Sita + metform: -0.46 Glime + metform: -0.52 Mean diff= 0.07 (95%CI -0.02, 0.16) NS	
				% of patients with HbA1c<7%	Sita + metform: 52.4% Glime + metform: 59.6% **Mean diff= -7.5% (**95%CI **-13.8, -1.1)** **SS**	
				Safety		
				Hypoglycaemia	Sita + metform: 7% Glime + metform: 22% **Mean diff=-15.0% (**95%CI **-19.3, -10.9)** **SS, p<0.001**	
				Serious adverse events	Sita + metform: 16/516 (3.1%) Glime + metform: 11/519 (2.1%) Mean diff= 1.0 (95%CI -1.0, 3.1) NS	
				Change in weight	Sita+metform -0.8kg Glime+metform +1.2kg **Mean diff = -2.0kg** **SS, p<0.001**	
				Death	Sita+metform: 0 Glime+metform: 1 (haemorrhagic stroke) Mean diff= -0.2 (95%CI -1.1, 0.6) NS	

6.2.2.3. bis. Summary and conclusions. Sitagliptin + metformin versus glimepiride + metformin

<table>
<tr><td colspan="7">Sitagliptin 100mg/d vs Glimepiride max 6mg/d, in addition to ongoing metformin (Arechavaleta 2011)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="4">Results</td></tr>
<tr><td rowspan="12">N=1,
n=
1035</td><td rowspan="12">30w</td><td rowspan="12">-mean age: 56y
-DMII duration: 6.8y
-Baseline HbA1c: 7.5%
-stable dose of metformin (>1500mg/d)</td><td rowspan="3">HbA1c (PE)</td><td colspan="4">Sita + metform: -0.46
Glime + metform: -0.52
Mean diff= 0.07 (95%CI -0.02, 0.16)
NS</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: High quality of evidence</td></tr>
<tr><td rowspan="3">Weight</td><td colspan="4">Sita+metform -0.8kg
Glime+metform +1.2kg
Mean diff = -2.0kg
SS, p<0.001</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: High quality of evidence</td></tr>
<tr><td rowspan="2">Hypoglycemia</td><td colspan="4">Sita + metform: 7%
Glime + metform: 22%
Mean diff=-15.0% (95%CI -19.3, -10.9)
SS, p<0.001</td></tr>
<tr><td colspan="4">Grade assessment: High quality of evidence</td></tr>
<tr><td rowspan="3">Serious adverse events</td><td colspan="4">Sita + metform: 16/516 (3.1%)
Glime + metform: 11/519 (2.1%)
Mean diff= 1.0 (95%CI -1.0, 3.1)
NS</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: High quality of evidence</td></tr>
</table>

In patients with type 2 diabetes and inadequate glycaemic control (HbA1c ≥6.5%) on metformin monotherapy, the addition of sitagliptin led to similar improvement after 30 weeks compared to the addition of glimepiride.
Weight loss is observed for sitagliptin and weight gain is observed for glimepiride. Mean difference between both groups is -2.0 kg (p<0.001).

GRADE: High quality of evidence

Compared to treatment with glimepiride, sitagliptin was associated with a lower risk of hypoglycaemia.

GRADE: High quality of evidence

6.2.2.4. Sitagliptin + metformin versus glipizide + metformin

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Nauck 2007 Design: DB RCT (PG) Non-inferiority Setting: NR	n=1172 mean age: 57y Prior R: OAD naive 4.5%; monotherapy 67%; bitherapy 28.5% (washed out during screening) DMII duration: 6.4y Baseline HbA1c: 7.7% <u>Inclusion</u> DMII, 18-78y; No treatment, monotherapy or biotherapy <u>Exclusion</u> History of typeI diabetes; insulin use within 8w of screening;renal function impairment	52w	Sitagliptin 100mg +metformin vs Glipizide 5mg (uptitrated to max. 20mg) + metformin Metformin ≥1500mg monotherapy dose titration/stabilisation period (>8w) 2w single- blind placebo run-in	Efficacy		- Jadad score ○ RANDO: 1/2 ○ BLINDING: 1/2 ○ ATTRITION: 1/1 - FU: 68 % - ITT: yes, LOCF - Multicenter: yes, n° of centers NR - Sponsor:Merck
				HbA1c change from baseline (PE) Per protocol analysis:	Sitagliptin -0.67% Glipizide -0.67% Diff sita-glipi -0.01 (-0.09, 0.08) NS	
				HbA1c change from baseline (PE) LOCF analysis:	Sitagliptin -0.51% Glipizide-0.56% Diff sita-glipi 0.04% (-0.04, 0.13) NS	
				HbA1c <7% Per protocol analysis:	Sitagliptin 63% Glipizide59% Diff sita-glipi 3.9% (-2.8, 10.7) NS	
				HbA1c <7% LOCF analysis:	Sitagliptin 52% Glipizide51% Diff sita-glipi 0.9% (-4.9, 6.7) NS	
				Body weight change from baseline	Sitagliptin -1.5kg Glipizide 1.1kg Diff sita-glipi **-2.5kg (-3.1, 2.0)** **SS; P<0.001** "clinically meaningful difference"	
				Safety		
				Gastro-intestinal AE: Abdominal pain Nausea vomiting diarrhoea	sitagliptine glipizide 2.7% 2.1% 2.6% 2.7% 0.9% 1.5% 5.8% 5.5% " not significantly different"	
				One or more AE	Sitagliptine 71.3% Glipizide 76.0% TNR	
				deaths	Sitagliptine 1 (0.2%)	

					(1 trauma) Glipizide 2 (0.3%) (1 sudden cardiac death, 1 myocardial infarction)	
				hypoglycaemia	Sitagliptine 4.9% Glipizide 32% “substantial and clinically important difference in proportion of patients reporting hypoglycaemia” , TNR	

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Seck 2010 Design: DB RCT (PG) 2y follow-up of study Nauck 2007 Setting: NR	Randomised: n=1172 PP cohort: n=504 mean age 57y Prior R: OAD naive 5%; monotherapy 75%; bitherapy 20% ((washed out during screening) DMII duration: 5.8y Baseline HbA1c: 7.3% <u>Inclusion</u> DMII, 18-78y; No treatment, monotherapy or bitherapy <u>Exclusion</u> History of typeI diabetes; insulin use within 8w of screening;renal function impairment	2 yr	Sitagliptine 100 mg + metformin Vs Glipizide 5mg (uptitrated to max. 20 mg) + metformin 2w single- blind placebo run-in	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING:2/2 ○ ATTRITION: 1/1 - FU: 44% - ITT: yes, LOCF - Other important methodological remarks: high dropout rate (56%) - Multicenter: yes, n° of centers NR - Sponsor: Merck
				HbA1c change from baseline (PE) Per protocol analysis:	Sitagliptin -0.54% Glipizide -0.51% Diff sita-glipi -0.03 (-0.13, 0.07)) NS	
				HbA1c change from baseline (PE) LOCF analysis:	Sitagliptin -0.33% Glipizide -0.35% Diff sita-glipi 0.01% (-0.08, 0.10) NS	
				HbA1c <7% Per protocol analysis:	Sitagliptin 63% Glipizide 59% Diff sita-glipi NR TNR	
				HbA1c <7% LOCF analysis:	Sitagliptin 42% Glipizide 39% Diff sita-glipi NR TNR	
				Safety		
				One or more AE	Sitagliptin 76.9% Glipizide82.2% **Diff sita-glipi -5.3 (-9.9, -0.7) SS**	
				Deaths	Sitagliptin 1 (0.2%) Glipizide8 (1.4%) **Diff sita-glipi -1.2% (-2.5, -0.2) SS**	
				Hypoglycaemia	Sitagliptine 5.3% Glipizide34.1% **Diff sita-glipi -28.8% (-33,-24.5) SS**	

				Other (serious) AE:	Sita	glipizid	diff (95%CI)	
				Cystitis	1.4%	0.2%	**1.2% (0.2, 2.5), SS**	
				Urinary tract infection	7.5%	4.3%	**3.2 % (0.5, 6.0), SS**	
				Weight decreased	1.0%	0.0%	**1.0 % (0.2, 2.2), SS**	
				Asthma	1.5%	0.3%	**1.2 %(0.0, 2.6), SS***	
				Cataract	0.5%	2.4%	**-1.9% (-3.5, -0.5), SS**	
				Peripheral oedema	2.2%	3.8%	-1.6% (-3.6, 0.4), NS	
				Hypoaesthesia	0.2%	1.7%	**-1.5% (-3.0, -0.4), SS**	
				Prostatitis	0.2%	1.2%	-1.0% (-2.3, -0.0), NS	
				pyelonephritis	n=1	n=3	TNR	

*in the text it is noted that the confidence interval excluded zero for asthma, which cannot be seen in the CI due to rounding

6.2.2.4.bis. Summary and conclusions. Sitagliptin + metformin versus glipizide + metformin

Sitagliptin 100mg vs Glipizide 5mg (uptitrated to max 20mg) in addition to ongoing Metformin treatment (Nauck 2007, Seck 2010)				
N/n	**Duration**	**Population**	**Results**	
N=1, n= 1172	Results after 1y and 2y	-mean age 57y -Prior R: OAD naive 5%, monotherapy 75%; bitherapy 20% -DMII duration: 5.8y -Baseline HbA1c: 7.3%	HbA1c (PE) Results after 1y	Sitagliptin -0.51% Glipizide-0.56% Diff sita-glipi 0.04% (-0.04, 0.13); NS
				Quality: OK; Consistency: NA; Directness: OK; Imprecision: OK
				Grade assessment: *High quality of evidence*
			HbA1c (PE) Results after 2y	Sitagliptin -0.33% Glipizide -0.35% Diff sita-glipi 0.01% (-0.08, 0.10); NS
				Quality: -1 high drop out; Consistency: NA; Directness: OK; Imprecision: OK
				Grade assessment: *moderate quality of evidence*
			Weight Results after 1y	Sitagliptin -1.5kg Glipizide 1.1kg Diff sita-glipi **-2.5kg (-3.1, 2.0)** **SS; P<0.001** "clinically meaningful difference"
				Quality: OK; Consistency: NA; Directness: OK; Imprecision: OK
				Grade assessment: *High quality of evidence*
			Deaths after 2y	Sitagliptin 1 (0.2%) Glipizide 8 (1.4%) **Diff sita-glipi -1.2% (-2.5, -0.2) SS**
				Quality: -1; Consistency: NA; Directness: OK; Imprecision: -1 low event rate
				Grade assessment:*low quality of evidence*
			Hypoglycemia after 2y	Sitagliptine 5.3% Glipizide 34.1% **Diff sita-glipi -28.8% (-33,-24.5) SS**
				Quality: -1; Consistency: NA; Directness: OK; Imprecision: OK
				Grade assessment: *moderate quality of evidence*
			Other AE (2y)	Sita / glipizid / diff (95%CI)
			Cystitis	1.4% / 0.2% / **1.2% (0.2, 2.5), SS**
			UTI	7.5% / 4.3% / **3.2 % (0.5, 6.0), SS**
			Weight decrease	1.0% / 0.0% / **1.0 % (0.2, 2.2), SS**
			Asthma	1.5% / 0.3% / **1.2 %(0.0, 2.6), SS**
			Cataract	0.5% / 2.4% / **-1.9% (-3.5, -0.5), SS**
			Peripheral oedema	2.2% / 3.8% / -1.6% (-3.6, 0.4), NS
			Hypoaesthesia	0.2% / 1.7% / **-1.5% (-3.0, -0.4), SS**
			Prostatitis	0.2% / 1.2% / -1.0% (-2.3, -0.0), NS
			Pyelonephritis	n=1 / n=3 / TNR
				Quality: -1; Consistency: NA; Directness: OK; Imprecision: -1
				Grade assessment: *low quality of evidence*

-This trial reported results of treatment after 1 (Nauck 2007) and 2 years (Seck 2010) with sitagliptin versus glipizide, in patients with type 2 diabetes and inadequate glycaemic control. In patients with type 2 diabetes adding sitagliptin to ongoing metformin therapy gives similar reduction of HbA1c compared to glipizide.

GRADE: High quality of evidence

Weight decreased with sitagliptin and increased with glipizide. The mean difference between treatment arms of 2.5kg was statisitically significant.

GRADE: High quality of evidence

-Hypoglycemia occurs less frequently with sitagliptin.

GRADE: moderate quality of evidence

Mortality is higher in the glipizide group.
Sitagliptin is associated with a higher risk of urinary tract infections and asthma.
More cataract and hypoesthesia is observed in the glipizide group

GRADE: low quality of evidence

6.2.2.5. Vildagliptin + metformin versus gliclazide + metformin

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Filozof 2010 Design: DB RCT (PG) Setting: "multicenter"	n=1007 mean age: 59.5y Prior R: metformin DMII duration: 6.6y Baseline HbA1c: 8.5% <u>Inclusion</u> DMII, age 18-78y, HbA1c 7.5-11%; Stable dose of metformin >=1500mg <u>Exclusion</u> DMI; acute metabolic complications; serious cardiac conditions; clinically significant renal or liver disease	52w	Vildagliptin 2x50 mg/d + metformin Vs Gliclazide uptitrated to max 320 mg/d + metformin	Efficacy		- Jadad score ○ RANDO: 1/2 ○ BLINDING:2/2 ○ ATTRITION: 1/1 - FU: 81.3% - ITT: yes but results not reported, "a sensitivity analysis based on the ITT population was performed to assess the robustness of the conclusion" - Multicenter: NR - Sponsor: Novartis
				Change in HbA1c PP analysis (PE)	Vilda+metform: -0.81% Glicla+metform: -0.85% Mean diff in graph (95% BI -0.11%, 0.20%) NS "comparable results in ITT population", TNR	
				% of patients with HbA1c <7%	Vilda+metform: 29.6% Glicla+metform: 31.9% TNR, "similar"	
				Safety		
				% of patients with serious adverse events	Vilda+metform: 11.8% Glicla+metform: 16.4% Mean diff NR; TNR	
				Body weight	Vilda+metform: +0.08kg Glicla+metform: +1.36kg **P<0.001** **SS**	
				Hypoglycaemic events	"Low in both groups, but nearly twice as high in the gliclazide group als in the vildagliptin group" (11 vs 6 events, TNR)	
				Clinically significant gastrointestinal AE	Vilda+metform: 0.6% Glicla+metform: 0.8% TNR	
				Deaths	1 in each group	

6.2.2.5. bis. Summary and conclusions. Vildagliptin + metformin versus gliclazide + metformin

<table>
<tr><td colspan="6">Vildagliptin 2*50mg/d vs Gliclazide max 320mg/d , in addition to ongoing metformin (Filozof 2010)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="10">N=1,
n=
1007</td><td rowspan="10">52w</td><td rowspan="10">mean age:
59.5y

Prior R: Stable dose of metformin >=1500mg/d

DMII duration:
6.6y
Baseline HbA1c:
8.5%</td><td rowspan="3">HbA1c (PE) (per protocol)</td><td colspan="3">Vilda+metform: -0.81%
Glicla+metform: -0.85%
Mean diff in graph (95% BI -0.11%, 0.20%)
NS
“comparable results in ITT population”, TNR</td></tr>
<tr><td><u>Quality</u>
-1 for low FU and no ITT reported</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Body weight</td><td colspan="3">Vilda+metform: +0.08kg
Glicla+metform: +1.36kg
P<0.001
SS</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="2">Hypo-glycaemic events</td><td colspan="3">“Low in both groups, but nearly twice as high in the gliclazide group als in the vildagliptin group” (11 vs 6 events, TNR)</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
<tr><td rowspan="2">% of patients with serious adverse events</td><td colspan="3">Vilda+metform: 11.8%
Glicla+metform: 16.4%
Mean diff NR; TNR</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
<tr><td rowspan="2">Clinically significant gastrointestinal AE</td><td colspan="3">Vilda+metform: 0.6%
Glicla+metform: 0.8%
TNR</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
</table>

In patients with type 2 diabetes and inadequate glycaemic control (HbA1c ≥7.5%) on metformin monotherapy, the addition of vildagliptin provided similar HbA1c-lowering efficacy compared with gliclazide after 52 weeks of treatment.

GRADE: Moderate quality of evidence

Weight doesn't decrease with vildagliptin (+0.08 kg) and increases with gliclazide (+1.36kg). the difference in weight gain between both groups is statistically significant (p<0.001).

GRADE: Moderate quality of evidence

There is no statistical test reported for adverse events.

GRADE: NA

6.2.2.6. Vildagliptin + metformin versus glimepiride + metformin

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Matthews 2010 (Ferrannini 2009) Design: DB RCT (PG) Setting: 'multicenter'	n=3118 mean age: 57 Prior R: metformin mean dose 1894mg DMII duration: 5.7y Baseline HbA1c: 7.3% <u>Inclusion</u> Age 18-73y, DMII, HbA1c 6.5-8.5%, stable dose of >=1500 mg metformin <u>Exclusion</u> DMI, acute metabolic complications, acute infections; serious cardiac conditions, clinically significant liver or renal disease	2y	Vildagliptin 2x50mg + metformin Vs Glimepiride up to 6mg (mean dose at 2y 4.6mg) + metformin	**Efficacy**		- Jadad score ○ RANDO: 1/2 ○ BLINDING:2/2 ○ ATTRITION: 1/1 - FU: 62.4% - ITT: yes, LOCF, but only results of PP analysis were reported - Multicenter: ? centers, ? countries - Sponsor: Novartis
				Change in HbA1c PP analysis (PE)	Vilda+metform: -0.1% Glime+metform: -0.1% ITT " similar results", NR	
				% of patients with HbA1c <7% in the group of patients with HbA1c>=7 at baseline (PP analysis)	Vilda+metform: 36.9% Glime+metform: 38.3% NS	
				% of patients with HbA1c <7% without hypoglycaemia (PP analysis)	Vilda+metform: 36.0% Glime+metform: 28.8% **P=0.004, SS** ITT "similar results", NR	
				Change in body weight	Vilda+metform: -0.3kg Glime+metform: +1.2kg **Mean diff=1.5kg** **SS, p<0.001**	
				Safety		
				Patients with serious adverse events	Vilda+metform: 15.2% Glime+metform: 16.4% TNR	
				Patients with hypoglycaemic events	Vilda+metform: 2.3% Glime+metform: 18.2% "14 fold difference", TNR	
				Deaths	Vilda+metform: 0.5% Glime+metform: 0.4%	
				Other adverse events: Diarrhoea Nausea Peripheral oedema	Vilda+metform glime+metform 7.4% 7.3% 4.9% 6.0% 2.9% 5.2% TNR	

6.2.2.6. bis. Summary and conclusions. Vildagliptin + metformin versus glimepiride + metformin

<table>
<tr><td colspan="6">Vildagliptin 2*50mg/d vs Glimepiride max 6mg/d, in addition to ongoing metformin (Matthews 2010, Ferranini 2009)</td></tr>
<tr><th>N/n</th><th>Duration</th><th>Population</th><th>Results</th><th colspan="3"></th></tr>
<tr><td rowspan="8">N=1,
n=
3118</td><td rowspan="8">2y</td><td rowspan="8">Mean age: 57

Prior R: metformin, mean dose 1894mg

DMII duration: 5.7y

Baseline HbA1c: 7.3%</td><td rowspan="3">HbA1c (PE)</td><td colspan="3">Change in HbA1c PP analysis :
Vilda+metform: -0.1%
Glime+metform: -0.1%
NS
ITT “ similar results”, NR</td></tr>
<tr><td><u>Quality</u>
-1 for low FU and not reporting ITT</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Moderate quality of evidence</td></tr>
<tr><td rowspan="3">Change in body weight</td><td colspan="3">Vilda+metform: -0.3kg
Glime+metform: +1.2kg
Mean diff=1.5kg
SS, p<0.001</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Moderate quality of evidence</td></tr>
<tr><td rowspan="2">Patients with serious adverse events</td><td colspan="3">Vilda+metform: 15.2%
Glime+metform: 16.4%
TNR</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
<tr><td rowspan="2">Patients with hypoglycaemic events</td><td colspan="3">Vilda+metform: 2.3%
Glime+metform: 18.2%
“14 fold difference”, TNR</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
</table>

In patients with type 2 diabetes and inadequate glycaemic control (HbA1c ≥6.5%) on metformin monotherapy, the addition of vildagliptin led to similar improvement in reduction of HbA1c after 52 weeks compared to glimepiride.

GRADE: Moderate quality of evidence

There is a small decrease in weight with vildagliptin and an increases with glimepiride. The mean difference between both groups is 1.5kg (p<0.001)

GRADE: Moderate quality of evidence

There is no statistical test reported for adverse events.

GRADE: NA

6.2.3. DPP-4 inhibitors + metformin versus pioglitazone + metformin

6.2.3.1.Vildagliptin + metformin versus pioglitazone + metformin

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Bolli 2008 *Bolli 2009* Design: RCT (DB) (PG) Non-inferiority trial Setting: NR	n=576 mean age: 57y predominantly Caucasian Prior R: metformin ≥1500mg/d DMII mean duration: 6.4y Baseline mean HbA1c: 8.4% Baseline mean FPG: 11.0mmol/l <u>Inclusion</u> - Type 2 diabetes - HbA1c 7.5-11% - Receiving stable dose of metformin ≥1500mg/d - 18-77y - BMI 22-45 - FPG<15mmol/l (eligible patients met all inclusion criteria) <u>Exclusion</u> - Type 1 or secondary forms of diabetes - Acute metabolic	24w *52w = 1y*	Vildagliptin 100mg/d Vs Pioglitazone 30mg/d Added to metformin >2000mg/d	Efficacy		- Jadad score ○ RANDO: 1/2 ○ BLINDING: 1/2 ○ ATTRITION: 1/1 (24w) ○ ATTRITION 0/1 (1y) - FU: 88% at 24w NR at 1y - ITT: no 'modified ITT) - Multicenter: 118 centers in 9 countries - Sponsor: Novartis Pharmaceuticals Corporation
				Change from baseline HbA1c (adjusted mean) (PE) 24w	vildagliptin -0.88% vs pioglitazone -0.98% between-group difference: 0.10% (95%CI: -0.05 to 0.26) **vildagliptin is non-inferior to pioglitazone when added to metformin** (non-inferiority margin: 0.3% and 0.4%)	
				52w	*vildagliptin -0.6% vs pioglitazone -0.6%* ***vildagliptin is non-inferior to pioglitazone when added to metformin*** *(p<0.001)*	
				Change from baseline FPG (adjusted mean) 24w	vildagliptin -1.4mmol/l vs pioglitazone -2.1mmol/l between-group difference: 0.10mmol/l (95%CI: -0.05 to 0.26) vildagliptin is <u>not</u> non-inferior to pioglitazone when added to metformin (non-inferiority margin: 0.6mmol/l)	
				52w	*vildagliptin -1.0mmol/l vs pioglitazone -1.6mmol/l (p<0.001)*	
				Change from baseline body weight (adjusted mean) 24w	**vildagliptin +0.3kg vs pioglitazone +1.9kg** between-group difference: -1.6kg (p<0.001) => SS	
				52w	*vildagliptin +0.2kg (NS change) vs pioglitazone +2.6kg (SS change: p<0.001)*	
				Safety		
				Any adverse event	vildagliptin 60.0% vs pioglitazone 56.4% => NT	
					vildagliptin 67.8% vs pioglitazone 68.2% => NT	
				Peripheral edema	vildagliptin 8.8% vs pioglitazone 6.1% => NT	
					vildagliptin 10.8% vs pioglitazone 11.1% => NT	

	diabetic complications - Myocardial infarction - Unstable angina - Coronary artery bypass in previous 6m - Congestive heart failure - Liver disease - Laboratory abnormalities*			Serious adverse event	vildagliptin 2.0% vs pioglitazone 4.6% => NT	
					vildagliptin 4.1% vs pioglitazone 8.9% => NT	
				Cardio-cerebrovascular adverse event (ACS, stroke, cardiac arrhythmia, TIA, syncope)	vildagliptin 0.7% vs pioglitazone 1.4% => NT	
					vildagliptin 0.7% vs pioglitazone 2.1% => NT	
				Hypoglycemia (mild)	vildagliptin 0.3% vs pioglitazone 0% => NT	
					vildagliptin 0.3% vs pioglitazone 0.3% => NT	
				Mortality	vildagliptin 0% vs pioglitazone 0%	
					NR in 2009	

*ALT or AST greater than 2.5 times the upper limit of normal, direct Bb >1.3 times upper limit of normal, serum creatinine≥132µmol/l (males) or ≥125µmol/l (females), clinically significant abnormal thyroid-stimulating hormone or fasting triglycerides>7.9mmol/l

6.2.3.1.bis. Summary and conclusions. Vildagliptin + metformin versus pioglitazone + metformin

<table>
<tr><td colspan="7">Vildagliptin 100mg/d vs Pioglitazone 30mg/d, in addition to ongoing metformin (Bolli 2008 (24w), Bolli 2009 (FU 1y))</td></tr>
<tr><th>N/n</th><th>Duration</th><th>Population</th><th colspan="4">Results</th></tr>
<tr><td rowspan="15">N=1,
n= 576</td><td rowspan="15">24w
52w</td><td rowspan="15">mean age: 57y

Prior R: metformin ≥1500mg/d

DMII mean duration: 6.4y

Baseline mean HbA1c: 8.4%</td><td rowspan="3">HbA1c (PE)
After 24w</td><td colspan="4">Vildagliptin -0.88%
Pioglitazone -0.98%
between-group difference: 0.10% (95%CI: -0.05 to 0.26)
vildagliptin is non-inferior to pioglitazone</td></tr>
<tr><td><u>Quality</u>
-1 for poor description and incorrect ITT</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Moderate quality of evidence</td></tr>
<tr><td rowspan="3">HbA1c (PE)
After 1y</td><td colspan="4">Vildagliptin -0.6%
Pioglitazone -0.6% (p<0.001)
vildagliptin is non-inferior to pioglitazone</td></tr>
<tr><td><u>Quality</u>
-2 +not reporting attrition</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Low quality of evidence</td></tr>
<tr><td>Weight (24w)</td><td colspan="4">Vildagliptin +0.3kg
Pioglitazone +1.9kg
between-group difference: -1.6kg (p<0.001)
=> SS</td></tr>
<tr><td>Weight (1y)</td><td colspan="4">vildagliptin +0.2kg
pioglitazone +2.6kg
Between-group difference: NT</td></tr>
<tr><td rowspan="2"></td><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Moderate quality of evidence</td></tr>
<tr><td rowspan="2">Hypoglycemia (mild)(1y)</td><td colspan="4">vildagliptin 0.3%
pioglitazone 0.3%
NT</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
<tr><td rowspan="2">Serious adverse event (1y)</td><td colspan="4">vildagliptin 4.1%
pioglitazone 8.9%
NT</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
<tr><td rowspan="2">Peripheral edema (1y)</td><td colspan="4">vildagliptin 10.8%
pioglitazone 11.1%
NT</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
</table>

In patients with type 2 diabetes inadequately controlled (HbA1C >7,5%) by metformin, the addition of vildagliptin is not inferior in reducing HbA1c after 24 and 52 weeks compared to the addition of pioglitazone.

GRADE: Moderate quality of evidence(24w)
Low quality of evidence (52w)

At 24 weeks, pioglitazone results in more weight gain compared to vildagliptin ($p<0.001$).

GRADE: Moderate quality of evidence

There is no statistical test reported on adverse events.

GRADE: NA

6.2.4. DPP-4 inhibitors + metformin versus insulin + metformin

6.2.4.1. Insulin glargine + metformin versus sitagliptin + metformin

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Aschner 2012 (EASIE) Design: RCT (OL) (PG) Setting: (univer-sity)	n=515 mean age: 53.6y Prior R: metformin, no insulin DMII duration: 4.5y Baseline HbA1c: 8.5% 49% women <u>Inclusion</u> - 35-70y - BMI: 25-45kg/m^2 - patients diagnosed with DMII for at least 6m - HbA1c: 7-11% <u>Exclusion</u> - Treated with oral glucose-lowering drugs other than metformin for past 3m - Treated with combination metformin plus sulphonylurea in past year - Previous treatment with glucagon-like peptide-1 agonists or DDP-4 inhibitors - FPG≥15.4mmol/l - Impaired renal or hepatic function	24w=6m	Insulin glargine (aim: FPG 4.0-5.5mmol/l) Vs Sitagliptin 100mg In addition to ongoing metformin treatment (+/-1850mg/d)	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING: 0/2 ○ ATTRITION: 1/1 - FU: 93% - ITT: no - Multicenter: 17 countries - Sponsor: Sanofi
				HbA1c (mean, %) (PE)	Insulin: -1.72% Sitagliptin: -1.13% Mean difference: -0.59% (CI: -0.77 to -0.42) **SS: p<0.0001 in favour of insulin glargine**	
				HbA1c <7% (at 6m)	Insulin: 68% Sitagliptin: 42% **SS: p<0.0001 in favour of insulin glargine**	
				HbA1c <6.5% (at 6m)	Insulin: 40% Sitagliptin: 17% **SS: p<0.0001 in favour of insulin glargine**	
				Safety		
				All hypoglycaemic episodes (per py)	Insulin: 4.21 vs Sitagliptin: 0.50 Ratio: 8.45 (CI: 5.55-12.87) **SS: p<0.0001 in favour of sitagliptin**	
				Severe hypoglycaemia (assistance needed, plasma glucose <2mmol/l)	Insulin: 1% vs Sitagliptin: <1% Ratio: 3.40 (CI: 0.35-32.72) NS: p=0.29	
				Nocturnal hypoglycaemia (per py)	Insulin: 0.92 vs Sitaglipitn: 0.07 Ratio:12.41 (CI: 5.43–28.35) **SS: p<0.0001 in favour of sitagliptin**	
				Serious treatment-emergent adverse event	Insulin: 6% vs Sitagliptin: 3% NT	

6.2.4.1.bis. Summary and conclusions. Insulin glargine + metformin versus sitagliptin + metformin

<table>
<tr><td colspan="6">Insulin glargine (dose titration) vs Sitagliptin 100mg, in addition to ongoing metformin therapy (Aschner 2012)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="13">N=1,
n= 515</td><td rowspan="13">24w</td><td rowspan="13">mean age:
53.6y

Prior R:
metformin
1800mg/d

DM2
duration: 4.5y

Baseline
HbA1c: 8.5%</td><td rowspan="3">HbA1c (PE)</td><td colspan="3">Insulin: -1.72%
Sitagliptin: -1.13%
Mean difference: -0.59% (CI: -0.77 to -0.42)
SS: p<0.0001 in favour of insulin glargine</td></tr>
<tr><td><u>Quality</u>
-1 for not blinding</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Moderate quality of evidence</td></tr>
<tr><td rowspan="3">All hypo-glycaemic episodes</td><td colspan="3">Insulin: 4.21/ patient-year
Sitagliptin: 0.50/patient-year
Ratio: 8.45 (CI: 5.55-12.87)
SS: p<0.0001 in favour of sitagliptin</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Moderate quality of evidence</td></tr>
<tr><td rowspan="3">Severe hypo-glycaemia</td><td colspan="3">Insulin: 1% of patients
Sitagliptin: <1% of patients
Ratio: 3.40 (CI: 0.35-32.72)
NS: p=0.29</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Moderate quality of evidence</td></tr>
<tr><td rowspan="3">Nocturnal hypoglycaemia</td><td colspan="3">Insulin: 0.92/patient-year
Sitaglipitin: 0.07/patient-year
Ratio:12.41 (CI: 5.43–28.35)
SS: p<0.0001 in favour of sitagliptin</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Moderate quality of evidence</td></tr>
<tr><td rowspan="2">Serious adverse event</td><td colspan="3">Insulin: 6%
Sitagliptin: 3%
NT</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
</table>

In patients with type 2 diabetes inadequately controlled (HbA1C >7%) by metformin, the addition of insulin glargine results in greater reduction in HbA1c after 24 weeks compared to the addition of sitagliptin to metformin.

GRADE: Moderate quality of evidence

More hypoglycaemic episodes and nocturnal hypoglycaemic episodes occurred with insulin glargine compared with sitagliptin. Severe hypoglycaemic episodes were not different between the treatment groups.

GRADE: Moderate quality of evidence

6.2.5. GLP-1 agonists + metformin versus sulphonylurea + metformin

6.2.5.1. Exenatide + metformin versus glimepiride+ metformin

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Gallwitz 2012 (EUREXA) Design: OL RCT (PG) Setting: Centers	n=1029 mean age: 56y Prior R: metformin DMII duration: 5.7y Baseline HbA1c: 7.5% <u>Inclusion</u> Type 2 diabetes; BMI>=25; 18-85y; stable dose of metformin; subobtimal glycaemic control <u>Exclusion</u> CI for metformin or glimepiride; malignancy; renal or liver disease; haemoglobinopathy or clinically significant chronic anaemia; retinopathy or macular oedema; severe GI disease; use of drugs affecting GI motility, chornic systemic glucocorticoids, weight loss drugs; treamtent	3y	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)	**Efficacy**		- Jadad score o RANDO: 2/2 o BLINDING:0/2 o ATTRITION: 1/1 - FU: 71% - ITT: no (authors stated 'yes' but excluded some patients with insufficient data) - Other important methodological remarks - Exenatide 5µg bid for 4 weeks, then 10µg bid - Glimepiride 1 mg /d, increase every 4 weeks up to maximum tolerated dose Open label study - Multicenter: 128 centers, 14 countries
				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=0.748 (95%CI 0.623, 0.899)** **SS, p=0.002**	
				Mean change in HbA1c	Exenatide: -0.36% Glimepiride: -0.21% **SS, p=0.002**	
				HbA1c<7%	Exenatide: 45% Glimepiride: 31% **SS, p<0.0001**	
				Safety		
				% of patients with -Nocturnal hypoglaecemia -Non-nocturnal hypoglycem -Severe hypoglycemia -Hypoglycaemia rate	Exenatide / Glimepiride **10%** / **16%** **p=0.007** **35%** / **66%** **p<0.0001** <1% / 0% p=0.319 **1.52/y** / **5.32/y** **p<0.0001**	
				Death	Exenatide: n=5 Glimepiride: n=5	
				Body weight	Exenatide: -3.32 kg Glimepiride: +1.15 kg	

	>2w with insulin, thiazolidinediones,alpha-glucosidase inhibitors, sulphonyluras or meglitinides				**SS, p<0.0001**			- Sponsor: Eli Lilly, Amylin
					Exenatide	glimepiride		
				Pancreatitis	n=1	n=1		
				Thyroid cancer	n=0	n=1		
				Coronary artery disease	n=0	n=4		
				Nephrolithiasis	n=3	n=0		
				Gastro-intestinal:				
				Nausea	29%	2%	TNR	
				Diarrhoea	12%	7%	TNR	
				Vomiting	9%	2%	TNR	
				Dyspepsia	5%	4%	TNR	
				Dropout due to GI events	4%	0%	TNR	
				Dropout due to diarrhoea	3%	0%	TNR	

6.2.5.1.bis. Summary and conclusions. Exenatide + metformin versus glimepiride + metformin

<table>
<tr><td colspan="5">Exenatide 20µg/d vs glimepiride 1-4 mg/d in addition to ongoing metformin (Gallwitz 2012: EUREXA)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td>Results</td><td></td></tr>
<tr><td rowspan="11">N=1
n=
1029</td><td rowspan="11">3y</td><td rowspan="11">Mean age:56y

Prior R: metformin, suboptimal glycaemic control

DMII duration: 5.7y
Baseline HbA1c: 7.5%

(Exenatide mean dose 17.35 µg/d)
Glimepiride mean dose 2.01mg/d)</td><td rowspan="2">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)</td><td>Exenatide: 180w
Glimepiride: 142w
SS, p=0.032</td></tr>
<tr><td><table><tr><td><u>Quality</u>
-1 low FU, no ITT</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
-1 for applicability composite</td><td><u>Imprecision</u>
OK</td></tr></table></td></tr>
<tr><td colspan="2">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="2">mean change in HbA1c</td><td>Exenatide: -0.36%
Glimepiride: -0.21%
SS, p=0.002</td></tr>
<tr><td><table><tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr></table></td></tr>
<tr><td colspan="2">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="2">Body weight</td><td>Exenatide: -3.32 kg
Glimepiride: +1.15 kg
SS, p<0.0001</td></tr>
<tr><td><table><tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr></table></td></tr>
<tr><td colspan="2">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="2">% of patients with
-Nocturnal hypoglaecemia
-Non-nocturnal hypoglycemia
-Severe hypoglycemia
-Hypoglycaemia rate</td><td>Exenatide Glimepiride

10% 16% p=0.007

35% 66% p<0.0001

<1% 0% p=0.319
1.52/y 5.32/y p<0.0001</td></tr>
<tr><td><table><tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr></table></td></tr>
<tr><td colspan="2">Grade assessment:moderate quality of evidence</td></tr>
<tr><td rowspan="2">Pancreatitis
Thyroid cancer
Coronary artery disease
Nephrolithiasis

Gastro-intestinal:
Nausea
Diarrhoea
Vomiting
Dyspepsia
Dropout due to GI events
Dropout due to diarrhoea</td><td>Exenatide glimepiride
n=1 n=1
n=0 n=1

n=0 n=4
n=3 n=0

29% 2% TNR
12% 7% TNR
9% 2% TNR
5% 4% TNR

4% 0% TNR

3% 0% TNR</td></tr>
<tr><td colspan="2">Grade assessment: NA</td></tr>
</table>

- This study examines the adding-on of exenatide to existing metformin treatment and compares it to the adding-on of glimepiride to existing metformin treatment in type 2 diabetics with suboptimal glycaemic control.
Note that the average study dose of glimepiride is relatively low compared to the recommended maximum dose.

The average time to 'therapeutic failure' is significantly longer with exenatide compared to glimepiride.

GRADE: low quality of evidence

Exenatide at an average dose of 17.35µg/d causes a significantly larger decrease in HbA1c than glimepirde at an average dose of 2mg/d.

GRADE: moderate quality of evidence

There is a significant difference in weight change between exenatide and glimepiride.

GRADE: moderate quality of evidence

More patients had hypoglycaemia episodes (both nocturnal as non-nocturnal) with glimepiride than with exenatide. The number of patients with severe hypoglycaemia is not significantly different.

GRADE: moderate quality of evidence

Note that the difference in gastro-intestinal symptoms was not statistically tested.

GRADE: NA

6.2.5.2. Liraglutide + metformin versus glimepiride + metformin

Liraglutide+metformin vs glimepiride+metformin vs placebo+metformin

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Nauck 2009 LEAD-III study Design: DB RCT (PG) Setting: multicenter	n=1091 mean age: 57y Prior R: Monotherapy: 36% Combination therapy 64% DMII duration: 8y Baseline HbA1c: 8.4% <u>Inclusion</u> 18-80y; DMII; AbH1c 7-11% (previous OAD monotherapy >= 3 months) or 7-10% (previous OAD combination therapy >= 3 months); BMI <=40 <u>Exclusion</u> Use of insuline during previous 3m (except short treatment)	26w	Liraglutide 0.6mg or 1.2mg or 1.8mg (injection) + metformin 1g bid Vs Glimepiride 4mg+metformin 1g bid Vs Placebo+metformin 1g bid Metformin run-in period (6w)	Efficacy		- Jadad score o RANDO: 2/2 o BLINDING:2/2 o ATTRITION: 0/1 - FU: 80.7% - ITT: yes - Other important methodological remarks: no information on dropout - Multicenter:170 centers, 21 countries - Sponsor: Novo Nordisk
				Change in HbA1c	Liraglutide 0.6mg: -0.7 Liraglutide 1.2mg: -1.0 Liraglutide 1.8mg: -1.0 Glimepiride 4mg: -1.0 Placebo: +0.1 Lira 0.6 vs plac: -0.8% (-1.0, -0.6)=>NS Lira 1.2 vs plac: -1.1% (-1.3, -0.9) =>NS Lira 1.8 vs plac: -1.1% (-1.3, -0.9) =>NS 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	
				HbA1c <7%	Liraglutide 0.6mg: 28.0% Liraglutide 1.2mg: 35.3% Liraglutide 1.8mg: 42.4% Glimepiride 4mg: 36.3% Placebo: 10.8% **Lira (all doses) vs plac p<0.02 =>SS** **Lira 1.2mg vs lira 1.8mg: 35.3% vs 42.4%, p=0.0265 =>SS** Lira vs glime “similar” TNR	
				Weight loss	Liraglutide 0.6mg: -1.8kg Liraglutide 1.2mg: -2.6kg Liraglutide 1.8mg: -2.8kg Glimepiride 4mg: +1.0kg Placebo: -1.5kg **Lira 1.2mg and 1.8mg vs plac p<=0.01 =>SS** **Lira (all doses) vs glime p<0.0001 =>SS**	

				Safety		
				Gastro-intestinal (nausea, vomiting, diarrhea)	Liraglutide 0.6mg: 35% Liraglutide 1.2mg: 40% Liraglutide 1.8mg: 44% Glimepride 4mg: 17% Placebo: 17% TNR	
				Deaths	No deaths after randomisation	
				Pancreatitis without prior history	Lira: n=1 Glime: n=1	
				Major hypoglycaemic events	None	
				Minor hypoglycaemic events	Liraglutide & placebo 3% Glimepiride 17% **Liraglutide vs glimepiride: p<0.001 =>SS**	

6.2.5.2.bis. Summary and conclusions. Liraglutide + metformin versus glimepiride + metformin

<table>
<tr><td colspan="6">Liraglutide 0.6-1.2-1.8mg/d + Metformin 2000mg/d vs Glimepiride 4mg + Metformin 2000mg/d (Nauck 2009)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="10">N=1,
n=
1091</td><td rowspan="10">Mean:
26w</td><td rowspan="10">Inadequately controlled type 2 diabetes

mean age:
57y
Prior R:
Monotherapy:
36%
Combination therapy 64%
DMII duration:
8y
Baseline
HbA1c: 8.4%</td><td rowspan="3">Change in HbA1c (PE)</td><td colspan="3">Liraglutide 0.6mg: -0.7%
Liraglutide 1.2mg: -1.0%
Liraglutide 1.8mg: -1.0%
Glimepiride 4mg: -1.0%
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</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: high quality of evidence</td></tr>
<tr><td rowspan="3">Change in body weight (SE)</td><td colspan="3">Liraglutide 0.6mg: -1.8kg
Liraglutide 1.2mg: -2.6kg
Liraglutide 1.8mg: -2.8kg
Glimepiride 4mg: +1.0kg
Liraglutide (all doses) vs glimepiride: p<0.0001
=>SS</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: high quality of evidence</td></tr>
<tr><td rowspan="3">Hypoglycemic events (minor)</td><td colspan="3">Liraglutide (all doses): 3.0%
Glimepiride: 17.0%
Liraglutide vs glimepiride: p<0.001
=>SS</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: high quality of evidence</td></tr>
<tr><td rowspan="2">Gastro-intestinal AEs</td><td colspan="3">Liraglutide 0.6mg: 35%
Liraglutide 1.2mg: 40%
Liraglutide 1.8mg: 44%
Glimepiride: 17%
NT</td></tr>
<tr><td></td><td colspan="3">Grade assessment: NA</td></tr>
</table>

In this 26-week study, inadequately controlled type 2 diabetes patients were randomly assigned to once-daily liraglutide (either 0.6, 1.2 or 1.8mg/day injected subcutaneously) or to glimepiride 4mg/day. All treatments were in combination with metformin treatment (1g twice daily).

- There was no significant difference in HbA1c decrease between liraglutide and glimepiride.

GRADE: high quality of evidence

- Body weight change differed significantly in the liraglutide groups compared to glimepiride (p<0.0001); while liraglutide (all doses) decreased body weight, glimepiride increased body weight.

GRADE: high quality of evidence

- Glimepiride led to significantly more minor hypoglycemic events than liraglutide (p<0.001).

GRADE: high quality of evidence

- The gastro-intestinal adverse events were not statistically tested.

GRADE: NA

6.2.6. GLP-1 agonists + metformin versus DPP-4 inhibitors + metformin

6.2.6.1. Liraglutide + metformin versus sitagliptin + metformin

<table>
<tr><th>Ref</th><th>n/Population</th><th>Duration</th><th>Comparison</th><th>Outcomes</th><th>Methodological</th></tr>
<tr>
<td>Pratley 2010
Design:

OL RCT (PG)

Setting:
office based sites</td>
<td>n= 665
mean age: 55y

Prior R:
NR
DMII duration:
6.4y
Baseline HbA1c: 8.5%

<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</td>
<td>26 w</td>
<td>Liraglutide 1.2mg (inj.)+ metformine
Vs
Liraglutide 1.8mg (inj.)+ metformine
Vs
Sitagliptine 100 mg + metformine</td>
<td>
Efficacy
Change in HbA1c (PE): Lira 1.2mg: –1.24%; Lira 1.8mg: –1.50%; Sita 100mg: –0.90%
Lira 1.2 vs sita mean diff= -0.34%(-0.51, -0.16), SS
Lira 1.8 vs sita mean diff= -0.60% (-0.77, -0.43), SS
HbA1c <7%: Lira 1.2mg vs sita: OR=2.75 (1.78,4.25), SS; Lira 1.8mg vs sita: OR=4.25 (2.55, 7.08), SS
Body weight: Lira 1.2mg: -2.86kg; Lira 1.8mg: -3.38kg; Sita 100mg: -0.96kg
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

Safety
<table>
<tr><th></th><th>Lira 1.2mg</th><th>Lira 1.2mg</th><th>Sita</th></tr>
<tr><td>Major hypoglycaemic episode</td><td>n=1</td><td></td><td></td></tr>
<tr><td>Minor hypoglycaemia</td><td>5%</td><td>5%</td><td>5%</td></tr>
<tr><td>Severe Adverse events:</td><td>NT</td><td></td><td></td></tr>
<tr><td>- Overall</td><td>3%</td><td>3%</td><td>4%</td></tr>
<tr><td>- Gastrointestinal disorders</td><td>1%</td><td>1%</td><td>2%</td></tr>
<tr><td>- Musculoskeletal and
- connective tissue disorders</td><td>1%</td><td><1%</td><td><1%</td></tr>
<tr><td>- Infections and infestations</td><td><1%</td><td><1%</td><td><1%</td></tr>
<tr><td>- Neoplasms</td><td><1%</td><td>0%</td><td><1%</td></tr>
<tr><td>- Cardiac disorders</td><td>0%</td><td><1%</td><td><1%</td></tr>
<tr><td>- Renal and urinary disorders</td><td>0%</td><td>0%</td><td><1%</td></tr>
<tr><td>- Deaths</td><td>0%</td><td><1%</td><td><1%</td></tr>
</table>
</td>
<td>
- Jadad score
○ RANDO: 2/2
○ BLINDING: 0/2
○ ATTRITION: 1/1

- FU: 83%
- ITT: yes, LOCF
- Methodological remarks: in the flow chart, a higher dropout is shown for lira 1.2mg (23.1%) than for lira 1.8mg (12.2%) and sita (11.4%) TNR

- Multicenter: 158 centers, 11 European countries

- Sponsor: Novo Nordisk
</td>
</tr>
</table>

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Pratley 2011 Design: OL extension trial	n= 497 (75% of original sample) see above	26w (52w after randomisation)	Liraglutide 1.2mg (inj.)+ metformine Vs Liraglutide 1.8mg (inj.)+ metformine Vs Sitagliptine 100 mg + metformine	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING:0 /2 ○ ATTRITION: 1/1 - FU: 66% - ITT: yes, LOCF
				Change in HbA1c	Lira 1.2mg: -1.29% Lira 1.8mg: -1.51% Sita 100mg: -0.88% **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**	
				% of patients with HbA1c<7%	Lira 1.2mg: 50.3% Lira 1.8mg: 63.3% Sita 100mg: 27.1% **Lira 1.2mg vs sita p=0.0119** **Lira 1.8mg vs sita p<0.0001**	
				Change in body weight	Lira 1.2mg: -2.78kg Lira 1.8mg: -3.68kg Sita 100mg: -1.16kg **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**	
				% of patients with HbA1c<7% with no weight gain and no confirmed hypoglycemia	Lira 1.2mg: 38.9% Lira 1.8mg: 49.9% Sita: 18.6% **lira 1.2 vs sita OR=2.8 (1.74, 4.48)** **lira 1.8 vs sita OR=4.37 (2.74, 6.98)** **both doses p<0.0001**	
				Safety		
				Serious adverse events	Lira 1.2: 4.5%; lira 1.8: 6%; sita: 5.5%	
				death	1 sudden cardiac death with sita	
				Minor hypoglycaemia rate (per patient per year)	Lira 1.2: 0.143; lira 1.8: 0.154; sita: 0.137	
				Major hypoglycaemia	None	
				Thyroid-related AE	Lira 1.2: 5.0%; lira 1.8: 5.5%; sita: 4.6%	

				Non-acute pancreatitis	1 patient in lira 1.8mg group	
				nausea	Figure; “weekly proportion of participants experiencing nausea did not differ significantly between liraglutide and sitagliptin”	

6.2.6.1.bis. Summary and conclusions. Liraglutide + metformin versus sitagliptin + metformin

<table>
<tr><td colspan="6">Liraglutide 1.2mg/d or 1.8mg vs Sitagliptin 100mg/d in addition to metformin (Pratley 2010, Pratley 2011)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="8">N=1
n= 665</td><td rowspan="8">26w initial study, extension to 52y</td><td rowspan="8">mean age: 55y

Prior R: NR
DMII duration: 6.4y
Baseline HbA1c: 8.5%</td><td>Change in HbA1c (52w)</td><td colspan="3">Lira 1.2mg: -1.29%
Lira 1.8mg: -1.51%
Sita 100mg: -0.88%
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 at 26 weeks also significant)</td></tr>
<tr><td><u>Quality</u>
-1 low FU, open label</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="3">Grade assessment: moderate quality of evidence</td></tr>
<tr><td>Change in body weight (52w)</td><td colspan="3">Lira 1.2mg: -2.78kg
Lira 1.8mg: -3.68kg
Sita 100mg: -1.16kg
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

(results at 26 weeks also significant)</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="3">Grade assessment: moderate quality of evidence</td></tr>
<tr><td>Safety</td><td colspan="3">adverse events reported but not tested or test not reported.</td></tr>
<tr><td colspan="3">Grade assessment:NA</td></tr>
<tr><td>(26 weeks)
major hypoglycaemic episode
minor hypoglycaemia</td><td colspan="3">Lira 1.2mg Lira 1.2mg Sita

n=1
5% 5% 5%</td></tr>
<tr><td colspan="3">Grade assessment:NA</td></tr>
<tr><td rowspan="2">Nausea
(at 52 weeks)</td><td colspan="3">“weekly proportion of participants experiencing nausea did not differ significantly between liraglutide and sitagliptin”
TNR</td></tr>
<tr><td colspan="3">Grade assessment:NA</td></tr>
</table>

This study compares liraglutide to sitagliptin, when added to existing metformin treatment in patients with inadequately controlled type 2 diabetes.

Liraglutide (both 1.2mg and 1.8mg) is associated with a larger decrease in HbA1c than sitagliptin 100mg.

GRADE: moderate quality of evidence

Liraglutide is associated with a larger decrease in weight than sitagliptin.

GRADE: moderate quality of evidence

- Adverse events were reported but not statistically tested.

GRADE: NA

6.2.7. GLP-1 agonists + metformin versus insulin + metformin

No studies met our inclusion criteria.

6.2.8. Long-acting insulin analogues + metformin versus NPH insulin + metformin

No studies met our inclusion criteria.

See also 7.2.4

6.3. Meta-analyses for dual therapy

Two meta-analyses have compared the addition of a second drug to the addition of placebo in patients with inadequate glycaemic control on metformin (Phung 2010, Mcintosh 2011), both in a traditional meta-analysis and a mixed-treatment meta-analysis.
One meta-analysis compared the DPP-4 inhibitors to other drug classes as an addition to ongoing metformin treatment (Karagiannis 2012).
The comparisons consist of drug classes rather than individual drugs and only intermediate endpoints are discussed. Therefore, we chose to report data from individual trials rather than from these meta-analyses.

7. Evidence tables and conclusions: Type 2 diabetes: triple therapy

7.1. Triple therapy versus dual therapy

7.1.1. Exenatide + metformin + sulphonylurea versus placebo +metformin + sulphonylurea

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Kendall 2005 Design: RCT DB PG Setting: Clinical setting	n= 733 mean age: 55y Prior R: metformin and sulfonylurea DMII duration: 8.7-9.4y Baseline HbA1c: 8.5% BMI 33.6 <u>Inclusion</u> -fasting plasma glucose <13.3 mmol/l -BMI 27-45 kg/m2 HbA1c 7.5-11.0% -metformin ≥1500mg -maximal effective sulfonylurea dose for 3 months before screening <u>Exclusion</u> - Weight instable (10%) for 3 mo before screening -cinically relevant abnormal lab tests -other clinically significant medical conditions -use of thiazolidinediones, meglitinides, glucosidase inhibitors, exogenous insulin, or weight loss drugs within the prior 3 m	30 weeks	5 µg exenatide SC Vs 10 µg exenatide Vs placebo in addition to ongoing metformin + sulphonylurea	Efficacy		- Jadad score o RANDO: 2/2 o BLINDING: 2/2 o ATTRITION: 1/1 - FU: 81 % - ITT: yes Other important methodological remarks: - Run-in period - MINimal effective and MAXimally effective sulphonylurea treatment groups - Any subject with either an A1C change of >1.5% from baseline at any clinic visit or an A1C >11.5% at week 18 or 24 could be withdrawn from the study. Similarly, subjects could be withdrawn if they had fasting plasma glucose values <13.3 mmol/l on two consecutive study visits during weeks 18–24 or if a subject consistently recorded finger-stick fasting blood glucose values_14.4 mmol/l for at least 2 weeks during weeks 18–24, not secondary to a readily identified illness or pharmacological treatment. - Multicenter: 91 centers in US - Sponsor: Amylin Pharmaceuticals and Eli Lilly.
				HbA1c change at 30w (PE) (%, mean)	Exenatide 5 µg: -0.55 (p<0.0001 vs pla) Exenatide 10 µg: -0.77 (p<0.0001 vs pla) Placebo: +0.23	
				Body weight	Exenatide 5 µg: -1.6kg (±0.2) (p≤0.01) Exenatide 10 µg: -1.6 (±0.2) (p≤0.01) Placebo: -0.9 kg (±0.02)	
				Safety		
				Nausea	Exenatide 5 µg: 39.2% Exenatide 10 µg: 48.5% Placebo: 20.6% **NT**	
				Hypoglycemia	Exenatide 5 µg: 19.2% Exenatide 10 µg: 27.8% Placebo: 12.6% **NT**	

7.1.1.bis. Summary and conclusions. Exenatide + metformin + sulphonylurea versus placebo + metformin + sulphonylurea

<table>
<tr><td colspan="6">Exenatide 5-10µg SC/d vs placebo, in addition to ongoing metformin + sulphonylurea (Kendall 2005)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td>Results</td><td colspan="2"></td></tr>
<tr><td rowspan="8">N=1
n=
733</td><td rowspan="8">30 w</td><td rowspan="8">-Mean age 55y
-baseline HbA1c 8.5%
-BMI 33.6
-8.7-9.4y duration of DM 2
-inadequate control of HbA1c , treatment with metformin and sulphonylurea</td><td rowspan="3">HbA1c (PE)</td><td colspan="2">Exenatide 5 µg: -0.55 (p<0.0001 vs pla)
Exenatide 10 µg: -0.77 (p<0.0001 vs pla)
Placebo: +0.23

Exenatide SS more HbA1c decrease</td></tr>
<tr><td><u>Quality</u>
OK
<u>Consistency</u>
NA
<u>Directness</u>
-1 for exclusion of bad responders
<u>Imprecision</u>
OK</td></tr>
<tr><td>Grade assessment: Moderate quality of evidence</td></tr>
<tr><td rowspan="3">BMI (kg/m^2)</td><td colspan="2">Exenatide 5 µg: -1.6kg (±0.2) (p≤0.01)
Exenatide 10 µg: -1.6 (±0.2) (p≤0.01)
Placebo: -0.9 kg (±0.02)

Exenatide SS more weight loss</td></tr>
<tr><td><u>Quality</u>
OK
<u>Consistency</u>
NA
<u>Directness</u>
-1
<u>Imprecision</u>
OK</td></tr>
<tr><td>Grade assessment: Moderate quality of evidence</td></tr>
<tr><td rowspan="2">Nausea</td><td colspan="2">Exenatide 5 µg: 39.2%
Exenatide 10 µg: 48.5%
Placebo: 20.6%
NT</td></tr>
<tr><td>Grade assessment: NA</td></tr>
<tr><td rowspan="2">Hypolycemia</td><td colspan="2">Exenatide 5 µg: 19.2%
Exenatide 10 µg: 27.8%
Placebo: 12.6%
NT</td></tr>
<tr><td>Grade assessment: NA</td></tr>
</table>

Exenatide 5 and 10 µg significantly reduced HbA1C compared to placebo in patients with type 2 diabetes unable to achieve adequate glycemic control with maximally effective doses of combined metformin-sulphonylurea treatment.
Significantly higher weight loss is observed with exenatide when compared to placebo.

GRADE: Moderate quality of evidence

No statistical analysis was performed for adverse events.

GRADE: NA

7.1.2. Liraglutide + metformin + sulphonylurea versus placebo + metformin + sulphonylurea

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Russell-Jones 2009 Design: RCT OL P	n=581 mean age 57 mean BMI 30.4 kg/m^2 mean duration of diabetes 9.4y 95% on combination therapy (metformin + sulfonylurea) Mean HbA1C 8.3% <u>Inclusion</u> - Adults with type 2 diabetes - HbA1c 7-10% - BMI≤45kg/m^2 <u>Exclusion</u> - Insulin treatment 3 months prior - Impaired renal or hepatic function - Significant cardiovascular disease - Proliferative retinopathy or maculopathy - Hypertension (≥180/100) - cancer	26w	Liraglutide 1.8mg/d vs insuline glargine (dose titration: FPG< 100mg/dl) vs placebo in addition to ongoing metformin 2000mg/d + glimepiride 4mg/d	Efficacy		- Jadad score o RANDO: 2/2 o BLINDING: 0/2 o ATTRITION: 1/1 - FU: 83-94% - ITT: yes - Other important methodological remarks: - 2 week screening period, 3 week dose-escalation period, 3 week maintenance period, 26 week treatment period - Liraglutide and placebo blind, insulin open label - Multicentre: 107 sites in 17 countries - Sponsor: Novo Nordisk
				HbA1c (PE)	Liraglutide: -1.33% Insulin: -1.09% Pla: -0.24% **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** **Insulin vs pla: -0.85% (95%CI -1.04 to -0.66), p < 0.0001; SS**	
				Weight:	Liraglutide: -1.8kg Insulin: +1.6kg Pla: -0.4kg **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**	
				Harms		
				Nausea	Liraglutide: 13.9% Insulin: 1.3% Pla: 3.5% **(p < 0.0001 for difference between 3 treatments)**	
				Diarrhoea	Liraglutide: 10% Insulin: 1.3% Pla: 5.3% **(p < 0.0001 for difference between 3 treatments)**	
				Dyspepsia	Liraglutide: 6.5% Insulin: 1.7% Pla:0.9% **(p=0.0042 for difference between 3 treatments)**	

7.1.2.bis. Summary and conclusions. Liraglutide + metformin + sulphonylurea versus placebo + metformin + sulphonylurea

<table>
<tr><td colspan="7">Liraglutide 1.8 mg/d vs placebo, in addition to ongoing metformin + sulphonylurea (Russel Jones 2009)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="4">Results</td></tr>
<tr><td rowspan="15">N=1,
n=
581</td><td rowspan="15">Mean:
26w</td><td rowspan="15">-Type 2 diabetes
-Mean age 57
-Mean BMI 30.4 kg/m^2
-mean HbA1c 8.3%
-95% on combination therapy (metformin + sulfonylurea)</td><td rowspan="3">HbA1c (PE)</td><td colspan="4">Liraglutide: -1.33%
Placebo: -0.24%
Difference: -1.09% (95%CI -1.28 to -0.9, p<0.0001)
SS in favour of liraglutide</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: High quality of evidence</td></tr>
<tr><td rowspan="3">Weight</td><td colspan="4">Liraglutide: -1.8kg
Pla: -0.4kg
Liraglutide vs pla: -1.39kg (95%CI -2.10 to -0.69, p=0.0001)
SS in favour of liraglutide</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: High quality of evidence</td></tr>
<tr><td rowspan="3">Nausea</td><td colspan="4">Liraglutide: 13.9%
Pla: 3.5%
(p < 0.0001)
SS more nausea with liraglutide</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: High quality of evidence</td></tr>
<tr><td rowspan="3">Diarrhoea</td><td colspan="4">Liraglutide: 10%
Pla: 5.3%
(p < 0.0001)
SS more diarrhoea with liraglutide</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: High quality of evidence</td></tr>
<tr><td rowspan="3">Dyspepsia</td><td colspan="4">Liraglutide: 6.5%
Pla:0.9%
(p=0.0042)
SS more dyspepsia with liraglutide</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: High quality of evidence</td></tr>
</table>

This trial compared liraglutide 1.8mg/d to placebo. The enrolled patients were already treated with metformin and glimepiride and showed a mean HbA1C of 8.3%.
After 26 weeks liraglutide results in a statistically significant greater reduction in HbA1c and weight.

GRADE: High quality of evidence

Liraglutide causes more adverse events compared with placebo. These adverse events are mainly gastro-intestinal.

GRADE: High quality of evidence

7.2. Triple therapy versus triple therapy

7.2.1. Exenatide + metformin + sulphonylurea versus insulin glargine + metformin + sulphonylurea

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Heine 2005 Design: RCT OL P Setting: outpatient study centers	n=551 mean HbA1c 8.2 mean age 59 mean BMI 31gk/m^2 mean DMII duration: 9.5y <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 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	26 weeks	Exenatide 10 µg 2*/d vs insulin glargine dose titrated to <100mg/dl FGP (average dose 25 U/d) in addition to ongoing metformin + sulphonylurea	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING: 0/2 ○ ATTRITION: 1/1 - FU: 80.6% exenatide (due to AE) and 90.3% insulin - ITT: yes - Other important methodological remarks: - Standardized test meal - Low insulin doses - Multicenter: 82 sites in 13 countries - Sponsor: Amylin Pharmaceuticals and Eli Lilly
				HbA1c (PE)	Exenatide: -1.11% Insuline glargine: -1.11% Difference 0.017% (95%CI: -0.123 to 0.157) NS	
				Body Weight	Exenatide: -2.3kg Insuline glargine: + 1.8kg **Difference -4.1kg (95%CI: -4.6 to -3.5)** **SS**	
				Safety		
				Nausea	Exenatide: 57.1% Insuline glargine: 8.6% **p<0.001**	
				Vomiting	Exenatide: 17.4% Insuline glargine: 3.7% **P<0.001**	
				Diarrhoea	Exenatide: 8.5% Insuline glargine: 3.0% **P = 0.006**	

7.2.1.bis. Summary and conclusions. Exenatide + metformin + sulphonylurea versus insulin glargine + metformin + sulphonylurea

<table>
<tr><td colspan="6">Exenatide 2*10µg/d vs insulin glargine (1 inj/d, dose titration), in addition to ongoing metformin + sulphonylurea (Heine 2005)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="15">N=1, n= 551</td><td rowspan="15">26 weeks</td><td rowspan="15">-mean age 59
-mean HbA1c 8.2%
-BMI 31
-9.5y duration of DM 2
-inadequate controle of HbA1c on max eff dose metformin and SU</td><td rowspan="3">Change in HbA1c (PE)</td><td colspan="3">Exenatide: -1.11%
Insuline glargine: -1.11%
Difference 0.017% (95%CI, -0.123 to 0.157)
NS</td></tr>
<tr><td><u>Quality</u>
-1 for not blinding</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
-1 for standardized test meal and low doses of insulin</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Low quality of evidence</td></tr>
<tr><td rowspan="3">Weight change</td><td colspan="3">Exenatide: -2.3kg
Insuline glargine: + 1.8kg
Difference -4.1kg (95%CI, -4.6 to -3.5)
SS</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
-1</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Low quality of evidence</td></tr>
<tr><td rowspan="3">Nausea</td><td colspan="3">Exenatide: 57.1%
Insuline glargine: 8.6%
p<0.001
SS more nausea with exenatide</td></tr>
<tr><td colspan="4">Grade assessment: Low quality of evidence</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
-1</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td rowspan="3">Vomiting</td><td colspan="3">Exenatide: 17.4%
Insuline glargine: 3.7%
P<0.001
SS more vomiting with exenatide</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
-1</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Low quality of evidence</td></tr>
<tr><td rowspan="3">Diarrhoea</td><td colspan="3">Exenatide: 8.5%
Insuline glargine: 3.0%
P = 0.006
SS more diarrhoea with exenatide</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
-1</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Low quality of evidence</td></tr>
</table>

Exenatide 2*10 µg/d and insulin glargine achieved equal improvements in HbA1c control in patients with type 2 diabetes suboptimally controlled with oral combination therapy (maximal effective dose of metformin and sulphonylurea).

GRADE: Low quality of evidence

Weight loss was observed with exenatide and weight gain was observed with insulin glargine. The difference between these treatment groups was statistically significant (-4.1kg).

GRADE: Low quality of evidence

Compared to insulin glargine, exenatide was associated with more gastro-intestinal adverse events: more nausea, vomiting and diarrhoea.

GRADE: Low quality of evidence

7.2.2. Liraglutide + metformin + sulphonylurea versus insulin glargine + metformin + sulphonylurea

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Russell-Jones 2009 Design: RCT OL P	n=581 mean age 57 mean BMI 30.4 kg/m^2 mean duration of diabetes 9.4y 95% on combination therapy (metformin + sulfonylurea) Mean HbA1C 8.3% <u>Inclusion</u> - Adults with type 2 diabetes - HbA1c 7-10% - BMI≤45kg/m^2 <u>Exclusion</u> - Insulin treatment 3 months prior - Impaired renal or hepatic function - Significant cardiovascular disease - Proliferative retinopathy or maculopathy - Hypertension (≥180/100) - cancer	26w	Liraglutide 1.8mg/d vs insuline glargine (dose titration: FPG< 100mg/dl) vs placebo in addition to ongoing metformin 2000mg/d + glimepiride 4mg/d	Efficacy		- Jadad score o RANDO: 2/2 o BLINDING: 0/2 o ATTRITION: 1/1 - FU: 83-94% - ITT: yes - Other important methodological remarks: - 2 week screening period, 3 week dose-escalation period, 3 week maintenance period, 26 week treatment period - Liraglutide and placebo blind, insulin open label - Multicentre: 107 sites in 17 countries - Sponsor: Novo Nordisk
				HbA1c (PE)	Liraglutide: -1.33% Insulin: -1.09% Pla: -0.24% **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** **Insulin vs pla: -0.85% (95%CI -1.04 to -0.66), p < 0.0001; SS**	
				Weight:	Liraglutide: -1.8kg Insulin: +1.6kg Pla: -0.4kg **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**	
				Harms		
				Nausea	Liraglutide: 13.9% Insulin: 1.3% Pla: 3.5% **(p < 0.0001 for difference between 3 treatments)**	
				Diarrhoea	Liraglutide: 10% Insulin: 1.3% Pla: 5.3% **(p < 0.0001 for difference between 3 treatments)**	
				Dyspepsia	Liraglutide: 6.5% Insulin: 1.7% Pla:0.9% **(p=0.0042 for difference between 3 treatments)**	

7.2.2.bis. Summary and conclusions. Liraglutide + metformin + sulphonylurea versus insulin glargine + metformin + sulphonylurea

<table>
<tr><td colspan="6">Liraglutide 1.8 mg/d vs Insuline glargine (1inj/d, dose titration), in addition to ongoing metformin + sulphonylurea (Russel Jones 2009)</td></tr>
<tr><th>N/n</th><th>Duration</th><th>Population</th><th colspan="3">Results</th></tr>
<tr><td rowspan="15">N=1, n= 581</td><td rowspan="15">Mean: 26w</td><td rowspan="15">-Type 2 diabetes
-Mean age 57
-Mean BMI 30.4 kg/m^2
-mean HbA1c 8.3%
-95% on combination therapy (metformin + sulfonylurea)</td><td rowspan="3">HbA1c (PE)</td><td colspan="3">Liraglutide: -1.33%
Insulin: -1.09%
Difference: -0.24% (95%CI -0.39 to -0.08, p =0.0015)
SS in favour of liraglutide</td></tr>
<tr><td><u>Quality</u>
-1 for open label</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Moderate quality of evidence</td></tr>
<tr><td rowspan="3">Weight</td><td colspan="3">Liraglutide: -1.8kg
Insulin: +1.6kg

Liraglutide vs insulin: -3.43kg (95%CI -4.00 to -2.86, p<0.0001)
SS in favour of liraglutide</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Moderate quality of evidence</td></tr>
<tr><td rowspan="3">Nausea</td><td colspan="3">Liraglutide: 13.9%
Insulin: 1.3% (p < 0.0001)
SS more nausea with liraglutide</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Moderate quality of evidence</td></tr>
<tr><td rowspan="3">Diarrhoea</td><td colspan="3">Liraglutide: 10%
Insulin: 1.3% (p < 0.0001)
SS more diarrhoea with liraglutide</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Moderate quality of evidence</td></tr>
<tr><td rowspan="3">Dyspepsia</td><td colspan="3">Liraglutide: 6.5%
Insulin: 1.7% (p=0.0042)
SS more dyspepsia with liraglutide</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: Moderate quality of evidence</td></tr>
</table>

This trial compared liraglutide 1.8mg/d to long-acting insulin glargine at a dose titrated based on fasting glucose concentration. The enrolled patients were already treated with metformin and glimepiride and showed a mean HbA1c of 8.3%. After 26 weeks liraglutide results in a statistically significant greater reduction in HbA1c~~.~~.

GRADE: Moderate quality of evidence

Weight decrease was observed with liraglutide and weight gain was observed with insulin glargine. The difference in weight change between treatment groups was statistically significant (-3.43kg).

GRADE: Moderate quality of evidence

Liraglutide causes more gastro- intestinal adverse events compared with insuline glargine.

GRADE: Moderate quality of evidence

7.2.3. Long acting insulin analogues + metformin + sulphonylurea versus insulin NPH + metformin + sulphonylurea

No studies met our inclusion criteria.
See 7.2.4. for alternative comparison.

7.2.4. Long acting insulin analogues + existing therapy versus insulin NPH + existing therapy

7.2.4.1. Insulin glargine+ existing therapy versus insulin NPH+ existing therapy

Ref	N/n	Comparison	Outcomes	
Waugh 2010 Design: meta-analysis	N= 10 n= 1948	Insulin glargin vs insulin NPH added to existing treatment (mainly insulin naieve on oral antihyperglycaemic drugs)	Change in HbA1c from baseline to endpoint	Mean difference: −0.00 (95%CI−0.11 to 0.10) NS Heterogeneity disappeared when Rosenstock 2001 was excluded
	N=8 n= 1437		Change in body weight	a meta-analysis could not be carried out due to too many missing SDs. Overall, the glargine groups gained 0.23 kg less weight than the NPH groups (range -1.10 to +0.23kg)
	N=6 n= 1437		Severe hypoglycaemia	Risk Ratio= 0.82 (0.45 to 1.49) NS
	N=7 n=1192		Overall hypoglycaemia	**Risk Ratio= 0.89 (0.83 to 0.96)** **SS in favour of insulin glargine**
	N=4 n=853		Symptomatic hypoglycaemia	Risk Ratio= 0.80(0.68 to 0.93) **SS in favour of insulin glargine**
	N=7 n=1372		Nocturnal hypoglycaemia	Risk Ratio= 0.54 (0.43-0.69) **SS in favour of insulin glargine**

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Eliaschewitz 2006	481	Type 2 diabetes inadequately controlled on oral hypoglycaemic agents (Su and metformin or acarbose) -- Insulin-naïve	24w	Insulin glargin bedtime vs Insulin NPH bedtime Both arms + glimepiride 4mg	- Jadad score: 2/5 - FU: 96 - ITT:yes - blood glucose self-monitoring at home and at each visit, Diabetes Treatment Satisfaction Questionnaire change (8-item scale a.o. 'Perceived frequency of hypoglycemia: how often have you felt that your blood sugars were unacceptably low recently?) - symptomatic confirmed hypoglycemia: FBG≤75mg/dl - severe hypoglycemia: symptoms consistent with hypoglycemia requiring assistance from another person and associated with blood glucose levels <50mg/dl or rapid recovery of patient after oral carbohydrates, glucose or glucagon administration - nocturnal hypoglycemia: hypoglycemic event that occurred while the patient was asleep between bedtime and getting up in the morning
Fritsche 2003	700	Type 2 diabetes inadequately controlled on oral hypoglycaemic agents Insulin-naïve	24w	Insulin glargine morning vs insulin glargine bedtime vs insulin NPH bedtime Both arms + glimepiride 3mg	- Jadad score: 3/5 - FU: 91.5% - ITT:yes - daily self-measured FBG and episodes of hypoglycemia written in standardised diary, blood was drawn at baseline and at 3 study visits and patients had to provide 8-point daily blood glucose profile on 2 consecutive days - hypoglycemia: symptomatic or asymptomatic (blood glucose level < 4.2mmol/l or <75mg/dl - severe hypoglycemia: event with symptoms consisted with hypoglycemia that required assistance of another person and that was associated with a blood glucose level < 2.8mmol/l or <50mg/dl or that was followed by the prompt recovery after oral carbohydrate or iv glucose or glucagon administration - nocturnal hypoglycemia: hypoglycemia that occurs while patient is asleep – between bedtime after evening injection and before patient awakes in morning
HOE 901/2003 1998	206	Type 2 diabetes inadequately controlled on oral hypoglycaemic agents (SU alone or +	4w	Insulin glargin (30) vs Insulin glargin (80) vs insulin NPH Both arms +prestudy	- Jadad score: 4 - FU: 99% - ITT:no - FPG measured from samples collected at beginning of screening period,

		metformin/acarbose--Insulin-naïve		OAD	beginning of dose-titration period and final visit. FBG measured daily, 3:00AM at least 5 times during 4w, blood glucose profile 5 times, determined by the patient via self-monitoring - hypoglycemia: either symptomatic or asymptomatic in the context of glucose level <2.8mmol/l - severe hypoglycemia: symptomatic event in which the patient required assistance to perform routine activities, confirmed by glucose level <2.8mmol/l or by patients' rapid recovery after administration of oral carbohydrate, IV glucose or glucagon - nocturnal hypoglycemia: hypoglycemic event that occurred between bedtime basal insulin administration and FBG determination the next morning
Massi Benedetti 2003	578	Type 2 diabetes inadequately controlled on oral hypoglycaemic agents (monotherapy or combinations metformin, SU, acarbose) 25% pretreated with insulin	52w	Insuling glargine bedtime vs insulin NPH bedtime Both arms + prestudy OAD	- Jadad score: 3/5 - FU: 92% - ITT:yes - plasma samples for FPG measurement were taken at the clinic at baseline and weeks 8, 20, 36 and 52. FBG was measured through self-monitoring during 7 consecutive days before each visit, nocturnal blood glucose (3am) and 24-hour blood glucose profile were recorded on one of the 7 consecutive days - symptomatic hypoglycemia: event with clinical symptoms related to hypoglycemia confirmed by blood glucose value <2.8mmol/l (50mg/dl) - severe hypoglycemia: hypoglycemic event in which the patient required assistance of another person and was associated with blood glucose level <2.8mmol/l (50mg/dl) or prompt recovery after oral carbohydrate or IV glucose or glucagon administration - nocturnal hypoglycemia: hypoglycemia occurring while subject is asleep, after evening injection and before either morning determination of FBG or morning injection, but was not confirmed taking blood glucose levels
Pan 2007	443	Type 2 diabetes inadequately controlled on oral hypoglycaemic agents--Insulin-naïve	24w	Insulin glargine vs NPH insulin once daily at bedtime Both arms + once-daily glimepiride (3 mg)	- Jadad score: 2/5 - FU: 90% - ITT: yes - daily self-measured FBG (before breakfast and administration of glimepiride), complete 24h-blood glucose profile (including nocturnal 3am blood glucose) at 3 times during study - severe hypoglycemia: event with symptoms consistent with

					hypoglycemia and associated with blood glucose level <50mg/dl (<2.8mmol/l) or with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration and the requirement of third party assistance - nocturnal hypoglycemia: hypoglycemia that occurred while the patient was asleep after the evening insulin injection and before getting up in the morning
Riddle 2003	756	Type 2 diabetes inadequately controlled on oral hypoglycaemic agents (1 or 2 OAD, mostly metformin + sulphonylurea) Insulin naive	24w	Insuling glargine bedtime vs insulin NPH bedtime Both arms + prestudy OAD	- Jadad score: 3/5 - FU: 91.5% - ITT:yes - subjects were asked to test glucose whenever they experienced symptoms that might be related to hypoglycemia and to record the results, they also performed morning fasting test for 7 consecutive days and 1-day blood glucose profiles before each visit - in this study the glucose threshold for hypoglycemia was chosen ≤72mg/dl (4mmol/l) because lower levels can induce hypoglycemia unawareness - severe hypoglycemia: symptoms consistent with hypoglycemia during which the subject required the assistance of another person and was associated with either a glucose level of <56mg/dl (3.1mmol/l) or prompt recovery after oral carbohydrate, IV glucose or glucagon - nocturnal hypoglycemia: hypoglycemia occurring after bedtime injection and before the measurement of glucose, eating breakfast, or administration of any oral antihyperglycemic agent in the morning
Rosenstock 2001	518	Type 2 diabetes prior insulin treatment (NPH +/- regular insulin preprandial)	26w	insulin glargine bedtime vs insulin NPH 1 or 2/d	- Jadad score: 2/5 - FU: 96% - ITT:yes - self-monitored blood glucose assessment on the 7 consecutive days before each visit - hypoglycemia: defined symptomatically and by a blood glucose level <2.8mmol/l - severe hypoglycemia: an event with symptoms consistent with hypoglycemia in which the subject required assistance of another person and was either accompanied by a blood glucose level <2.0mmol/l or had prompt recovery after oral carbohydrate, iv glucose or glucagon administration

					- nocturnal hypoglycemia: hypoglycemia occurring while the subject was asleep between bedtime after the evening injection and before getting up in the morning (before morning determination of FBG and morning injection)
Wang 2007	24	Type 2 diabetes inadequately controlled with SU or combination treatment	12w	Insulin glargine vs insulin NPH Both arms + extended release glipizide	- Jadad score: 1/5 - FU: NR - ITT: NR - continuous glucose monitoring system (sensor inserted through needle into sc tissue of anterior abdominal wall with spring-loaded device, enzyme-mediated oxidation of glucose in interstitial fluid generates electrical current that is carried by a cable to a monitoring device) during 3 days in the second and 12th week, calibrated 3-4 times each day, measuring finger capillary blood glucose and writing a diary with hypoglycemic events - nocturnal hypoglycemia: nocturnal plasma glucose <3.0mmol/l - hypoglycemic event: sensor glucose value <3.5mmol/l for >15min
Yki-Järvinen 2000	426	Type 2 diabetes inadequately controlled with oral hypoglycaemic agents (SU, metformin and/or acarbose)--Insulin naive	12m	Insulin glargine bedtime vs insulin NPH Both arms+ prestudy OAD	- Jadad score:2/5 - FU: NR - ITT:yes - daily recording of hypoglycemic symptoms by patients and home glucose monitoring (FBG) on 7 consecutive days immediately preceding and on the day of the next visit, also provide a 24-h blood glucose profile including 3am nocturnal measurement - symptomatic hypoglycemia: clinical symptoms were confirmed by measurement of a blood glucose value <2.8mmol/l (50mg/dl) - severe hypoglycemia: event with symptoms consistent with hypoglycemia for which the subject required assistance of another person and that was associated with a blood glucose level <2.8mmol/l (50mg/dl) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration - nocturnal hypoglycemia: hypoglycemia occurring while the subject was asleep between the evening injection and getting up in the morning before the morning determination of FBG
Yki-Järvinen 2006	110	Type 2 diabetes inadequately controlled on oral hypoglycaemic	36w	Insulin glargine bedtime vs Insulin NPH bedtime	- Jadad score: 2/5 - FU: 98% - ITT:yes

		agents (metformin + SU or metformin alone)--Insulin-naïve		Both arms + metformin continued	- daily measurements of FPG every morning, diurnal profile (before and 2h after breakfast, lunch and dinner, at 22pm and 3am) once every 3-4 weeks, these FPG values and symptoms of hypoglycemia were noted in a diary (subjects were asked to self-monitor glucose values whenever they experienced symptoms that they thought might be the result of hypoglycemia - hypoglycemia: plasma glucose ≤4mmol/l - severe hypoglycemia: event with symptoms consistent with hypoglycemia during which the subject required the assistance of another person and with either a plasma glucose level <3.1mmol/l or with prompt recovery after oral carbohydrate iv glucose or glucagon administration - nocturnal hypoglycemia: definition NR

7.2.4.1.bis. Summary and conclusions. Insulin NPH + existing therapy versus insulin glargine + existing therapy

<table>
<tr><td colspan="6">Insulin glargine vs insulin NPH added on to existing treatment (Waugh 2010)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="13">MA
N=10,
n= 1948</td><td rowspan="13">Mean:
28w</td><td rowspan="13">Type 2 diabetes inadequately controlled on oral hypoglycaemic agents - Insulin-naïve

(1 trial: previous insulin treatment)</td><td rowspan="2">HbA1c (change from baseline to endpoints)</td><td colspan="3">Reported in 10/10 trials
Mean difference: −0.00 (95%CI−0.11 to 0.10)
NS</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: high quality of evidence</td></tr>
<tr><td rowspan="2">Change in body weight</td><td colspan="3">A meta-analysis could not be carried out
Overall, the glargine groups gained 0.23 kg less weight than the NPH groups (range -1.10 to +0.23kg)</td></tr>
<tr><td colspan="4">Grade assessment:NA</td></tr>
<tr><td>Severe hypoglycaemia</td><td colspan="3">Reported in 6/10 trials
Risk Ratio= 0.82 (95%CI 0.45 to 1.49)
NS</td></tr>
<tr><td>Overall hypoglycaemia</td><td colspan="3">Reported in 7/10 trials
Risk Ratio= 0.89 (95%CI 0.83 to 0.96)
SS in favour of insulin glargine</td></tr>
<tr><td>Symptomatic hypoglycaemia</td><td colspan="3">Reported in 4/10 trials
Risk Ratio= 0.80(95%CI 0.68 to 0.93)
SS in favour of insulin glargine</td></tr>
<tr><td>Nocturnal hypoglycaemia</td><td colspan="3">Reported in 7/10 trials
Risk Ratio= 0.54 (95%CI 0.43-0.69)
SS in favour of insulin glargine</td></tr>
<tr><td rowspan="2"></td><td><u>Quality</u>
OK</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
-1</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
</table>

- A meta-analysis was performed comparing insulin glargin to insulin NPH in addition to (oral) existing treatment in people with type 2 diabetes. All but 1 trial consisted of insulin-naive patients.

-HbA1c change was not significantly different between both treatments.

GRADE: high quality of evidence

-A meta-analysis on change in body weight could not be carried out.
GRADE: NA

- There was no significant difference between treatments for risk of severe hypoglycaemia.
Risk of overall hypoglycaemia as well as risk of symptomatic hypoglycaemia was significantly lower in the insulin glarine group (Risk ratio 0.89 (95%CI 0.83 to 0.96) and 0.80(95%CI 0.68 to 0.93)).
There was a significantly lower risk of nocturnal hypoglycaemia in the insulin glargin group compared to the insulin NPH group. (Risk Ratio= 0.54 (95%CI 0.43-0.69)).

The recording and reporting of symptomatic hypoglycaemia was mostly done by the patient and differed between studies. The measurement of nocturnal hypoglycaemia in the studies was unclear.

GRADE: moderate quality of evidence

7.2.4.2. Insulin NPH + existing therapy versus insulin detemir + existing therapy

No studies met our inclusion criteria.

8. Evidence tables and conclusions: Pre-diabetes

8.1. Pre-diabetes: Metformin versus placebo or lifestyle intervention

Metformin vs Lifestyle modification vs metformin and lifestyle modification vs control

Ref	n/Population	Duration	Comparison	Outcomes					Methodological
Ramachandran 2006 Design: RCT (PG-OL) Setting: 1st line	n= 531 <u>Inclusion</u> - IGT* - mean age: 45.9 y - mean BMI: 25.8 kg/m^2 - male 83.5% - Asian Indians	Median follow-up: 30 m	Lifestyle modification (LSM: dietary recommendation and 30 min/day physical activity) Vs Metformin 500 mg/d (MET) Vs Lifestyle modification and metformin (combi) Vs control	Efficacy					- Jadad score ○ RANDO: 1/2 ○ BLINDING: 0/2 ○ ATTRITION: 1/1 - FU: 94.5% - ITT: NR - Other important methodological remarks: not placebo-controlled, blinded study but principal investigators were blinded to the outcome until they were asked to close the study - Sponsor: NR Indian Diabetes Prevention Programme
				Development of diabetes (PE)	Control	LSM	MET	Combi	
				cum. incidence at 3y (%)	55.0	39.3	40.5	39.5	
				ARR (%)		**15.7**	**14.5**	**15.5**	
				RRR (%)		**28.5**	**26.4**	**28.2**	
				p value vs control		0.018	0.029	0.022	
				NNT (3y)		6.4	6.9	6.5	
				Weight increase (kg)	NR P<0.01 **SS**	NR P=0.035 at 24m, NS at other times of FU	NR NS	NR NS	
				HbA1c	NR				
				Safety (NT)					
				Mortality	1	1		1	
				Cardiovascular events	2	4		5	
				Hospitalization	28 in total				
				Hypoglycaemia			22		
				Gastrointestinal symptoms			5		

* WHO criteria

IGT: 2h value ≥ 7.8 to < 11.0 mmol/l (140-199 mg/dl)
fasting < 7.0 (<126 mg/dl)

Author's conclusion:
It was possible to prevent diabetes in native Asian Indians with IGT using lifestyle modification. Surprisingly, the effects of LSM and LSM+MET were not different.
The progression rate of IGT to diabetes was very high in Asian Indians, as shown by a cumulative incidence of 55% in 3 years (18.3% per year) in the controls.

Metformin vs intensive lifestyle intervention vs placebo

Ref	n/Population	Duration	Comparison	Outcomes					Methodological
DPP: DPPRG 2002 Design: RCT (PG-DB) DPPOS: DPPRG 2009 Design: RCT (PG – OL) (unblinded) Setting: 1st line	DPP n=3234 DPPOS n= 2766 -mean age: 55.2y -mean BMI=34.2 -54% white, 20% black, 4.5% Asian <u>Inclusion</u> - Fasting plasma glucose:5.3-6.9mmol/l and - IGT: 2h postload glucose 7.8-11.0mmol/l and - BMI≥24 or ≥22 in Asian Americans	Original DPP trial: 2.8y DPPOS Median additional follow-up: 5.7y Mean follow up Combined trials + bridge: 10.0y	Intensive lifestyle intervention (-7% weight loss and ≥150min physical activity) vs metformin 2x850mg vs placebo	Efficacy					- Jadad score ○ RANDO: 1/2 ○ BLINDING: 1-0/2 ○ ATTRITION: 0-1/1 - FU DPP: NR - FU DPPOS: 93% - ITT: yes - Other important methodological remarks: all three groups were offered group-implemented lifestyle intervention; participants were unmasked to assignment after DPP at 3.2y - Sponsor: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
						Lifestyle	Metformin	Placebo	
				Cumulative diabetes* incidence (/100py) (PE) AR	DPP	4.8 (4.1-5.7)	7.8(6.8-8.8)	11.0(9.8-12.3)	
					DPPOS	5·9 (5·1–6·8)	4·9 (4·2–5·7)	5·6 (4·8–6·5)	
					Combined trials (DPP, bridge, DPPOS)	5.3(4.8-5.8)	6.4 (5.9-7.1)	7.8 (7.2-8.6)	
				Cumulative diabetes incidence at 3y	DPP	14.4%	21.7%	28.9%	
				Incidence reduction (RRR)(%) vs placebo	DPP	**58% (48-66)**	**31(%17-43)**	-	
					Combined trials	**34% (24–42)**	**18% (7–28)**		
				Incidence reduction (%) vs metformin	DPP	**39%(24-51)**	-	NR	
				Delay to onset of diabetes* (y)	Combined trials	4	2	-	
				Return to normoglycaemia (%)	Combined trials	13	11	10	
				Mean weight loss (kg)	DPP	**5.6 (SS)**	**2.1 (SS)**	0.1	
					Combined trials	2	2.5	<1	
				Mean HbA1c (%)	Combined trials	5.95	5.9	6.0	
				Safety (NT)					
				Gastrointestinal symptoms (/100 py)	DPP	12.9	77.8	30.7	
				Musculoskeletal symptoms (/100 py)		24.1	20.0	21.1	
				Hospitalization ≥ 1admission (% of participants)		15.6	15.9	16.1	
				Deaths (/100py)		0.1	0.2	0.1	

* ADA criteria (American Diabetes Association):

Diabetes symptoms (polyuria, polydipsia, polyphagia, increased fatigue, weight loss, blurred vision, growth impairment) and casual plasma glucose ≥200mg/dl (11.1 mmol/l) *OR* FPG >126mg/dl (7.0 mmol/l) *OR* plasma glucose ≥200mg/dl (11.1 mmol/l) during an OGTT

8.1.bis. Summary and conclusions. Pre-diabetes: Metformin versus placebo or lifestyle intervention

Metformin 500-1700mg/d vs control (1. Ramachandran 2006, 2. DPP2002/ 2'. DPPOS 2009)							
N/n	**Duration**	**Population**	**Results**				
N= 2, n= 3297	Trial 1+2 Median follow-up: 2.7y Trial 2' 10y OL extension	- IFG <7.0mmol/l (<126mg/dl) – IGT 2h value ≥ 7.8 to < 11.0 mmol/l (140-199mg/dl) Trial 1 -100% Asians (500mg Met) Trial 2 -54% white, 20% black, 4.5% Asian (2x850mg Met)	Development of DMII: cumulative incidence at 3y		1) **Met 40.5% vs control 55.0% =>SS in favour of Met** 2) **Met 21.7% vs placebo 28,9% =>SS in favour of MET**		
			Progression to DMII (RRR)	3y	1**) 26.4% reduction in MET =>SS in favour of Met** 2**) 31%(17-43)=> SS in favour of Met**		
				10y	*2') **18% (7-28) =>SS in favour of Met***		
			Quality -1		Consistency OK	Directness OK	Imprecision OK
			GRADE: moderate quality of evidence				
			Weight evolution (mean weight loss)	3y	Reported in 2/2 trials 1) NS ***2)*** **2.1 vs 0.1 kg => SS in favour of Met**		
				10y	*2') 2.o vs <1kg NT*		
			Quality -1		Consistency OK	Directness OK	Imprecision OK
			GRADE: moderate quality of evidence				
			Mortality		Reported in 2/2 trials; NT		
			Quality -2		Consistency NA	Directness OK	Imprecision -1
			GRADE: very low quality of evidence				
			Cardiovascular events		Reported in 1/2 trials; NT		
			Quality -2		Consistency NA	Directness OK	Imprecision -1
			GRADE: very low quality of evidence				

Metformin 500-1700mg/d vs lifestyle modification (diet, physical activity) (1. Ramachandran 2006, 2. DPP2002/ 2'. DPPOS 2009)							
N/n	**Duration**	**Population**	**Results**				
N= 2, n= 3297	Trial 1+2 Median follow-up: 2.7y Trial 2' 10y OL extension	- IFG <7.0mmol/l (<126mg/dl) Or IGT 2h value ≥ 7.8 to < 11.0 mmol/l (140-199mg/dl) Trial 1 -100% Asians (500mg Met) Trial 2 -54% white, 20% black, 4.5% Asian (2x850mg Met)	Development of DMII: cumulative incidence at 3y		1. Met 40.5% vs LSM 39.3% =>NS 2. **Met 21.7% vs LSM 14.4% =>SS in favour of LSM**		
			Progression to DMII (RRR)		1. NS 2. **-39%(24-51) in LSM =>SS in favour of LSM**		
			Quality -1		Consistency OK	Directness -1	Imprecision OK
			GRADE: low quality of evidence				
			Weight evolution (loss in kg)	3y	Reported in 2/2 trials 1. NS 2. 2.1kg Met vs 5.6kg LSM =>SS in favour of LSM		
				10y	2' 2.5 kg Met vs 2 kg LSM NT		
			Quality -1		Consistency OK	Directness -1	Imprecision OK
			GRADE: low quality of evidence				
			Mortality		Reported in 1/2 trials => NT		
			GRADE: NA				
			Cardiovascular events		Reported in 1/2 trials => NT		
			GRADE: NA				

- Two studies compared metformin treatment with intensive lifestyle modification (diet, physical activity, education) and with placebo for diabetes prevention in impaired glucose tolerance.
The studies were very heterogeneous. Study 1 tested 500mg metformin exclusively in an Indian population. Study 2 tested a dose of 2x850mg in mainly white Americans. Study 2 was continued after unblinding and a bridging period, as an unblended follow-up study that collected data up to 10 years.

Metformin versus control/placebo
Metformin is significantly better than placebo at avoiding evolution to diabetes. This effect seems to be maintained after 10 years of treatment. There could possibly be a small decrease in weight.

GRADE: moderate quality of evidence

Metformin versus lifestyle intervention
An intensive lifestyle intervention could be more effective than metformin in avoiding the development of diabetes type 2. In 1 large study, there is 39% less diabetes in the lifestyle group as opposed to the metformin group. The other study however(100% Asian), does not show a significant difference.

GRADE: low quality of evidence

We would like to point out that in both studies, lifestyle intervention was significantly better than placebo.

- Potential harms due to treatment were not always reported or not statistically tested. Information on hard endpoints (mortality, cardiovascular events) is not uniformly reported in the studies and also not statistically tested. Therefore we cannot really make a statement about these endpoints.
GRADE: very low quality of evidence

8.2. Pre-diabetes: Pioglitazone versus placebo

Pioglitazone 30 mg vs placebo

Ref	n/Population	Duration	Comparison	Outcomes			Methodological
Ramachandran 2009 Design: community-based placebo-controlled (quasi-randomised°, double blinded)	n=407 <u>Inclusion</u> - Persistent IGT* - Age: 35-55y - 87% male - Mean age: 45.3y - Mean BMI: 25.9 - Asian Indians	3y	Pioglitazone 30mg vs placebo (in addition to lifestyle modification)	Efficacy			- Jadad score ○ RANDO: 1/2 ○ BLINDING: 1/2 ○ ATTRITION: 1/1 - FU: 91% - ITT: yes - Sponsor: India Diabetes Research Foundation
				Progression to diabetes (PE)	pioglitazone= 29.8% vs placebo 31.6% (corrected cumulative incidence at 36m) adjusted HR= 0.98 (CI: 0.67-1.44) = NS		
				Reversal to normoglycemia (SE)	pioglitazone 40.9% vs placebo 32.3% = NS		
				HbA1c (%)	Pioglitazone: 5.7 -> 6.2 Placebo: 5.8 -> 6.3 = SS (p <0.001)		
				BMI (kg/m2)	Pioglitazone: 25.9 -> 26.2 Placebo: 26.0 -> 25.9 = NS		
				Blood pressure (mmHg)	Systolic	Pioglitazone: 117.8 -> 122.2 Placebo: 118.1 -> 123.6 = SS (p <0.001)	
					Diastolic	Pioglitazone: 75.3 -> 77.3 Placebo: 75.5 -> 79.1 = SS (p =0.02)	
				Safety			
				Mortality (n)	Pioglitazone 2 vs placebo 0 NT		
				Cardiovascular disease (n)	Pioglitazone 4 vs placebo 2 NT		
				Elevated transaminases (<120U/l)	Pioglitazone 1 vs placebo 3 = SS in favour of pioglitazone (p<0.001)		
				Weight change (kg)	Pioglitazone +0.68 vs placebo -0.40 = SS in favour of placebo (p<0.0001)		

* WHO criteria IGT: 2h value ≥ 7.8 to < 11.1 mmol/l DM: fasting ≥ 7.0 and/or 2h ≥ 11.1 mmol/l

° Participants were assigned to each group in sequential order.

Pioglitazone 30-45mg vs placebo

Ref	n/Population	Duration	Comparison	Outcomes			Methodological
DeFronzo 2011 Design: RCT DB	n=602 <u>Inclusion</u> - IGT: fasting plasma glucose level 95-125mg/dl and BMI ≥25 + min. 1 other risk factor for DM and ≥18y - 42% male - Mean age: 52.3y - Mean BMI: 34.5 - Americans: 54% white, 26% Hispanics, 17% black, 3% others <u>Exclusion</u> - /	Mean: 2.2y	Pioglitazone 30-45mg vs placebo (in addition to dietary instruction)	Efficacy			- Jadad score ○ RANDO: 1/2 ○ BLINDING: 1/2 ○ ATTRITION: 1/1 - FU: 73% - ITT: NR Methodological remarks: Loss to follow-up was relatively high in both study groups (24% placebo, 30% pioglitazone, NS) but withdrawal rates and baseline characteristics were similar between groups - Sponsor: Takeda Pharmaceuticals and others
				Progression to diabetes (PE)	pioglitazone 2.1% vs placebo 7.6% (annual incidence) adjusted HR= 0.28 (95% CI: 0.16-0.49) = SS (p <0.001) **in favour of pioglitazone** NNT=18 for 1 year (treatment of 18 patients for 1 year prevented 1 case of diabetes)		
				Reduction in glucose levels (mg/dl)	fasting	Between-group difference: 2.5	
					2-hour	Between-group difference: 14.3	
					In favour of pioglitazone (p<0.001)		
				HbA1c (%)	Pioglitazone: no change Placebo: + 0.2 = SS (p <0.001) **In favour of pioglitazone**		
				BMI (kg/m^2)	Pioglitazone: 34.1 -> 35.5 Placebo: 34.5 -> 34.7 = SS (p<0.001) **in favour of placebo**		
				Blood pressure (mmHg)	Systolic	Declined slightly in both groups, NS	
					Diastolic	Lower in pioglitazone group = SS (p =0.01)	
				Harms			
				Mortality	Pioglitazone 1% vs placebo 0,3%		
				Cardiovascular disease	Pioglitazone 8.6% vs placebo 7.7% P=0.8		
				Edema	Pioglitazone 13% vs placebo 6.4% P= 0.007		
				Weight gain (>1kg)	Pioglitazone 67% vs placebo 43% P<0.001		
				Elevated transaminases	Pioglitazone: levels are lower than placebo P<0.001		

8.2.bis. Summary and conclusions. Pre-diabetes: Pioglitazone versus placebo

<table>
<tr><td colspan="5">Pioglitazone 30-45mg/d vs placebo (Ramachandran 2009 (a), DeFronzo 2011(b))</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td>Results</td><td></td></tr>
<tr><td rowspan="15">N= 2, n= 1009</td><td rowspan="15">Mean: 2.6y</td><td rowspan="15">- IGT: FPG 65-125mg/dl or 2h value ≥ 7.8 to < 11.1 mmol/l

- Asian Indians with mean BMI= 25.9 (a)
Or
Americans with mean BMI= 34.5 (b)</td><td rowspan="3">Progression to diabetes (PE)</td><td>a) (cumulat. incidence) pio 29.8% vs placebo 31.6%
adjusted HR= 0.98 (CI: 0.67-1.44)
= NS
b) (annual incidence) pio 2.1% vs placebo 7.6%
adjusted HR= 0.28 (CI: 0.16-0.49)
= SS (p<0.001) in favour of pioglitazone</td></tr>
<tr><td><u>Quality</u> | <u>Consistency</u> | <u>Directness</u> | <u>Imprecision</u>
-1 (for inadequate randomisation) | OK | -1 | OK</td></tr>
<tr><td>Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">HbA1c (%)</td><td>a) pioglitazone: 5.7 -> 6.2 vs placebo: 5.8 -> 6.3
= SS (p <0.001) change in both groups
b) pioglitazone: 5.5 -> 5.5 vs placebo: 5.5 -> 5.7
= NS change in pioglitazone group vs SS change in placebo group (p<0.001)</td></tr>
<tr><td><u>Quality</u> | <u>Consistency</u> | <u>Directness</u> | <u>Imprecision</u>
-1 | OK | -1 | OK</td></tr>
<tr><td>Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">BMI (kg/m^2)</td><td>a) pioglitazone: 25.9 -> 26.2 vs placebo: 26.0 -> 25.9
= NS
b) pioglitazone: 34.1->35.5 vs placebo: 34.5 -> 34.7
= SS (p<0.001) in favour of placebo</td></tr>
<tr><td><u>Quality</u> | <u>Consistency</u> | <u>Directness</u> | <u>Imprecision</u>
-1 | OK | -1 | OK</td></tr>
<tr><td>Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="2">Mortality</td><td>a) pioglitazone 0.5% vs placebo 0% -> NT
b) pioglitazone 1% vs placebo 0,3% -> NT</td></tr>
<tr><td>Grade assessment:NA</td></tr>
<tr><td rowspan="3">Cardiovascular disease</td><td>a) pioglitazone 1% vs placebo 0.5% -> NT
b) pioglitazone 8.6% vs placebo 7.7% (p=0.8)</td></tr>
<tr><td><u>Quality</u> | <u>Consistency</u> | <u>Directness</u> | <u>Imprecision</u>
-2 | NA | -1 | OK</td></tr>
<tr><td>Grade assessment: very low quality of evidence</td></tr>
<tr><td>Edema</td><td>a) NR
b) pioglitazone 13% vs placebo 6.4% (p= 0.007)</td></tr>
<tr><td>Elevated transaminases</td><td>a) pioglitazone 0.25% vs placebo 0.75%
= SS in favour of pioglitazone (p<0.001)
b) levels in pioglitazone lower than in placebo
= SS in favour of pioglitazone (p<0.001)</td></tr>
<tr><td>Weight gain</td><td>a) pioglitazone +0.68kg/3y vs placebo: -0.40kg/3y
= SS in favour of placebo (p<0.0001)
b) pioglitazone 67% +>1kg/2.4y vs placebo 43% +>1kg/2.4y
= SS in favour of placebo (p<0.001)</td></tr>
</table>

- Two studies compared pioglitazone with placebo treatment for diabetes prevention in impaired glucose tolerance but the study population was very heterogeneous. One study only included Asian Indians with normal BMI, while the other study regarded obese Americans. There is no statistically significant effect on 'progression to diabetes' of pioglitazone compared to placebo in Asian Indians (adjusted HR= 0.98, 95%CI: 0.67-1.44). On the other hand, Americans benefit from pioglitazone (adjusted HR= 0.28, 95%CI: 0.16-0.49).

GRADE: low quality of evidence

There is insufficient information to evaluate the impact on hard endpoints such as mortality or cardiovascular disease

GRADE: NA

- Treatment with pioglitazone was associated with significant weight gain and edema. Pioglitazone reduced levels of both alanine and aspartate aminotransferase (p-value <0.001).

8.3. Pre-diabetes: GLP-1 agonists versus placebo or lifestyle intervention

No studies were found.

8.4. Pre-diabetes: Origin trial: Insulin glargine versus placebo

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
ORIGIN trial investigators 2012 Design: RCT (OL) (PG) Setting: cardiology, diabetes and other clinical sites	n=12537 mean age: 63.5y Prior R: 59% oral glucose-lowering agent Duration diabetes: mean 5.4y Baseline median HbA1c: 6.4% 6% new diabetes[1], 82% prior diabetes, 12% IGT 35% female <u>Inclusion</u> - ≥50y and IGT, impaired FPG [2] or DMII (stable on 0 GLA, HbA1c<9% or 1 OAD, HbA1c <8%) and other cardiovascular risk factors[3] - <u>Exclusion</u> - inability to inject insulin, intolerance to insulin - heart failure - coronary artery bypass surgery in prior 4y - cancer affecting survival	Median follow-up: 6.2y	Insulin glargine (add ins glargine to glycemic control regimen and increase dose)(target FPG 95mg/dl)[4] Vs Standard care (investigator's best judgment and local guidelines[5])	Efficacy		- Jadad score o RANDO: 1/2 o BLINDING: 0/2 o ATTRITION: 1/1 - FU: 99% - ITT: no (intention reported but not executed) - Multicenter: 573 centers in 40 countries - Important methodological remarks: - This study also compared n- fatty acids vs placebo in a 2-by-2 design - 10 day placebo run-in - Definition of 'new diabetes' in this trial differs from standard ADA/WHO definition - No specific target defined in standard care group - Sponsor: Sanofi
				Nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes (per 100 person-years) (PE)	Insulin: 2.94 vs Standard: 2.85 HR=1.02 (CI: 0.94-1.11) NS: p=0.63	
				Nonfatal myocardial infarction, nonfatal stroke, death from cardiovascular causes, revascularization or hospitalization for heart failure (per 100 person-years)(PE)	Insulin: 5.52 vs Standard: 5.28 HR=1.04 (CI: 0.97-1.11) NS: p=0.27	
				All-cause mortality	Insulin: 2.57 vs Standard: 2.60 HR=0.98 (CI0.90-1.08) NS: p=0.70	
				Composite microvascular outcomes	Insulin: 3.87 vs Standard: 3.99 HR=0.97 (CI 0.90-1.05) NS: p=0.43	
				New onset diabetes [6](among 1456 participants without baseline diabetes)	Insulin: 30% vs Standard: 35% OR=0.80 (CI: 0.64-1.00) NS: p=0.05	
				HbA1c (%) at 7y	Insulin: 6.2 vs Standard: 6.5 NT	
				Safety		
				Severe hypoglycemia (per 100 person-years)	Insulin: 1.00 vs Standard: 0.31 **SS: p<0.001 in favour of standard**	
				Weight (median change)	Insulin: +1.6kg vs Standard: -0.5kg NT	
				Cancers	HR=1.00 (CI: 0.88-1.13) NS: p=0.97	

7. Definition of newly detected diabetes in this trial based on either a FPG ≥ 6.1 mmol/L [110 mg/dL] or a 2 hour plasma glucose ≥ 7.8 mmol/L [140 mg/dL] after a 75 g oral glucose load.
8. FPG ≥ 6.1 mmol/L [110 mg/dL]
9. prior CV event (myocardial infarction, stroke or revascularization), angina with documented ischaemia, albuminuria, left ventricular hypertrophy, stenosis of coronary, carotid or leg artery
10. If target FPG levels could not be achieved without symptomatic hypoglycemia, investigators were permitted to: replace glyburide used at baseline with a comparable dose of glimepiride; to reduce or stop any other glucose-lowering drugs; and/or to add metformin. If participants developed uncontrolled hyperglycemia, investigators were permitted to add rapid-acting insulin.
11. investigators were advised to avoid insulin until maximal doses of 2 different oral glucose-lowering agents were required in the standard care group.
12. New diabetes was diagnosed during the trial if 2 consecutive FPG levels within a 4-month period were > 7 mM (126 mg/dL); or if a diagnosis of diabetes was made by a physician, and the participant was taking a pharmacologic glucose lowering agent and there was documentation of either a FPG > 7 mM (126 mg/dL) or any glucose value > 11.1 mM (200 mg/dL). New diabetes was diagnosed during down-titration of glargine insulin (i.e. before the last visit) if at least 1 capillary glucose level was ≥ 11.1 mM (200 mg/dl) with a FPG ≥ 7 mmol/l (126 mg/dl); or a random plasma glucose was ≥ 11.1 mM (200mg/dl). New diabetes was diagnosed after the last visit if any FPG was ≥ 7 mM (126 mg/dl) or 2 hour plasma glucose was > 11.1 mM (200 mg/dl) during the first OGTT (3-4 w after), and durability of the effect was assessed by the second test (10-12 w after).

8.4.bis. Summary and conclusions. Pre-diabetes: Origin trial: Insulin glargine versus placebo

<table>
<tr><td colspan="5">Insulin Glargine (added to existing regimen) Vs Standard care (ORIGIN trial investigators 2012)</td></tr>
<tr><th>N/n</th><th>Duration</th><th>Population</th><th>Results</th><th></th></tr>
<tr><td rowspan="10">1/
12537</td><td rowspan="10">Median follow-up: 6.2y</td><td rowspan="10">DMII or IGT or IFG and cardiovascular disease

Prior R: 59% oral glucose-lowering agent
Duration diabetes: mean 5.4y
Baseline median HbA1c: 6.4%

6% new diabetes[1], 82% prior diabetes, 12% IGT</td><td rowspan="3">Nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes (per 100 person-years) (PE)</td><td>Insulin: 2.94 vs Standard: 2.85(per 100 person-years)
HR=1.02 (CI: 0.94-1.11)
NS: p=0.63</td></tr>
<tr><td><u>Quality</u>
-1 for low JADAD and no ITT
<u>Consistency</u>
NA
<u>Directness</u>
OK
<u>Imprecision</u>
OK</td></tr>
<tr><td>Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Nonfatal myocardial infarction, nonfatal stroke, death from cardiovascular causes, revascularization or hospitalization for heart failure (per 100 person-years)(PE)</td><td>Insulin: 5.52 vs Standard: 5.28
HR=1.04 (CI: 0.97-1.11)
NS: p=0.27</td></tr>
<tr><td><u>Quality</u>
-1
<u>Consistency</u>
NA
<u>Directness</u>
OK
<u>Imprecision</u>
OK</td></tr>
<tr><td>Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">New onset diabetes during or after trial (among 1456 participants without baseline diabetes)</td><td>Insulin: 30% vs Standard: 35%
OR=0.80 (CI: 0.64-1.00)
NS: p=0.05</td></tr>
<tr><td><u>Quality</u>
- 1
<u>Consistency</u>
NA
<u>Directness</u>
-1different diabetes definition
<u>Imprecision</u>
OK</td></tr>
<tr><td>Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Severe hypoglycemia (per 100 person-years)</td><td>Insulin: 1.00 vs Standard: 0.31
SS: p<0.001 in favour of standard</td></tr>
<tr><td><u>Quality</u>
-1
<u>Consistency</u>
NA
<u>Directness</u>
OK
<u>Imprecision</u>
OK</td></tr>
<tr><td>Grade assessment: moderate quality of evidence</td></tr>
<tr><td>Weight (median change)</td><td>Insulin: +1.6kg vs Standard: -0.5kg
NT</td></tr>
</table>

In this study, patients with a documented cardiovascular disease and type 2 diabetes, IFG or IGT were randomised between adding insulin glargine to existing therapy or standard care. After a median follow-up of 6.2 years there is no significant difference for a composite endpoint of non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality (HR=1.02, 95%CI: 0.94-1.11).

GRADE: *moderate quality of evidence*

In the group treated with insulin glargine there are significantly more cases of severe hypoglycemia than in the standard care group (1.00/100py vs 0.31/100py, p<0.001).

GRADE: *moderate quality of evidence*

In a predefined subgroup analysis in patients without baseline diabetes, there is no significant difference in developing diabetes [OR=0.80 (95%CI: 0.64-1.00)].

GRADE: low quality of evidence

9. Adverse events of anti-diabetic drugs

9.1. Adverse effects of metformin

- **Gastro-intestinal: diarrhea, anorexia, nausea and vomiting: very frequent (>10%)**
- **Taste disturbances: frequent (1-10%)**
- **Headache: frequent (1-10%)**
- **Asthenia: frequent (1-10%)**
- **Skin reactions (erythema, urticaria): very rare (<0.01%)**
- **Lactic acidosis: very rare but often fatal**
    - The risk of lactic acidosis has been studied in a Cochrane systematic review[1] This systematic review of RCTs and cohort studies revealed no increased risk of lactic acidosis in metformin users compared to non-metformin users. The review reported rates of 4.3 cases/100.000 person-years for metformin users and 5.4 cases/100.000 py in non-metformin users (other oral antidiabetic agents or placebo). However: study conditions are different from real life situations and many studies exclude patients with risk factors for lactic acidosis.
- **Vitamin B12 deficiency in chronic use**
- **Metformin and cancer**

There is some evidence that diabetes is associated with an increased risk of cancer[2].
Several meta-analyses of RCTs and observational studies, published in the last 2 years, have evaluated the association between metformin and the (lower) risk of cancer in patients with type 2 diabetes. Metformin seems to be associated with a lower risk of all cancers[3] [4] , pancreatic cancer[3] and liver cancer[5] compared to other antidiabetic agents. There is conflicting evidence on colorectal cancer[6,3]. It is unclear whether the decrease in risk of cancer is because of a protective effect of metformin, or an increased cancer risk in the comparison group or an unknown confounder. (GRADE: very low quality of evidence). (See also: sulphonylurea and cancer)

- **Metformin and cardiovascular events**

The trials that study metformin for hard endpoints as primary endpoint (UKPDS34) have been included in this review. Several meta-analyses of varying quality have been performed with metformin, analysing cardiovascular outcomes and mortality in type 2 diabetes. These use data from UKPDS, combined with data from trials that were not designed for these long-term outcomes but register these events as safety outcomes. These meta-analyses find either a significant benefit for metformin treatment compared to other glucose-lowering agents and compared to placebo for cardiovascular events or mortality (because the main trial UKPDS weighed heavy on results)[7], or found no significant difference between metformin and comparators (placebo with or without concomitant therapy[8]), (placebo or active drug, analysed together[9]). Inclusion criteria and comparators used in all meta-analyses were different. The level of evidence is low to very low, because included trials were of variable quality, trials were not designed for cardiovascular outcomes, clinically very heterogeneous and of short duration.

[1] Salpeter SR. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD002967. DOI: 10.1002/14651858.CD002967.pub4.

[2] Noto H, Tsuijmoto T, Takehiko S et al. Significantly increased risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis. Endocr Pract 2011;17:616–628

[3] DeCensi A. Metformin and Cancer Risk in Diabetic Patients: A Systematic Review and Meta-analysis. *Cancer Prev Res* 2010;3:1451-1461. Published OnlineFirst October 12, 2010.

[4] Soranna D. Cancer Risk Associated with Use of Metformin and Sulfonylurea in Type 2 Diabetes: A Meta-Analysis *The Oncologist* 2012;17:813–822.

[5] Zhang Z. Metformin for Liver Cancer Prevention in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. *J Clin Endocrinol Metab*, July 2012, 97(7):2347–2353.

[6] Zhang Z. Reduced Risk of Colorectal Cancer With Metformin Therapy in Patients With Type 2 Diabetes:A meta-analysis. *Diabetes Care* 34:2323–2328, 2011

[7] Saenz A, Fernandez-Esteban I, Mataix A, Ausejo Segura M, Roqué i Figuls M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD002966. DOI: 10.1002/14651858.CD002966.pub3

[8] Boussageon R, Supper I, Bejan-Angoulvant T, Kellou N, Cucherat M, et al. (2012) Reappraisal of Metformin Efficacy in the Treatment of Type 2 Diabetes:A Meta-Analysis of Randomised Controlled Trials. PLoS Med 9(4): e1001204. doi:10.1371/journal.pmed.1001204

[9] Selvin E. Cardiovascular Outcomes in Trials of Oral Diabetes Medications: A Systematic Review. *Arch Intern Med*. 2008 October 27; 168(19): 2070–2080. doi: 10.1001/archinte.168.19.2070

9.2. Adverse effects of sulphonylurea

- **Hypoglycemia, especially with products with a long duration of action, in particular, glibenclamide, and in the elderly: frequent (1-10%)**
- **Weight gain**
- **Gastro-intestinal discomfort**
- **Skin and mucosal reactions, similar to those with the antibacterial sulfamides, with cross allergy**
- **Hyponatriemia**
- **Photosensitisation**
- **Cholestatic jaundice: rare**
- **Hematologic abnormalities (thrombocytopenia, leucopenia and agranulocytosis): rare**
- **Use of sulfonylurea with ethanol can result in a disulfiram-like reaction**
- **Sulphonylurea and cancer**

A recent nationwide Danish cohort study [1] examined the association between different glucose-lowering drugs and cancer occurrence. People in the population taking glucose lowering agents had a higher incidence of cancer than people in the population not taking glucose-lowering agents. When analysed by drug class, insulin and sulphonylurea users had a significantly higher cancer incidence rate than non- users. However, the first 30-day period after initiation of glucose-lowering treatment was associated with a very pronounced increase in relative risk of cancer for most agents (RR ≈ 2.0 to 4.0), which subsequently declined rapidly during the first year of treatment, resulting in a RR of 1 after approximately a half to 1 year of treatment. This phenomenon argues against a causal effect.

- **Sulphonylurea and cardiovascular events**

Trials that study sulphonyurea for hard endpoints as primary endpoint (UKPDS33) have been included in this review.

A meta-analyses has been performed for sulphonylurea and cardiovascular outcome[2], using data from these trials, combined with data from trials that were not designed for these long-term outcomes but register these events as safety outcomes. No significant difference between sulphonylurea treatment and comparator (placebo or active drug analysed together) was found for cardiovascular events or mortality The level of evidence is low, because included trials were of variable quality, trials were not designed for these outcomes and were clinically very heterogeneous and trials were of short duration..

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[1] Andersson C, Vaag A, Selmer C, et al. Risk of cancer in patients using glucose-lowering agents: a nationwide cohort study of 3.6 million people. BMJ Open 2012;2:e000433. doi:10.1136/bmjopen-2011-000433

[2] Selvin E. Cardiovascular Outcomes in Trials of Oral Diabetes Medications: A Systematic Review. *Arch Intern Med*. 2008 October 27; 168(19): 2070–2080. doi: 10.1001/archinte.168.19.2070

9.3. Adverse effects of meglitinides

- **Hypoglycemia: frequent (1-10%)**
- **Gastro-intestinal disorders (diarrhea, nausea): frequent (1-10%)**
- **Weight gain**
- **Cardiovasculaire disease: rare (0.01-0.1%)**
- **Increased liver enzymes: very rare (<0.01%)**

9.4. Adverse effects of pioglitazone

- Weight gain: frequent (1-10%)
- Water and salt retention, possibly provoking or worsening heart failure
    - A higher incidence of heart failure was also found in the PRO-active study, see chapter 6.1.4.
- **Gastro-intestinal disorders**
- **Fatigue, headache, dizziness**
- **Increased risk of fracture in the extremities: frequent (1-10%)**
    - The increased risk of fracture has not only been found in observational studies[1] but also in RCTs. In the PRO-active study[2], there was no significant difference in fracture rate in men between pioglitazone and placebo treatment groups. However, in women, the fracture incidence was 5.1%/100 py for pioglitazone vs 2.5% for placebo (p=0.006). Another RCT [3] (periscope trial) compared pioglitazone with glimepiride and found a significant difference in fracture risk: 3% with pioglitazone vs 0% with glimepiride (p=0.004)
- **Upper respiratory tract infection: frequent (1-10%)**
- **Hypoglycemia: rare**
- **Hepatic impairment: rare**
- **Anemia**
- **Macular edema**
- **Suspicion of increased risk of bladder cancer**
    - The risk of bladder cancer has also been assessed in a meta-analysis of 4 RCTs and 5 observational studies[4]. The meta-analysis of 4 RCTs (use of pioglitazone or rosiglitazone) shows no significant risk increase of bladder cancer in TZD use. GRADE: *low quality of evidence*. The meta-analysis of 5 cohort studies shows an increased risk of bladder cancer in TZD users vs no TZD users [pooled adjusted RR=1.15 (95%CI 1.04-1.26)]. Grade assessment: *very low quality of evidence*. The meta-analysis of the 3 cohort studies with pioglitazone shows an increased risk of bladder cancer (Pooled RR 1.22 (95%CI 1.07-1.39)). Grade assessment: *low quality of evidence.*
- **In combination with metformin: anemia, headache, arthralgia, hematuria, erectile dysfunction**
- **Pioglitazone and cardiovascular events**

The trials that study pioglitazone for hard endpoints as primary endpoint (PROactive) have been included in this review. A meta-analysis studied pioglitazone for cardiovascular outcomes, using data from this trial, combined with data from trials that were not designed for these long-term outcomes but register these events as safety outcomes[5]. No significant difference between pioglitazone treatment and comparator (placebo or active drug analysed together) for cardiovascular morbidity was found. The level of evidence is low, because included trials were of variable quality, trials were not designed for these outcomes and were clinically very heterogeneous and trials were of short duration.

1. Betteridge DJ.Thiazolidinediones and fracture risk in patients with Type 2 diabetes. Diabet Med. 2011 Jul;28(7):759-71. doi: 10.1111/j.1464-5491.2010.03187.x.
2. Dormandy J, Bhattacharya M, van Troostenburg de Bruyn AR. PROactive investigators. Safety and tolerability of pioglitazone in high-risk patients with type 2 diabetes: an overview of data from PROactive. Drug Saf 2009; 32: 187–202.
3. Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A et al.; PERISCOPE Investigators Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes. The PERISCOPE randomised controlled trial. J Am Med Assoc 2008; 299: 1561–1573.
4. Isabelle N. Use of thiazolidinediones and the risk of bladder cancer among people with type 2 diabetes: a meta-analysis. CMAJ 2012. DOI:10.1503/cmaj.112102
5. Selvin E. Cardiovascular Outcomes in Trials of Oral Diabetes Medications: A Systematic Review. Arch Intern Med. 2008 October 27; 168(19): 2070–2080. doi: 10.1001/archinte.168.19.2070

9.5. Adverse effects of dipeptidyl peptidase-4 inhibitors

- **Gastro-intestinal disorders**
- **Infections (upper airways, urinary tract, gastro-intestinal): frequent (1-10%)**
  - This was also studied in a meta-analysis of 67 RCTs that evaluated safety of DPP-4 inhibitors. Here, no significant difference between DPP-4 inhibitors and placebo was found for infections (upper airway or urinary tract). A significant difference in rhinopharyngitis versus placebo was found for sitagliptin RR= 1.35 (1.03-1.77). (GRADE: very low quality of evidence)
- **Headache**
- **Vomiting**
- **Hypoglycemia in association with sulphonylurea: very frequent (>10%)**
  - This was also found in a meta-analysis[1] of 67 RCTs that evaluated safety of DPP-4 inhibitors. 10 studies (n=4765) that compared DPP-4 inhibitors vs placebo with insulin/SU co-medication found a higher risk for hypoglycemia with DPP-4 inhibitors (RR 1.36 (95%CI 1.17-1.58) compared to placebo. Analysis per individual gliptin showed a higher risk for hypoglycemia with linagliptin and sitagliptin. (GRADE: low quality of evidence)
- **Allergic reactions, sometimes severe, including Stevens-Johnson syndrome**
- **Increased risk of pancreatitis**
- **Sitagliptin: suspicion of pancreatic and thyroid cancer**
  - This was also studied in a recent meta-analysis. A meta-analysis[2] of 53 trials (n=33881), comparing DPP-4 inhibitors with placebo or active drug (in monotherapy or association with other OAD), studied risk of cancer, pancreatitis and major cardiovascular events. No significant difference in cancer or pancreatic cancer incidence was found. No significant difference in pancreatitis was found between DPP-4 inhibitor group versus other active treatment or placebo. (GRADE: very low quality of evidence)
- **Sitagliptin: indications for a risk of depression and myalgia. Dose dependent increase in serum creatinine was seen, its meaning is unclear**
- **Vildagliptin: liver disorders, including hepatitis: rare**
- **Vildagliptin: indications for a risk of atrial-ventricular conductiondisorders and edema**
- **Vildagliptin: abnormal renal function**
- **Saxagliptin: mild to moderate edema in combination with glitazones, higher risk of bone fractures**
- **DPP-4 inhibitors and cardiovascular events**

To this date no trials have been published that look at long-term hard outcome measures as primary endpoint for DPP-4 inhibitors. The only existing data on cardiovascular events and mortality are derived from studies that report these outcomes as adverse events. Recently, several meta-analyses have evaluated cardiovascular outcomes based on these existing data. The results are contradictory. The level of evidence is very low, because included trials were of variable quality, trials were not designed for these outcomes, clinically very heterogeneous and of short duration.

- A meta-analysis[3] of 18 RCTs (n=8544) comparing DPP-4 inhibitor monotherapy with other oral glucose-lowering agents or placebo, found a lower risk of adverse CV events with DPP-4

inhibitors (RR0.48, 95%CI 0.31 to 0.75) compared to placebo or other oral active agents. Trial duration was ≤54 weeks in 13 out of 18 trials.

- A meta-analysis[1] of 67 RCTs evaluated safety of DPP-4 inhibitors. There was a trend towards a higher risk of cardiac disorders (RR 1.37 (1.00-1.89) versus placebo. No definition of 'cardiac' disorders was given. No significant difference in vascular disorders was observed for DPP-4 inhibitors versus placebo, but linagliptin had a significantly higher risk of vascular disorders than placebo (RR1.74 [1.05, 2.86]). No definition for 'vascular disorders' was given. There was no significant difference in mortality.
  Trial duration inclusion criterium was ≥18 weeks.
- A meta-analysis[2] of 53 trials (n=33881), comparing DPP-4 inhibitors with placebo or active drug (as monotherapy or association with other OAD), studied risk of cancer, pancreatitis and major cardiovascular events. There was no significant difference in all-cause or cardiovascular death. DPP-4 inhibitors were associated with a lower incidence of major cardiovascular events when compared to active treatment or placebo (OR=0.689 (95%CI 0.528 – 0.899), and when compared to placebo only (OR=0.705(95%CI 0.500-0.993). The level of evidence is very low, because included trials were of variable quality, trials recorded these outcomes as adverse events and not as primary outcome and trials were clinically very heterogeneous. Trial duration was < 52weeks in 41 out of 53 trials.

[1] Goosen K. Longer term safety of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus: systematic review and meta-analysis. *Diabetes, Obesity and Metabolism* 2012. doi:10.1111/j.1463-1326.2012.01610.x

[2] Monami M. Safety of dipeptidyl peptidase-4 inhibitors:a meta-analysis of randomised clinical trials. *Curr med res opin*. 2011. Vol. 27, No. S3 , 57–64

[3] Patil H. Meta-Analysis of Effect of Dipeptidyl Peptidase-4 Inhibitors on Cardiovascular Risk in Type 2 Diabetes Mellitus. *Am J Cardiol* 2012. epub ahead of print
http://dx.doi.org/10.1016/j.amjcard.2012.04.061

9.6. Adverse effects of glucagon-like peptide-1 agonists

- **Gastro-intestinal disorders (nausea, vomiting and diarrhea): very frequent (> 10%)**
- **Local reactions at injection-site: frequent (1-10%)**
- **Higher risk of hypoglycemia in association with sulphonylurea than with sulphonylurea alone.**
- **Angio-edema, anaphylaxis: very rare**
- **Renal failure: very rare**
- **Exenatide: In clinical trials up to 6% of patients produced high levels of antibodies against exenatide, with half of them resulting in a reduction of the hypoglykemic effect. What this means in the long term is unclear.**
- **Exenatide: asthenia, dizziness, feeling nervous, headache: frequent (1-10%)**
- **Exenatide and liraglutide: suspicion of increased risk of pancreatitis and pancreatic and thyroid cancer**
- **Liraglutide: thyroidfunction-disorders: rare**
- **GLP-1 agonists and cardiovascular events**

To this date no trials have been published that look at long-term hard outcome measures for GLP-1 agonists as a primary outcome. The only existing data on cardiovascular events and mortality are from studies that report these outcomes as adverse events.

A meta-analysis[1] of 20 trials (n=10485) with a duration of ≥12 weeks, comparing GLP-1-agonists with placebo or active drug (in monotherapy or add-on treatment), studied risk of major adverse cardiovascular events. There was no significant difference in risk of major cardiovascular event between GLP-1 agonist and other glucose-lowering drugs. GLP-1 agonists were associated with a lower risk of major cardiovascular events when compared to placebo [(OR=0.459 (95%CI 0.255-0.826]. The level of evidence is very low, because trials of low quality were not excluded, trials were not designed for these outcomes and trials were clinically very heterogeneous. Trial duration was also short: only one trial was 52 weeks.

[1] Monami M. Glucagon-Like Peptide-1 Receptor Agonists and Cardiovascular Events: A Meta-Analysis of Clinical Trials. Experimental diabetes research. Volume 2011, Article ID 215764, 10 pages doi:10.1155/2011/215764

9.7. Adverse effects of alpha-glucosidase inhibitors

- **Gastro-intestinal disorders (diarrhea, flatulence, meteorism, abdominal discomfort): very frequent (>10%)**
- **Edema: rare (0.01-0.1%)**
- **Jaundice: rare (0.01-0.1%)**
- **Liver abnormalities: rare (0.01-0.1%)**

9.8. Adverse effects of insulin (long acting)

- **Hypoglycemia: very frequent (>10%)**
- **Weight gain**
- **Edema**
- **Acute peripheral neuropathy: rare (0.1-0.01%)**
- **Lipodystrophy at the site of injection, especially under conditions of poor injection technique, this may reduce the absorption of insulin**
- **Formation of circulating antibodies with possible neutralisation of the administered insulin**
- **Allergic skin reactions (rash, pruritus) of the delayed type at the start of the treatment, they usually disappear with further treatment**
- **Hypokaliemia can occur when a ketoacidosis or hyperosmolar coma is corrected with insulin**

Sources:

- BCFI (Belgian centre for pharmacotherapeutical information)
- EMA (European Medicines Agency)
- Micromedex (via Cebam link)
- Farmacotherapeutisch kompas
- Meyler's side effect of drugs
- Additional references per drug class

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Bolli G, Dotta F, Colin L, et al. Comparison of vildagliptin and pioglitazone in patients with type 2 diabetes inadequately controlled with metformin. Diabetes Obes Metab 2009;11:589-595.

Bolli G, Dotta F, Rochotte E, et al. Efficacy and tolerability of vildagliptin vs. pioglitazone when added to metformin: a 24-week, randomized, double-blind study. Diabetes Obes Metab 2008;10:82-90.

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Appendix 1: conversion table HbA1c % to mmol/mol

HbA1c (%)	HbA1c (mmol/mol)
4.0	20
5.0	31
6.0	42
6.5	48
7.0	**53**
7.5	58
8.0	64
8.5	69
9.0	75
9.5	80
10.0	86
10.5	91
11.0	97
11.5	102
12.0	108

Source: www.bcfi.be