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Safety and efficacy of dipeptidyl peptidase-4 inhibitors vs sulfonylurea in metformin-based combination therapy for type 2 diabetes mellitus: Systematic review and meta-analysis

Abstract

Purpose: The purpose of this study was to compare the safety and efficacy of DPP-4 inhibitors *versus* sulfonylurea as adjunctive second-line therapy in patients with type 2 diabetes mellitus, inadequately controlled with metformin mono-therapy.

Sources: A systematic review of published randomized controlled trials (RCTs) was performed in MEDLINE, EMBASE, PubMed and Cochrane library. Two reviewers independently selected the studies, extracted the data and assessed the risk of bias. Clinical outcomes were cardiovascular events, HbA1c % change from baseline, body weight and hypoglycemic event rate. A direct comparison meta-analysis using a random effect model was conducted to calculate mean differences in treatment effects and risk ratio between DPP-4 inhibitors and sulfonylurea.

Principle findings: Ten RCTs on adult patients with type 2 diabetes and inadequate glycemic control were included in the final analysis. DPP-4 inhibitors compared to sulfonylureas produced a non-significant difference in HbA1c% change in 10,139 subjects, whereas a significant decrease in the rate of hypoglycemic events was observed in favor of DPP-4 inhibitors (RR= 0.12; P<0.00001) involving 10,616 patients, with at least one hypoglycemic event during the follow-up period (12-104 weeks). Body weight decreased by 2.2 kg (95% CI 1.7-2.7) with DPP-4 inhibitors, compared with sulfonylureas. There were insufficient data to assess a difference in the risk for cardiovascular events.

Conclusion: The review shows that, in terms of clinical efficacy, there is no significant difference between DPP4-inhibitors and sulfonylurea when either is added to metformin mono-therapy. In contrast, the safety assessment analysis showed a significant decrease in the risk of hypoglycemic events in patients using DPP4-inhibitors.

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Metformin is the most commonly prescribed first-line oral hyperglycemic agent (OHA) for patients with type 2 diabetes. It produces a reduction in HbA1c of between 1% and 2% in patients with a low frequency of hypoglycaemia [1, 2]; however, in patients with type 2 diabetes, due to progressive failure of insulin secretion over time, metformin fails to maintain glycemic control and the addition of second-line medications are required to achieve plasma glycemic levels consistent with current guidelines (e.g., haemoglobin A1c (HbA1c) < 7 or <6.5%) [3]. Sulfonylureas (SU) are the most common second-line therapeutic drugs and can help patients achieve or maintain glycaemic control when added to metformin [4, 5] but can result in hypoglycaemia [6] and weight gain [7]. Over the last decade, dipeptidyl peptidase 4 (DPP-4) inhibitors have been introduced worldwide as an alternative to SU as second-line therapy in patients in whom metformin mono-therapy is no longer sufficient [8].

In the present study, we have evaluated the safety and efficacy of DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin) as alternatives to sulfonylurea for second-line therapy in conjunction with metformin. Diabetes micro- and macro-vascular complications (cardiovascular events; CVE) were the primary efficacy outcomes to be evaluated and HbA1c is a secondary (surrogate) outcome. Hypoglycemia was the primary adverse (safety) outcome assessed as this would be the most frequent serious adverse effect associated with oral hypoglycemic therapies [8].

Materials and Methods

Systematic search of literature

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [9]. A medical librarian developed the search strategy, in collaboration with the primary investigator (NF). Search filters for the concepts “diabetes mellitus type 2, sulfonylurea and DPP-4 inhibitors” were constructed using a combination of database terms and text words. Database terms were adapted for each electronic database searched. The OVID interface was applied to perform electronic searches in MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations (n=269) and EMBASE (n=2753) as well as PubMed (n=438) and the Cochrane Central Register of Controlled Trials (n=101) searching for randomized controlled trials (RCTs) published in any language from 1980 to June 2015 (Appendix I).

The research question and study eligibility criteria for this systematic review are based upon the following PICOS descriptions [10]:

- *Population*: all adults with type 2 diabetes mellitus requiring an OHA to be added to metformin because of inadequate glycemic control (HbA1c > 6.5%, fasting plasma glucose > 7 mmol/L or 2-hour postprandial glucose > 10 mmol/L);
- *Intervention*: any DPP-4 inhibitor (alogliptin, linagliptin, saxagliptin, sitagliptin or vildagliptin);
- *Comparator*: Sulfonylurea compounds (gliclazide, glipizide, glyburide and glimepiride) in the treatment of type 2 diabetes (as second-line adjunctive therapy);
- *Patient important outcome(s)*: Cardiovascular events (refer to any incidents that may cause damage to the heart muscle; e.g., high blood pressure, arterial stiffness, etc.), HbA1c (%) (mean change from baseline), body weight (kg), body mass index (BMI) (kg/m²) and severe hypoglycemic event rate (confirmed hypoglycaemia was defined as a finger-stick glucose value ≤2.8 mmol/dl with associated symptoms); and,
- *Study type(s)*: randomized controlled trials (RCTs) on humans, with at least 12 weeks of follow-up duration and published in any language.

Studies were excluded if they were (1) *post hoc* analyses of previous RCTs, (2) unpublished trials, abstracts or conference proceedings, (3) trials with no active comparator or (4) trials that do not measure any of the primary clinical outcomes.

Study selection, data abstraction and quality assessment

Two review authors (NF and SM) independently selected studies for inclusion from the list of 3,081 pertinent papers (after deleting duplicates). From the titles and abstracts of all studies identified by the electronic search, those that clearly did not satisfy inclusion criteria were excluded. Full copies of the remaining studies were obtained and reviewed to identify those suitable for inclusion and data abstraction. Disagreements or uncertainty were resolved by consensus and if they persisted, were arbitrated through discussion with a third review author. Two review authors (NF and SM) also independently assessed risk of bias for included RCTs using the Cochrane Collaboration's Risk of Bias tool and abstracted data using a study-specific data extraction form. Disagreements or uncertainty were resolved by consensus. The primary author (NF) entered the final data into the Cochrane Collaboration's Review Manager (RevMan®) Analysis Version 5.3 statistical software for meta-analysis. Data from RevMan 5.3 was then exported into GRADEprofiler® (GRADE Working Group) to

assess the quality of evidence per outcome and ultimately to create the summary of findings table and evidence profile. No formal assessment of publication bias could be performed as there were too few studies to generate a meaningful funnel plot per outcome.

Statistical Analysis

To compare the treatment effects between the two treatment groups (SU *vs.* DPP-4 inhibitors), a meta-analysis was planned where identified studies were sufficiently homogeneous in terms of participants, interventions and outcomes. In the case of continuous outcomes (i.e., HbA1c % and body weight), pooled results were summarized using a mean difference and a 95% confidence interval (CI). In the case of dichotomous outcomes (hypoglycemic events) pooled results were summarized using a relative risk (RR) and a 95% CI and the Mantel-Haenszel method was used to pool effect estimates. The meta-analysis was carried out using a random-effects model that awards relatively more weight to smaller studies compared to a fixed-effects meta-analysis. Regarding the assessment of heterogeneity and the *a priori* hypotheses for sub-group analysis, following the GRADE guidelines we assessed the source of heterogeneity considering patient baseline HbA1c%, intervention and differences in follow-up duration. Heterogeneity also was evaluated statistically using the I^2 and the degree of overlap of CIs for the results of individual studies. Sensitivity analysis was performed between low and high risk of bias, and with or without biased studies.

Results

Study selection. The database search results are summarized in Figure 1. Among the 34 full-text articles that were assessed for eligibility, 10 [11-20] fulfilled all the inclusion criteria and none of the exclusion criteria. The reasons for excluding 24 potential RCTs [8, 21-43] were as follows: more than one drug being added to metformin mono-therapy at one time; non-randomization; less than 12 weeks of follow-up; not a full manuscript; *post hoc* analysis of a previous trial; and, duplicate studies (Appendix II).

Study and patient characteristics. Table 1 summarizes the characteristics of the 10 RCTs: 10,139, 9,187 and 10,616 participants were included for evaluating the HbA1c% change from baseline, body weight and the hypoglycemia event rate, respectively.

Methodological quality and risk of bias. As shown in Table 2, the studies were found to be of “low risk of bias”. Incomplete outcome data (missing data) was quite high in four

FIGURE 1. PRISMA flow diagram of search results

studies [15, 16, 18, 19] and there were concerns about risk of bias in these four studies [14-16, 19]; thus, the ultimate quality of evidence per outcome according to GRADE guidelines [44-46] was reported as “moderate” (Appendix III, summary of finding tables).

Efficacy assessment

Cardiovascular events (CVE): As per efficacy primary outcome, no studies measured CVE. One RCT [17] evaluated efficacy of DPP-4 inhibitors *vs.* SUs plus metformin on related CV outcomes in which 16 subjects were tested for arterial stiffness and 34 participants were examined for systolic and diastolic blood pressure (surrogates). After three months follow-up no changes were observed from baseline regarding arterial stiffness (MD=-1.43, 95% CI -6.54- 3.68, P=0.58) and nonsignificant decreases in systolic (MD=-0.9, 95% CI -4.97- 3.17, P=0.66) and diastolic blood pressure (MD=0.54, 95% CI -2.98- 4.06, P=0.76) occurred during the study period (Appendix IV).

HbA1c% difference from baseline: As illustrated in Figure 2, the results of the meta-analysis showed a non-significant

Table1. Characteristics of studies and patients in 10 included studies

First Author, Year (ref)	Interventions	No of randomized patients	Patients Characteristics	Duration (weeks)	Outcome Measures
Arechavaleta 2011	1-sitagliptin 100 mg qd +metformin (≥ 1500 mg/day); 2-glimepiride up to 6 mg per day +metformin (≥ 1500 mg/day)	1,035	≥ 18 years of age, with type 2 diabetes and with inadequate glycaemic control (defined as HbA1c 6.5-9.0%)	30	HbA1c (post-intervention), percentages of patients with HbA1c values at goals of <7.0 and $<6.5\%$, change from baseline in FPG and fasting lipid parameters, EQ-5D
Derosa 2014	1-vildagliptin 50 mg bid + metformin (≥ 1500 mg/day); 2-glimepiride up to 6 mg per day+metformin (≥ 1500 mg/day)	167	≥ 18 years of age, of either sex with type 2 diabetes and with inadequate glycaemic control (defined as HbA1c 7.0-9.0%)	24	HbA1c (post-intervention), BMI, FPG, PPG, HOMA-IR, FPPr/FPI ratio, TC, LDL-C, HDL-C, Tg, resistin, RBP-4, visfatin and vaspilin, euglycemic hyperinsulinemic clamp to evaluate Mvalue and OFL
Ferrannini 2009	1-vildagliptin 50 mg bid + metformin (≥ 1500 mg/day); 2-glimepiride up to 6 mg per day +metformin (≥ 1500 mg/day)	2,789	≥ 18 years of age, of either sex with type 2 diabetes and with inadequate glycaemic control (defined as HbA1c 6.5–8.5%)	52	HbA1c (change score), FPG and body weight and all adverse events (including hypoglycemia)
Filozof 2010	1-vildagliptin 50 mg bid + metformin (≥ 1500 mg/day); 2-gliclazide (up to 320 mg/day)+metformin (≥ 1500 mg/day)	1,007	≥ 18 years of age, of either sex with type 2 diabetes and with inadequate glycaemic control (defined as HbA1c 7.5–11.0%)	52	HbA1c (change score), proportion of patients achieving HbA1c targets of 6.5-7.0%, changes in FPG, body weight, B-cell function and insulin resistance (fasting insulin, HOMA-IR)
Gallwitz 2012	1-linagliptin 5 mg qd + metformin (≥ 1500 mg/day); 2-glimepiride up to 4 mg per day+metformin (≥ 1500 mg/day)	1,551	≥ 18 years of age, of either sex with type 2 diabetes and with inadequate glycaemic control (defined as HbA1c 6.5–10.0%)	104	HbA1c (change score), body weight, BMI, fasting plasma glucose, adverse events (hypoglycemia)
Goke 2013	1-saxagliptin 5 mg qd + metformin (≥ 1500 mg/day); 2-glipizide up to 20 mg per day+metformin (≥ 1500 mg/day)	858	≥ 18 years of age, of either sex with type 2 diabetes and with inadequate glycaemic control (defined as HbA1c 6.5–10.0%)	104	HbA1c (change score), FPG and weight from baseline, adverse events (hypoglycemia)
Koren 2012	1-sitagliptin 100 mg qd +metformin (≥ 1500 mg/day); 2-glibenclamide 5 mg qd +metformin (≥ 1500 mg/day)	40	≥ 18 years of age, of either sex with type 2 diabetes and with inadequate glycaemic control (defined as HbA1c $>7.0\%$)	12	CVD (arterial stiffness, blood pressure), lipid profile, oxidative stress and high-sensitivity C-reactive protein (hsCRP)

Table 1. Characteristics of studies and patients in 10 included studies (cont.)

First Author, Year (ref)	Interventions	No of randomized patients	Patients Characteristics	Duration (weeks)	Outcome Measures
Matthews 2010	1-vildagliptin 50 mg bid + metformin (≥ 1500 mg/day); 2- glimepiride (up to 6 mg/day)+metformin (≥ 1500 mg/day)	3,120	≥ 18 years of age, of either sex with type 2 diabetes and with inadequate glycaemic control (defined as HbA1c 6.5–8.5%)	96	HA1c (change score), FPG, body weight, adverse events (including hypoglycemia)
Seck 2010	1-sitagliptin 100 mg qd +metformin (≥ 1500 mg/day); 2-glipizide up to 20 mg per day +metformin (≥ 1500 mg/day)	1,172	≥ 18 years of age, of either sex with type 2 diabetes and with inadequate glycaemic control (defined as HbA1c 6.5–10.0%)	96	HA1c (post-intervention), FPG, serum insulin, serum proinsulin, and plasma lipid parameters, beta cell function (HOMA-b), proinsulin/insulin ratio, HOMA-insulin resistance (HOMAIR) and the quantitative insulin sensitivity check HbA1c index (QUICKI), adverse events (including hypoglycemia)
Srivastava 2012	1-sitagliptin 50/100 mg qd up to 200mg/day +metformin; 2-glimepiride 1/2 mg qd up to 4 mg/day+metformin	50	≥ 18 years of age, of either sex with type 2 diabetes and with inadequate glycaemic control (defined as HbA1c 7.0–10.0%)	18	HbA1c (change score), FPG, 2hPPG, BMI, adverse events (including hypoglycemia)

FIGURE 2. Comparison of HbA1c% change from baseline between the metformin plus DPP-4 inhibitors and the metformin plus sulfonylurea groups. SD= standard deviation; CI= confidence interval; df= degrees of freedom.

FIGURE 3. Comparison of hypoglycemic event rate between the metformin plus DPP-4 inhibitors and the metformin plus sulfonylurea groups. SD= standard deviation; CI= confidence interval; df= degrees of freedom.

FIGURE 4. Comparison of body weight (kg) change from baseline between the metformin plus DPP-4 inhibitors and the metformin plus sulfonylurea groups. SD= standard deviation; CI= confidence interval; df= degrees of freedom.

FIGURE 5. Comparison of BMI (kg/m²) change from baseline between the metformin plus DPP-4 inhibitors and the metformin plus sulfonylurea groups. SD= standard deviation; CI= confidence interval; df= degrees of freedom.

difference between the test and the control groups (MD=0.06, 95% CI -0.00- 0.13, $P=0.07$) from the 10 studies evaluating HbA_{1c}% (difference from baseline) in 10,139 subjects. Following a sensitivity analysis that was performed to test the robustness of the results comparing high risk of bias (for missing data >20%) studies [15, 16, 18, 19] to low risk, the results changed to a significant difference in favor of SUs and heterogeneity (I^2) decreased from 73% to less than 50%. No

change was observed in the results following a sensitivity analysis of assessing studies with low *vs.* high risk of bias.

Safety assessment: Figure 3 shows the results of the meta-analysis of eight RCTs [11, 13, 15-20] involving 10,616 diabetic patients, with at least one hypoglycemic event during the follow-up period. Patients on metformin plus DPP-4inhibitors were found to experience significantly fewer hypoglycemic events compared to the metformin plus SU

group (RR= 0.15; 95% CI, 0.11-0.22; $P<0.00001$). There was substantial heterogeneity ($I^2=77\%$), but by removing two outliers [11, 20] and one high risk of bias study [15] the heterogeneity (I^2) equaled zero for the remaining five studies [13, 16-19]. The result from these five studies was similar to the eight study analysis for hypoglycemic event rates (RR= 0.12; 95% CI, 0.1-0.15; $P<0.00001$).

Body Weight: Figures 4 and 5 show the impact of the two drugs on weight and BMI. DPP-4 inhibitors produced a reduction in weight while SUs produced an increase in weight. The net difference was a decrease of 2.2 kg (95% CI 1.7 - 2.7) with DPP-4 inhibitors. Change in BMI from baseline was not different between the two drugs.

Discussion

There is broad consensus that metformin should be the first-line pharmacologic therapy for patients with type 2 diabetes mellitus in whom lifestyle modification is insufficient to control hyperglycemia; however, there is still no consensus as to which drug should be added to metformin when a second therapy is necessary. SUs are a common conventional second-line therapy that stimulate insulin secretion in type 2 diabetes mellitus and reduce hyperglycemia but are associated with an increased risk of hypoglycemia. A newer drug class, the DPP-4 inhibitors, selectively inhibit the DPP-4 enzyme that degrades two major incretin hormones: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide [47]. They are reported to have glucose-lowering efficacy, but without the risk of hypoglycemia, when added to the treatment regimen of patients in whom metformin mono-therapy is no longer sufficient. There is also a theory that DPP-4 inhibitors could be superior to SUs with regard to the risk of cardiovascular complications [17]. To assess these potential benefits, we performed a systematic review and a meta-analysis comparing the safety and efficacy of DPP-4 inhibitors versus SUs as second-line (adjunctive) therapy when added to metformin mono-therapy for insufficiently controlled type 2 diabetic patients [8, 48].

The results of the meta-analysis indicate that the addition of DPP-4 inhibitors to metformin mono-therapy achieves glycemic benefits similar to SUs. The reduction in HbA1c% from baseline with the addition of DPP-4 inhibitors to metformin was not significantly different than that seen with the addition of SUs to metformin mono-therapy. There were no data available to assess CVE outcomes. For other CV outcomes (arterial stiffness and blood pressure) there was no difference between the two therapies. With respect to adverse

effects, metformin plus DPP-4 inhibitors was found to have a significantly lower risk of hypoglycemia compared to metformin plus SU.

The present study appears to be the first systematic review meta-analysis that compares the efficacy and safety of DPP-4 inhibitors as a group (i.e., all DPP-4 inhibitors) *vs.* SUs, when added to metformin mono-therapy in the treatment of patients with type 2 diabetes mellitus experiencing inadequate glycemic control. We limited the inclusion criteria to only published double-blind RCTs to obtain the highest quality evidence for addressing this clinical issue in diabetes management.

The most important limitation of this review was the high rate of missing data (>20%) in the RCTs with long-term follow-up duration (>2 years), which resulted in a considerable amount of heterogeneity in the meta-analysis results. Moreover, a range of 12-104 weeks in follow-up duration was observed for the 10 studies included in this review; which could explain the high degree of heterogeneity in the final results. Finally, there remains a need for additional long-term RCTs evaluating efficacy assessment for CVEs.

Conclusions

This systematic review shows that there is no significant difference between the efficacy of DPP-4 inhibitors and SU when used in combination with metformin mono-therapy. In contrast, the analysis showed a significant decrease in the risk of hypoglycemic events and body weight in patients using DPP-4 inhibitors. Future research should include an economic and financial analysis of DPP-4 inhibitors compared with SUs, as the medication added to metformin mono-therapy in type 2 diabetic patients with inadequate glycemic control. This would inform policy makers and clinicians by providing a comprehensive overview of the efficacy, safety and economic-financial impact of each treatment.

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46. Guyatt, G.H., et al., GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. *J Clin Epidemiol*. 66(2): p. 173-83.
47. Godinho, R., et al., The Place of Dipeptidyl Peptidase-4 Inhibitors in Type 2 Diabetes Therapeutics: A "Me Too" or "the Special One" Antidiabetic Class? *J Diabetes Res*, 2015. 2015: p. 806979.
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Appendix I: Search Strategy

THIS SEARCH STRATEGY DOES NOT INCLUDE THE RCT LIMIT.

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1980 to Present>

Search Strategy

#	Searches	Results
1	exp Sulfonylurea Compounds/	16264
2	sulfonylurea.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	7943
3	(Acetohexamida or Acetohexamide or Acetohexamidum or BRN 2225115 or CCRIS 4 or Dimelin or Dimelor or Dymelor or EINECS 213-530-4 or Gamadiabet or HSDB 3280 or Hypoglicil or Metaglutina or Minoral or NCI-C03247 or Ordimel or Tsiklamid or U 14812 or UNII-QGC8W08I6I).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	279
4	(Alentin or Aminophenurobutane or BRN 2218915 or Bucarban or Bucrol or Bukarban or Burcol or Butisulfina or BZ 55 or Ca 1022 or Carbutamid or Carbutamida or Carbutamide or Carbutamidum or Diabetin or Diabetoplex or Diaboral or Diabutan or EINECS 206-424-4 or Emedan or Glucidoral or Glucofren or Glybutamide or HSDB 5488 or Inbuton or Invenol or Nadisan or Nadizan or Norboral or NSC 242409 or Oranil or U 6987 or UNII-E3K8P4869P).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	600
5	(Adiabene or Asucrol or Bioglumin or BRN 2218363 or Catanil or CCRIS 155 or Chlorodiabina or Chloronase or Chloropropamide or Chloropropamid or Chloropropamidum or Clorpropamid or Clorpropamida or Clorpropamide or Diabaril or Diabechlor or Diabenal or Diabeneze or Diabeneza or Diabetoral or Diabexan or Diabinese or Diamel Ex or Dynalasen or EINECS 202-314-5 or Glisemam or Glucamide or HSDB 2051 or Insogen or Insulase or Meldian or Melitase or Mellinese or Millinese or NCI-C01752 or NSC 44634 or NSC 626720 or Oradian or P 607 or Prodiaben or Stabinol or U-3818 or UNII-WTM2C3IL2X).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	189
6	(BRN 1657836 or Diamicon or EINECS 244-260-5 or Gliclazida or Gliclazide or Gliclazidum or Glimicon or Nordalex or S 1702 or S 852 or SE 1702 or UNII-G4PX8C4HKV).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1133
7	(Adiab or Apo-Glibenclamide or Azuglucon or Bastiverit or Benclamin or Betanase or Betanese 5 or BRN 2230085 or Calabren or Cytagon or Daonil or Debtan or Diabeta or Dibelet or Duraglucon or EINECS 233-570-6 or Euclamin or Euglucon or Euglucon 5 or Euglykon or GBN 5 or Gen-Glybe or Gewaglucon or Gilemal or Glamide or Gliben or Glibenbeta or Glibenclamid or Heumann or Glibenclamida or Glibenclamide or Glibenclamidum or Glibenil or Glibens or Glibesyn or Glibet or Glibetic or Glibil or Gliboral or Glicem or Glidiabet or Glimel or Glimide or Glisulin or Glitisol or Glubate or Gluben or Glucobene or Glucohexal or Glucolon or Glucomid or Glucoremed or Glucoven or Glyben or Glybenclamide or Glybenzcyclamide or Glyburide or Glycomin or Glynase or HB 419 or Hemi-Daonil or Hexaglucon or Humedia or Lederlib or Libanil or Lisaglucon or Maninil or Med-Glionil or Melix or Micronase or Miglucon or Nadib or Neogluconin or Norglicem 5 or Normoglucon or Novo-Glyburide or Orabetic or Pira or Praeciglucon or Prodiabet or Renabetic or Semi-daonil or Semi-Euglucon or Semi-Gliben-Puren N or Sugril or Suraben or Tiaabet or U 26452 or UNII-SX6K58TVWC UR 606 or Yuglucon).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	10548
8	(AI3-50826 or BRN 1323565 or CCRIS 591 or Diabewas or EINECS 214-588-3 or HSDB 3192 NCI-C03327 or Norglycin or NSC 70762 or Tolanase or Tolazamida or Tolazamide or Tolazamidum or Tolinase or U 17835 or UNII-9LT1BRO48Q).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	210

Appendix I: Search Strategy cont.

#	Searches	Results
9	(Aglicid or Arcosal or Arkozal or Artosin or Artozin or Beglucin or BRN 1984428 or Butamid or Butamide or Butamidum or CCRIS 592 D 860 or Diaben or Diabesan or Diabetamid or Diabetol or Diabuton or Diasulfon or Dirastan or Dolipol or Drabet or EINECS 200-594-3 or Toluva or Tollylsulfonylbutylurea or U 2043 or UNII-982XCM1FOI or Willbutamide or Glyconon or HLS 831 or HSDB 3393 or Ipoglicone or Mobenol or NCI-C01763 or NSC 23813 or Orabet or Oralin or Orezan or Orinase or Orinaz or Oterben or Pramidex or Rastinon or SK-Tolbutamide or Tarasina or Tolbet or Tolbusal or Tolbutamid or Tolbutamida or Tolbutamide or Tolbutamidum or Tolbutone or Toluina or Tolumi).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	6318
10	(Aldiab or Apamid or "BRN 0903495" or CP 28720 or Digrin or Dipazide or EINECS 249-427-6 or Glibenese Glibetin or Glican or Glide or Glidiab or Glipid or Glipizida or Glipizide or Glipizidum or Gluco-Rite or Glucolip or Glucotrol or Glucozide or Glupitel or Glupizide or Glyde or Glydiazinamide or K 4024 or Melizide or Mindiab or Minidab or Minidiab or Minodiab or Napizide or Ozidia or Sucrazide or TK 1320 or UNII-X7WDT95N5C).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	2400
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	25927
12	(NIDDM or Maturity-Onset Diabetes or Diabetes Mellitus or Noninsulin-Dependent or Diabetes Mellitus, Adult-Onset or Adult-Onset Diabetes Mellitus or Diabetes Mellitus, Ketosis-Resistant or Ketosis-Resistant Diabetes Mellitus or Diabetes Mellitus, Maturity-Onset or Diabetes Mellitus, Non Insulin Dependent or Diabetes Mellitus, Slow-Onset or Diabetes Mellitus, Stable or Diabetes Mellitus, Type II or Maturity-Onset Diabetes Mellitus or MODY or Type 2 Diabetes Mellitus or Noninsulin-Dependent Diabetes Mellitus).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	308739
13	(Dipeptidyl Peptidase IV Inhibitors or Inhibitors, Dipeptidyl-Peptidase IV or Gliptins or Dipeptidyl-Peptidase 4 Inhibitors or Dipeptidyl Peptidase 4 Inhibitors).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	2127
14	Saxagliptin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	318
15	(HSDB 7516 or Januvia or Sitagliptin or Tesavel or UNII-QFP0P1DV7Z or Xelevia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1140
16	(Anagliptin or UNII-K726J96838).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	12
17	(Galvus or Jalra or LAF 237 or UNII-I6B4B2U96P or Vidagliptin or Xiliarx).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	19
18	(BI 1356 or BS 1356 BS or Linagliptin or ONDERO or Tradjenta or UNII-3X29ZEJ4R2).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	280
19	Kombiglyze.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1
20	Janumet.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	10
21	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	2822
22	(CCRIS 9321 or Diabetosan or Diabex or Dimethyl or biguanide or Dimethyldiguanide or DMGG or EINECS 211-517-8 or Fluamine or Flumamine or Glifage or Gliguanid or Haurymelin or Islotin or LA-6023 or Melbin or Metformin or Metformina or Metformine or Metforminum or Metiguanide or NNDG or Siofor or UNII-9100L32L2N).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	78300
23	11 and 12 and 21 and 22	239

Appendix II. Characteristics of excluded studies

Study, year [ref]	Reason for exclusion
Saab 2015 [39]	Non-RCT
Hou 2015 [28]	Review
Genuth 2015 [8]	Review
Matsui 2015 [34]	Not related to the research question
Jax [29]	Unpublished phase 1 trial
Tolentino-Wilson [43]	Not measuring primary outcome
Sicras-Mainar [42]	Non-RCT
Otsuki [38]	Different patient population (dialysis)
Moses [36]	Metformin +SU as comparator
Morgan [35]	Non-RCT
Lukashevich [33]	Metformin +SU as comparator
Asai [22]	Not measuring primary outcome and not meeting inclusion criteria
Amate [21]	Systematic review
Kim [30]	Non-RCT
Galwitz [26]	<i>Post-hoc</i> analysis
Berndt-zipfel [24]	Same paper; different journals
Babu [23]	Conference proceedings
Seck [40]	Conference proceedings
Seck [41]	<i>Post-hoc</i> analysis
Nauck [37]	Same study as Seck 2010 (shorter follow-up)
Lee [32]	Non-randomized
Goke [27]	Same study as Goke 2013 with shorter follow up
Berndt-Zipfel [25]	Non-RCT
Kim [31]	<12 weeks follow- up duration

Appendix III: Evidence profile and Summary of findings tables for efficacy and safety outcomes.

Date: 2015-09-22

Question: Efficacy assessment of DPP-4 inhibitors vs. SUs for Diabetes Mellitus Type2

Settings: Systematic Review, meta-analysis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Efficacy Assessment	Control	Relative (95% CI)	Absolute		
HbA1c% difference from baseline (Better indicated by lower values)												
10	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	5104	5035	-	MD 0.06 higher (0 to 0.13 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Body weight kg (Better indicated by lower values)												
7	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	4632	4555	-	MD 2.2 lower (2.68 to 1.71 lower)	⊕⊕⊕O MODERATE	IMPORTANT

¹ Four studies had "incomplete outcome data" greater than 20%

Authour(s): Foroutan, N

Date: 2015-09-22

Question: Safety assessment of DPP-4 inhibitors vs. SUs for Diabetes Mellitus Type2

Settings: Systematic Review/ meta-analysis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe Adverse Events	Control	Relative (95% CI)	Absolute		
Hypoglycemia												
8	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	200/5315 (3.8%)	1279/5301 (24.1%)	RR 0.15 (0.11 to 0.22)	205 fewer per 1000 (from 188 fewer to 215 fewer)	⊕⊕⊕○ MODERATE	IMPORTANT
								28%		238 fewer per 1000 (from 218 fewer to 249 fewer)		

¹ Four studies had "incomplete outcomes data" greater than 20%

Efficacy Assessment for Diabetes Mellitus Type2

Patient or population: patients with Diabetes Mellitus Type2

Settings: Systematic Review, meta-analysis

Intervention: Efficacy Assessment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Efficacy Assessment				
HbA1c% difference from baseline		The mean hba1c% difference from baseline in the intervention groups was 0.06 higher (0 to 0.13 higher)		10139 (10 studies)	⊕⊕⊕⊖ moderate ¹	
Body weight (kg)		The mean body weight in the intervention groups was 2.2 lower (2.68 to 1.71 lower)		9187 (7 studies)	⊕⊕⊕⊖ moderate ¹	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Severe Adverse Events for Diabetes Mellitus Type2

Patient or population: patients with Diabetes Mellitus Type2

Settings: Systematic Review, meta-analysis

Intervention: Severe Adverse Events

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Efficacy Assessment				
Hypoglycemia	Study population		RR 0.15 (0.11 to 0.22)	10616 (8 studies)	⊕⊕⊕⊖ moderate ¹	
	241 per 1000	36 per 1000 (27 to 53)				
	Moderate					
	280 per 1000	42 per 1000 (31 to 62)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Four studies had "incomplete outcomes data" greater than 20%

Appendix IV: CVD meta-analyses results-Forest plots

Comparison of Arterial stiffness (Augmentation index, mm Hg) change from baseline between the metformin plus DPP-4 inhibitors and the metformin plus sulfonylurea groups. SD= standard deviation; CI= confidence interval; df= degrees of freedom.

Comparison of systolic blood pressure (mm Hg) change from baseline between the metformin plus DPP-4 inhibitors and the metformin plus sulfonylurea groups. SD= standard deviation; CI= confidence interval; df= degrees of freedom.

Comparison of diastolic blood pressure (mm Hg) change from baseline between the metformin plus DPP-4 inhibitors and the metformin plus sulfonylurea groups. SD= standard deviation; CI= confidence interval; df= degrees of freedom.