Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

A safety and tolerability profile comparison between dipeptidyl peptidase-4 inhibitors and sulfonylureas in diabetic patients: A systematic review and meta-analysis

Daniela Farah [a], *Graziella Malzoni Leme* [b], *Freddy Goldberg Eliaschewitz* [c], *Marcelo Cunio Machado Fonseca* [a,d,*]

[a] *Women's Health Technology Assessment Center, Federal University of Sao Paulo (Universidade Federal de São Paulo), Sao Paulo, Brazil*
[b] *Takeda Pharmaceuticals, Sao Paulo, Brazil*
[c] *CPCLIN - Centro de Pesquisas Clínicas, Sao Paulo, Brazil*
[d] *AxiaBio Life Sciences, Sao Paulo, Brazil*

ARTICLE INFO

Article history:
Received 4 October 2018
Received in revised form
14 December 2018
Accepted 21 January 2019
Available online 30 January 2019

Keywords:
Dipeptidyl peptidase-4 inhibitors
Sulfonylurea
Diabetes mellitus type 2
Safety
Adverse events

ABSTRACT

Background: The first treatment approach for type 2 diabetes mellitus is lifestyle change and metformin, but it is usually not sufficient. For some time, the anti-hyperglycemic classes of sulfonylureas and dipeptidyl peptidase-4 (DPP-4) inhibitors were considered second-line of treatment, since they show similar efficacy effect. However, the recent ADA-EASD consensus gives the preference to DPP-4 inhibitors compared to sulfonylureas, except if cost is a major problem. We performed a meta-analysis for safety and tolerability profile to comprehend which treatment has less adverse events.

Methods: PUBMED and EMBASE databases were searched from inception until July 2017 to retrieve RCT studies comparing DPP-4 inhibitors and sulfonylureas treatments in adult type 2 diabetes patients. There was no language restriction. We extracted and combined data from studies comparison that reported safety profile and weight change. A random effect, meta-analytic model was applied to all calculations. Cochrane collaboration tool was used to assess quality and bias of the included studies. Trial registered with PROSPERO (CRD42017075823).

Findings: Out of 1472 articles identified in our search and screened for eligibility, 36 studies comparing DPP-4 inhibitors and sulfonylureas were identified. DPP-4 inhibitors in combination with metformin had less overall adverse events (RR: 0·90; 95% CI, 0·86–0·94; $p < 0·0001$; $I^2 = 83\%$; 17 studies), cardiovascular events (RR: 0·54; 95% CI, 0·37–0·79; $p = 0·002$; $I^2 = 0\%$; 6 studies), hypoglycemia (RR: 0·17; 95% CI, 0·13–0·22; $p < 0·00001$; $I^2 = 76\%$; 17 studies) and severe hypoglycemic events (RR: 0·10; 95% CI, 0·05–0·19; $p < 0·00001$; $I^2 = 0\%$; 12 studies). The mean difference of the weight change was 1·92 kg in favor of DPP-4 inhibitors in combination with metformin in relation to sulfonylureas in combination with metformin. Monotherapy with DPP-4 inhibitors also had less rates of hypoglycemia (RR: 0·31; 95% CI, 0·24–0·41; $p < 0·00001$; $I^2 = 0\%$; 8 studies) and severe hypoglycemic events (RR: 0·26; 95%

* Corresponding author at: Department of Gynecology, Federal University of Sao Paulo, Rua Napoleao de Barros, 632, Sao Paulo 04024-002, Brazil.
E-mail addresses: graziella.leme@takeda.com (G.M. Leme), freddy.g@uol.com.br (F.G. Eliaschewitz), mcmf64@globo.com (M.C.M. Fonseca).
https://doi.org/10.1016/j.diabres.2019.01.025

CI, 0·10–0·66; p = 0·004; I^2 = 0%; 8 studies) and patients did not gain 1·19 kg.
Interpretation: These results suggest better safety profile for DPP-4 inhibitors than sulfonylureas for both comparisons, and it is more notable when the treatment regimen includes metformin.
Funding: This study was funded by Takeda Pharmaceuticals, Brazil.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic and progressive disease characterized by insulin resistance and relative insulin deficiency [1]. The diagnosis can occur at any age but it is often made with onset of symptoms or during a routine check-up. Treatment goals are to thwart microvascular and macrovascular complications as well as metabolic dysfunctions and diminish symptoms. Near normal levels of glucose are an ideal aim.

Since its introduction in the 1950s, metformin has become the first-line pharmacotherapy, along with lifestyle changes for most DM patients [2]. The American College of Physicians, American Association of Clinical Endocrinologists, and American College of Endocrinology recommend that, when glycemic control is not achieved with metformin and lifestyle intervention, a second drug should be added to the treatment [3,4]. Among these second-line drugs are sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, glucagon-like peptide-1 receptor agonist, and sodium-glucose cotransporter 2 inhibitors [5–9]. The DPP-4 inhibitors are relatively new when compared to sulfonylureas, and have become widely used due to their low risk to hypoglycemia and neutral effect on body weight [2,10]. Also, the timing of the glucose-lowering effect is different between them, with a more rapid and potent initial action, but less sustained glucose-lowering efficacy of sulfonylureas compared to DPP-4 inhibitors [11,12].

Considering the broad use of these two classes of drugs and that generally they are considered equally efficient at aiding glycemic control, we performed a systematic review followed by meta-analysis focusing on safety and tolerability parameters comparing DPP-4 inhibitors and sulfonylureas monotherapy or dual therapy with metformin [7,13,14].

2. Methods

We conducted the systematic review and meta-analysis in accordance with recommendations from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol was registered with PROSPERO (CRD42017075823)[15].

2.1. Search strategy

We performed a computerized search of The United States National Library of Medicine and National Institutes of Health (PUBMED) and Excerpta Medica dataBASE (EMBASE) for relevant papers from inception until July 2017. The following keywords were used in the search strategy: “Sulfonylurea”, “Dipeptidyl peptidase-4 inhibitors”, “adverse events”, and “safety” (see Appendix 1 for search strategy details).

2.2. Study selection

Both reviewers independently (DF and MCMF) screened title and abstracts and sequentially reviewed full-text articles of the selected eligible studies. Disagreements were resolved by joint review and consensus.

Included studies met the following criteria: (1) comparing sulfonylureas *versus* DPP-4 inhibitors; (2) adult patients with T2DM; (3) reported adverse events; (4) randomized controlled trial (RCT). Only studies published as full articles were included. There was no language restriction. Duplicate publications, abstracts, case reports, letters to the editor, surveys, and review articles were excluded, although a manual search for the references was performed in the last type of studies.

Study quality and bias were evaluated using the Cochrane collaboration tool [16].

2.3. Outcomes of interest

The meta-analytic outcomes of interest were overall adverse events, dizziness, headache, fatigue or asthenia, cardiovascular events, pancreatitis, nausea, abnormal hepatic function, diarrhea, infections, cough, nasopharyngitis, hypoglycemia, severe hypoglycemia, weight change, and mortality. All the above-mentioned adverse events were characterized as number of patients that reported such adverse event during the study. Weight change was computerized as the difference between the beginning of treatment and the end of the study.

2.4. Data extraction, synthesis, and statistical analysis

Two reviewers (DF and MCMF) using a standardized form independently of extracted data. Discrepancies were resolved through consensus. To combine results across studies, we applied a random-effects meta-analytic model using the inverse variance in all calculations. We used the Review Manager statistical software (Review Manager version 5·3) from the Cochrane Collaboration to combine results across studies. The dichotomic results are expressed as risk ratio (RR) and weight change is expressed as mean difference, both, with 95% confidence intervals (CIs). Heterogeneity was evaluated using Q test (χ^2 test) and I^2 test. To detect potential publication bias, we used funnel plots [12].

Analysis was performed in two parts: the studied drugs in monotherapy, and in combination with metformin.

2.5. *Role of funding source*

The study funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had all the responsibility for the decision to submit to publication.

3. Results

A total of 1472 potentially eligible studies were identified, of which 1115 were excluded after reviewing titles and abstracts, leaving 152 studies for a full-text evaluation. In total, 36 studies were included in the meta-analysis. Among these 36 studies, 13 studies compared DPP-4 inhibitors and sulfonylureas in monotherapy, and 23 studies were in combination with metformin (Fig. 1).

The studies included in the analyses without metformin present high risk when blinding participants and personnel and, we also had unclear risk of bias in blinding of outcome assessment, according to Cochrane Collaboration tool. For the analyses with metformin, we had high risk of bias in other potential threats to validity and unclear risk of bias in blinding of outcome assessment (Appendix 2).

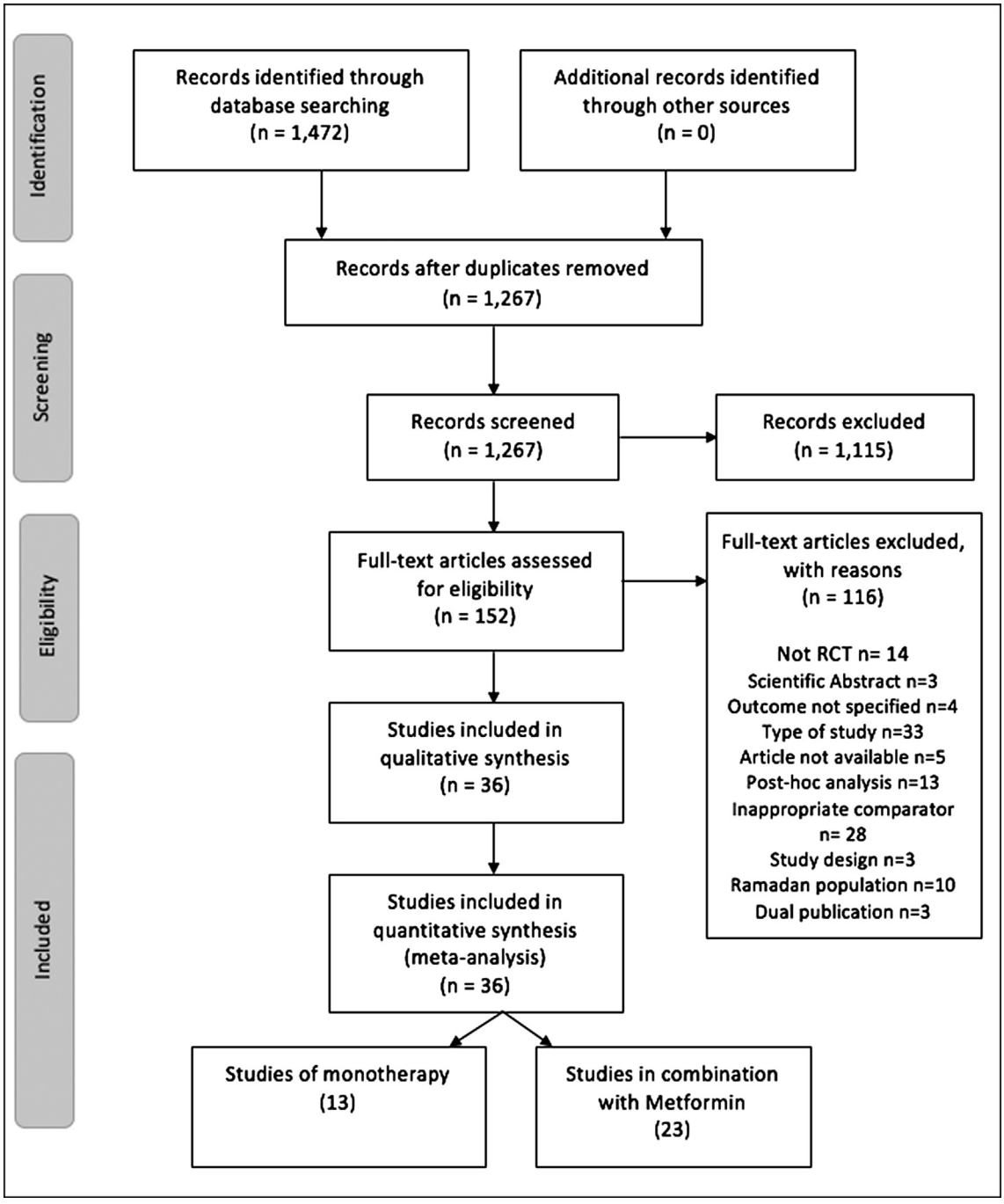


Fig. 1 – Flowchart of literature search results.

Table 1 – Characteristics of the included studies in monotherapy.

Study	ClinTrial.gov Reference	Drug and Dose dipeptidyl peptidase-4 inhibitor	Drug and Dose Sulfonylurea	n (Male/Female)	Age (years)	Outcome measure	Follow-up time	Population
Vianna et al. [17] Brazil	NCT01679899	Vildagliptin 50 mg orally twice daily	Gliclazide MR 120 mg orally once daily	0/56	>40	Mortality CV events	12 months	Post-menopause women
Terauchi et al. [18] START-J trial Japan	NCT01183104	Sitagliptin 50 mg orally once daily	Glimepiride 0.5 mg orally once daily	153/119	>60	Overall AE Nasopharyngitis Mortality Abnormal hepatic function Infections Diarrhea Weight change Hypoglycemia	104 weeks	Japanese
Dei Cas et al. [19] Italy	NCT01822548	Vildagliptin 100 mg orally twice daily	Glibenclamide 2.5 mg to a maximal dose of 5 mg twice daily	43/21	≥35	Hypoglycemia Severe hypoglycemia	12 months	–
Park et al. [20] STABLE study group South Korea	NCT01890629	Gemigliptin 50 mg orally or Sitagliptin 100 mg orally	Glimepiride 2 mg orally	48/18	20–70	Overall AE Hypoglycemia	12 weeks	–
Tahara et al. [21] Japan	NCT02528019	Anagliptin 100 to 200 mg orally twice a day	Glimepiride 0.5 to 4 mg orally once daily	33/17	30–90	Weight change	6 months	–
Kondo et al. [22] Japan	NR	Sitagliptin 25 to 100 mg orally once daily	Glimepiride 0.25 to 1.0 mg orally once daily	98/35	<80	Hypoglycemia Severe hypoglycemia Abnormal hepatic function	52 weeks	Japanese
Hartley et al. [5] Switzerland	NCT01189890	Sitagliptin 100 mg orally once daily or 50 mg orally once daily	Glimepiride 1 mg orally, up-titrate as needed up to maximum dose of 6 mg once daily	170/218	≥65 and <85	Overall AE Pancreatitis Weight change Hypoglycemia Severe hypoglycemia Mortality	30 weeks	Elderly patients
Tamez-Perez et al. [7] SUMER trial Mexico	NR	Sitagliptin 100 mg orally once daily	Glimepiride 2 mg orally, up-titrate to maximum dose of 6 mg once daily	Not reported	18–70	Overall AE Hypoglycemia Severe hypoglycemia Mortality	24 weeks	–
Shimoda et al. [23] Japan	NR	Sitagliptin 50 mg orally once daily	Glimepiride 0.5 to 2 mg orally once daily	31/19	≥20	Hypoglycemia Severe hypoglycemia	16 weeks	Japanese

Table 1 – (*Continued*)

Study	ClinTrial.gov Reference	Drug and Dose dipeptidyl peptidase-4 inhibitor	Drug and Dose Sulfonylurea	n (Male/Female)	Age (years)	Outcome measure	Follow-up time	Population
Rosenstock et al. [24] USA	NCT 00707993	Alogliptin 25 mg orally once daily	Glipizide 5 mg titrated to 10 mg orally once daily	198/243	65–90	Overall AE Pancreatitis Weight change Hypoglycemia Severe hypoglycemia Headache Dizziness Mortality CV events	12 months	Elderly patients
Arjona Ferreira et al. [25] USA	NCT00509236	Sitagliptin 25 mg orally once daily	Glipizide 2.5 mg orally daily and titrated up to a potential maximum dose of 10 mg twice daily	77/52	>30	Overall AE Cough Weight change Hypoglycemia Severe hypoglycemia Headache Infections Diarrhea Mortality CV events	54 weeks	Patients at end stage renal disease
Arjona Ferreira et al. [26] France	NCT00509262	Sitagliptin 25 mg or 50 mg orally once daily	Glipizide 2.5 mg orally daily and titrated up to a potential maximum dose of 10 mg twice daily	158/119	≥ 30	Overall AE Weight change Hypoglycemia Severe hypoglycemia Dizziness Infections Diarrhea Mortality CV events	54 weeks	Patients with renal insufficient
Foley et al. [27] USA	NCT00102388	Vildagliptin 50 mg orally twice daily	Gliclazide up to 320 mg orally once daily	609/483	≥ 18	Fatigue/asthenia Nasopharyngitis Weight change Hypoglycemia Headache Diarrhea	2 years	–

NR = Not registered.

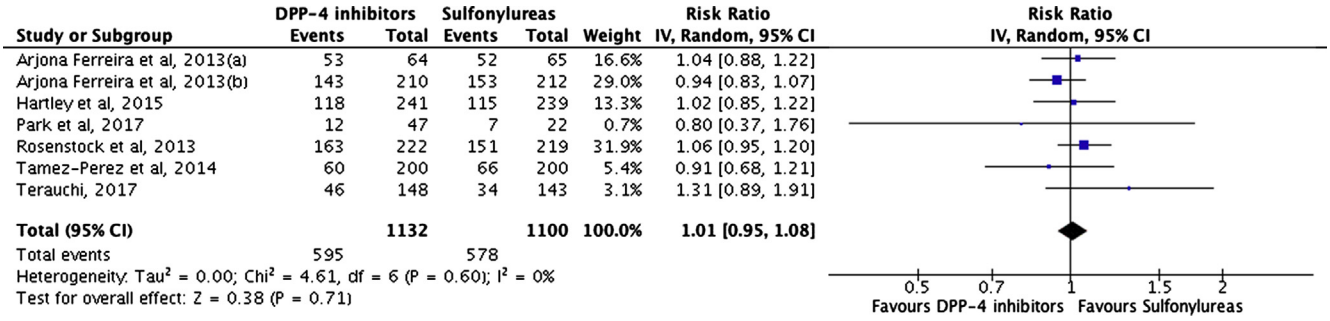


Fig. 2 – Forest plot of comparison between DPP-4 inhibitors *versus* sulfonylureas for overall adverse events.

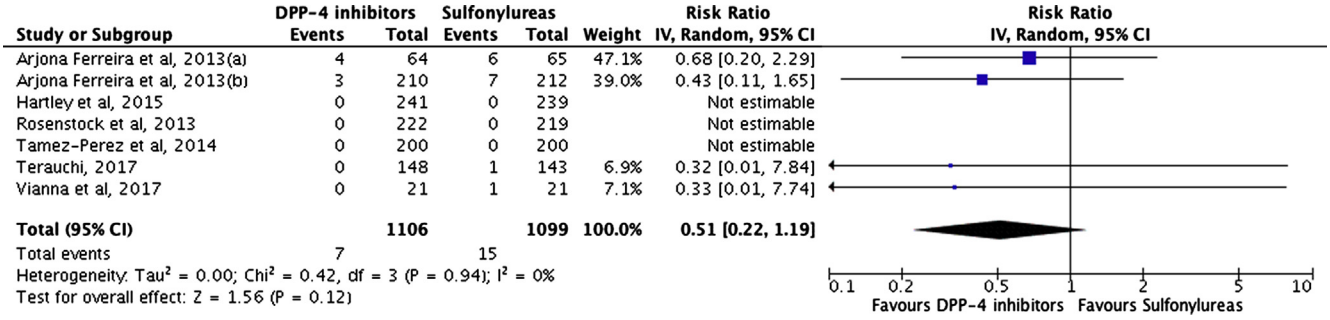


Fig. 3 – Forest plot of comparison between DPP-4 inhibitors *versus* sulfonylureas for mortality.

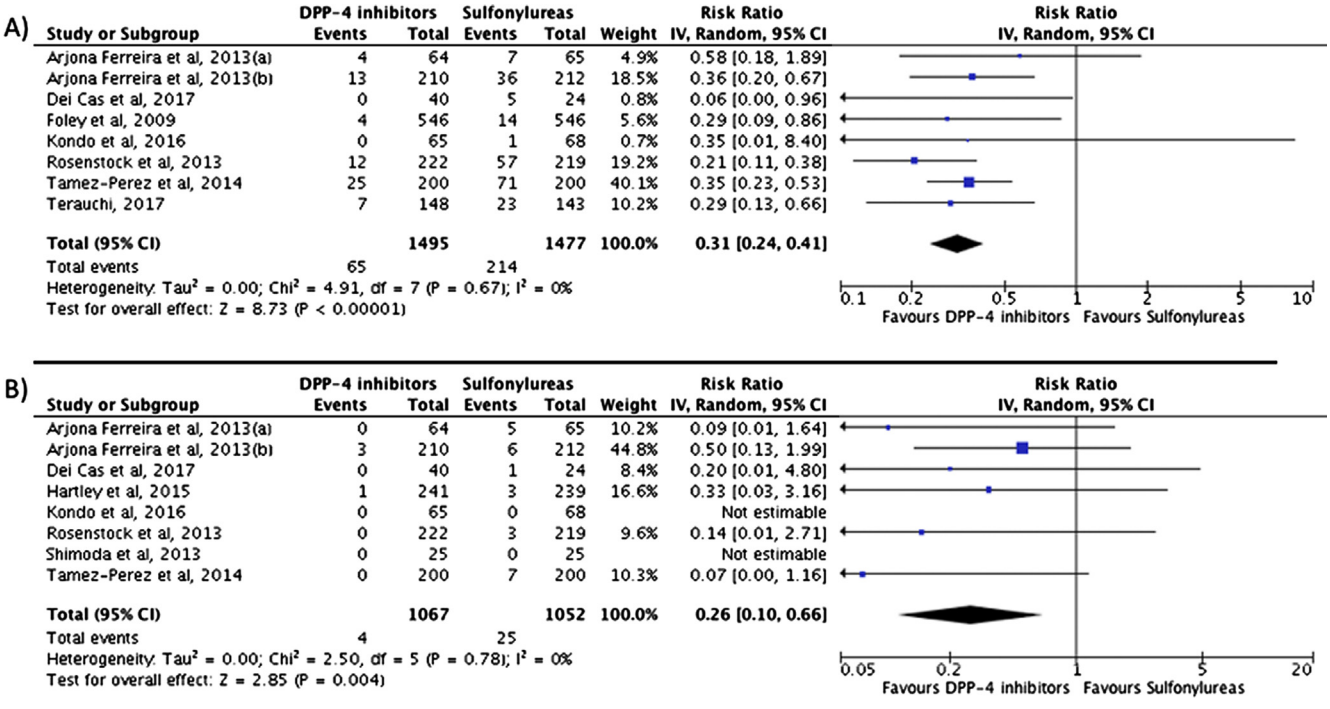


Fig. 4 – Forest plot of comparison between DPP-4 inhibitors *versus* sulfonylureas for hypoglycemia and severe hypoglycemia.

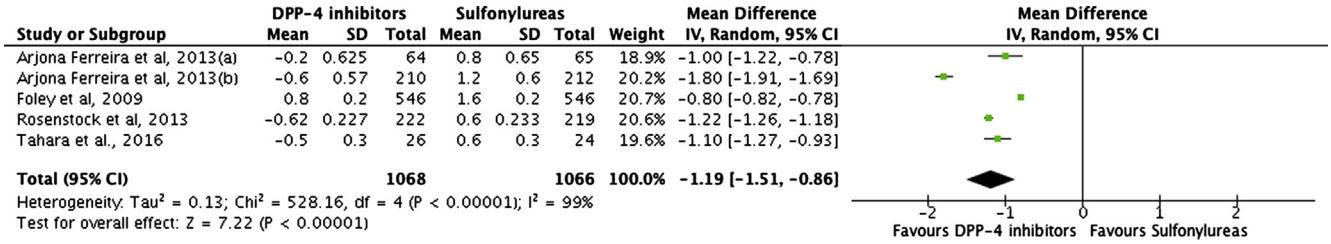


Fig. 5 – Forest plot of comparison between DPP-4 inhibitors *versus* sulfonylureas for weight change.

Based on visual inspection of funnel plot, there was no evidence of publication bias in the comparison with metformin (Appendix 3).

3.1. *Comparison between DPP-4 inhibitors and sulfonylureas in monotherapy*

There were 13 studies included with a total of 3621 adult patients, 1832 patients in the DPP-4 inhibitors group and 1789 patients in the sulfonylureas group [5,7,17–27]. The characteristics of the included studies are described in Table 1.

There was no significant difference between groups for overall adverse events and mortality (Figs. 2 and 3). There were also no significant difference for dizziness (RR: 0·49; 95% CI, 0·21–1·14; p = 0·10; I^2 = 8%), headache (RR: 1·14; 95% CI, 0·74–1·74; p = 0·55; I^2 = 3%), abnormal hepatic function (RR: 1·38; 95% CI, 0·30–6·35; p = 0·68; I^2 = 4%), diarrhea (RR: 0·99; 95% CI, 0·66–1·47; p = 0·94; I^2 = 0%), infections (RR: 1·24; 95% CI, 0·56–2·72; p = 0·59; I^2 = 75%) and nasopharyngitis (RR: 1·15; 95% CI, 0·77–1·71; p = 0·50; I^2 = 0%) between treatments (Appendix 4).

The publication by Arjona Ferreira et al. (2013_b) was the only one to describe cardiovascular events [25]. They reported no significant difference between treatments, and the incidence of cardiovascular events was 4% and 5% for DPP-4 inhibitors and sulfonylureas group, respectively [25]. Cough was described by Arjona Ferreira et al. (2013_a), and was reported in more than five percent of the patients, however without significant difference between treatments [26]. Fatigue or asthenia was reported only by Foley and colleagues (2009) and the incidence of fatigue/asthenia in sulfonylureas group was twice of that reported in DPP-4 inhibitors [27]. Pancreatitis and nausea were not reported in any study with monotherapy.

Patients treated with DPP-4 inhibitors experienced less hypoglycemia and less severe hypoglycemic events when compared to patients treated with sulfonylureas (Fig. 4).

The mean difference of the weight change during the treatment with DPP-4 inhibitors or sulfonylureas was 1·19 kg in favor of DPP-4 inhibitors (Fig. 5).

3.2. *Comparison between DPP-4 inhibitors and sulfonylureas in combination with metformin*

A total of 19,356 adult patients, 10,146 patients on DPP-4 inhibitors in combination with metformin group and 9210 patients on sulfonylureas in combination with metformin group were included from 23 RCT [10,13,14,28–47]. The characteristics of the included studies are described in Table 2.

The risks of overall adverse events and cardiovascular events in patients treated with DPP-4 inhibitors in combination with metformin were statistically lower when compared to those treated with sulfonylureas in combination with metformin (Figs. 6 and 7). On the other hand, less patients had infections when treated with sulfonylureas in combination with metformin when compared to DPP-4 inhibitors in combination with metformin [p = 0.04] (Fig. 8).

There was no significant difference between groups for mortality (RR: 0·83; 95% CI, 0·49–1·41; p = 0·49; I^2 = 0%), headache (RR: 0·80; 95% CI, 0·57–1.13; p = 0·20; I^2 = 77%), fatigue or asthenia (RR: 0·78; 95% CI, 0·52–1·17; p = 0·23; I^2 = 84%), pancreatitis (RR: 0·42; 95% CI, 0·08–2·17; p = 0·30; I^2 = 6%), nausea (RR: 0·98; 95% CI, 0·76–1·25; p = 0·85; I^2 = 40%), cough (RR: 1·07; 95% CI, 0·78–1·46; p = 0·69; I^2 = 44%), abnormal hepatic function (RR: 1·72; 95% CI, 0·22–13·22; p = 0·60; I^2 = 41%), diarrhea (RR: 1·00; 95% CI, 0·75–1·33; p = 0·99; I^2 = 65%), dizziness (RR: 0·71; 95% CI, 0·49–1·03; p = 0·07; I^2 = 77%) and nasopharyngitis (RR: 0·93; 95% CI, 0·80–1·08; p = 0·34; I^2 = 64%) between groups (Appendix 5).

Patients treated with DPP-4 inhibitors in combination with metformin had 83% less risk of a hypoglycemic event and 90% less risk of a severe hypoglycemia when compared to sulfonylureas in combination with metformin (Fig. 9).

The mean difference of the weight change during the treatment with DPP-4 inhibitors in combination with metformin or sulfonylureas in combination with metformin was 1·92 kg in favor of DPP-4 inhibitors in combination with metformin (Fig. 10).

4. Discussion

The efficacy of these two anti-hyperglycemic drug classes (DPP-4 inhibitors and sulfonylureas) that are recommended as second-line treatment for T2DM when monotherapy and lifestyle interventions are insufficient is similar, therefore safety becomes an even more important differential [2]. This study refers to the safety and tolerability profile. Our meta-analysis, composed by RCTs only, showed some important safety results for T2DM patients, regarding hypoglycemic events, cardiovascular events, weight change, and overall adverse events, even though in some other adverse events there were no difference among treatments. These results were more evident when the treatment is combined with metformin, suggesting safer clinical effects.

Table 2 – Characteristics of the included studies in combination with metformin.

Study	ClinlTrial.gov Reference	Drug and Dose DPP-4 inhibitor	Drug and Dose Sulfonylurea	n (M/F)	Age (years)	Outcome measure	Follow-up time	Population
Hissa et al. [47] Brazil	NR	Vildagliptin 100 mg orally twice daily	Gliclazide 120 mg orally once daily	18/18	18–70	Weight change	16 weeks	–
Forst et al. [28] Germany	NCT01565096	Linagliptin 5 mg orally once daily	Glimepiride individually titrated in the range of 1–4 mg orally once daily	27/12	45–75	Overall AE Weight change Severe hypoglycemia	12 weeks	–
Arechavaleta et al. [29] USA	NCT00701090	Sitagliptin 100 mg orally daily	Glimepiride 1 mg orally daily could be up-titrated to a maximum dose of 6 mg daily	563/472	≥ 8	Overall AE Nasopharyngitis Weight change Hypoglycemia Severe hypoglycemia Mortality	30 weeks	–
Nauck et al. [30] Germany	NCT00094770	Sitagliptin 100 mg orally twice daily	Glipizide 5 mg orally once day up-titrated to a maximum of 20 mg daily	694/478	18–78	Overall AE Fatigue/asthenia Nasopharyngitis Weight change Hypoglycemia Dizziness Infections Mortality CV events Diarrhea	52 weeks	–
Handelsman et al. [14] USA	NCT00094770	Omarigliptin 25 mg orally once weekly	Glimepiride up to 6 mg orally once daily	414/337	≥18	Overall AE Pancreatitis Cough Weight change Diarrhea Nausea Abnormal hepatic function Nasopharyngitis Hypoglycemia Severe hypoglycemia Infections Headache Mortality	54 weeks	–
Jax et al. [10] Germany	NCT01703286	Linagliptin 5 mg orally daily	Glimepiride 1 mg orally titrated to a maximum of 4 mg daily	28/14	18–70	Overall AE Hypoglycemia Severe hypoglycemia Mortality	4 weeks	–
Kim et al. [31] Korea	NCT00993187	Sitagliptin 50 mg orally twice daily	Glimeripide 1 mg orally titrated up to 6 mg once daily	165/127	≥18	Overall AE Nasopharyngitis Weight change Diarrhea Nausea Hypoglycemia Mortality Infections Dizziness	30 weeks	–

Table 2 – (*Continued*)

Study	ClinlTrial.gov Reference	Drug and Dose DPP-4 inhibitor	Drug and Dose Sulfonylurea	n (M/F)	Age (years)	Outcome measure	Follow-up time	Population
Amblee et al. [32] USA	NCT01267448	Saxagliptin 5 mg orally daily	Glipizide XL 10 mg orally daily	81/19	>18	Hypoglycemia Severe hypoglycemia	12 weeks	Severe hypoglycemic patients
Schernthaner et al. [33] GENERATION trial Austria	NCT01006603	Saxagliptin 5 mg orally daily	Glimepiride 1 mg orally titrated to a maximum of 6 mg daily	445/275	≥65	Overall AE Cough Pancreatitis Weight change Nasopharyngitis Hypoglycemia Severe hypoglycemia Dizziness Headache Diarrhea Infections Mortality	52 weeks	Elderly patients
Del Prato et al. [36] Italy	NCT00856284	Alogliptin 12.5 mg or 25 mg orally once daily	Glipizide 5 mg orally titrated to a maximum of 20 mg once daily	1312/1327	18–80	Overall AE Nasopharyngitis Pancreatitis Hypoglycemia Severe hypoglycemia Headache Infections Mortality Diarrhea	104 weeks	–
Derosa et al. [34] Italy	NR	Vildagliptin 50 mg orally twice a day	Glimepiride 2 mg orally three times a day	82/85	≥18	Weight change Hypoglycemia	6 mo	–
He et al. [35] USA	NR	Vildagliptin 50 mg orally twice daily	Glimepiride 2 mg orally once daily	19/5	18–70	Overall AE Hypoglycemia Mortality	30 days	–
Göke et al. [37] Sweden Extension of Göke et al. [38]	NCT00575588	Saxagliptin 5 mg orally daily	Glipizide 5 mg orally titrated up to 20 mg once daily	444/412	≥18	Overall AE Hypoglycemia Infections Mortality Diarrhea Abnormal hepatic function Nasopharyngitis	104 weeks	–
Berndt-Zipfel et al. [39] Germany	NR	Vildagliptin 50 mg orally twice a day	Glimepiride 0.5 mg orally titrated up to 4 mg once daily	28/16	30–80	Severe hypoglycemia Infections	24 weeks	–
Derosa et al. [40] Italy	NR	Sitagliptin 100 mg orally once a day	Glibenclamide 5 mg orally three times a day	220/225	>18	Nasopharyngitis Headache Hypoglycemia	1 year	–

Table 2 – (*Continued*)

Study	ClinlTrial.gov Reference	Drug and Dose DPP-4 inhibitor	Drug and Dose Sulfonylurea	n (M/F)	Age (years)	Outcome measure	Follow-up time	Population
Gallwitz et al. [41] Germany	NCT00622284	Linagliptin 5 mg orally once daily	Glimepiride 1 mg orally titrated up to 4 mg once daily	933/618	18–80	Overall AE Nasopharyngitis Cough Pancreatitis Weight change Hypoglycemia Severe hypoglycemia Headache Dizziness Mortality Cardiovascular events Infections Diarrhea	24 mo	–
Jeon et al., 201[42] Korea	NR	Vildagliptin 50 mg orally twice daily	Glimepiride 2 mg orally twice daily	66/36	<80	Weight change Hypoglycemia Severe hypoglycemia Overall AE Nausea Diarrhea	32 weeks	–
Göke et al. [38] Germany	NR	Saxagliptin 5 mg orally daily	Glipizide 5 mg orally titrated up to 20 mg once daily	444/414	≥18	Severe Hypoglycemia Pancreatitis	52 weeks	–
Matthews et al. [43] United Kingdom	NR	Vildagliptin 50 mg orally twice a day	Glimepiride 2 mg orally titrated up to 6 mg daily	1667/ 1451	18–73	Overall AE Fatigue or asthenia Nasopharyngitis Cough Mortality Weight change Headache Dizziness Infections Nausea Hypoglycemia Severe hypoglycemia	24 mo	–
Filozof C & Gautier JF [13] France	NR	Vildagliptin 50 mg orally twice daily	Gliclazide 80 mg orally once daily	524/483	18–78	Overall AE Fatigue or asthenia Nasopharyngitis Weight change Diarrhea Mortality Headache Cardiovascular events	52 weeks	–
Seck et al. [44] USA	NCT00094770	Sitagliptin 100 mg orally once daily	Glipizide 5 mg orally titrated to a maximum of 20 mg daily	303/201	18–78	Overall AE Fatigue or asthenia Cough Weight change Nasopharyngitis Hypoglycemia Infections Dizziness Mortality Cardiovascular events	24 mo	–

Table 2 – (Continued)

Study	ClinlTrial.gov Reference	Drug and Dose DPP-4 inhibitor	Drug and Dose Sulfonylurea	n (M/F)	Age (years)	Outcome measure	Follow-up time	Population
Ferrannini et al. [45] France	NCT00106340	Vildagliptin 50 mg orally twice daily	Glimepiride 2 mg orally titrated to a maximum of 6 mg daily	1490/ 1299	18–73	Overall AE Fatigue or asthenia Nasopharyngitis Weight change Hypoglycemia Headache Dizziness Mortality Cardiovascular events Nausea Diarrhea	52 weeks	–
Hong et al. [46] VISUAL study South Korea	NCT01099137	Vildagliptin 50 mg orally twice daily	Glimepiride or Gliclazide (dose-increasing by 50%)	194/150	Not reported	Hypoglycemia Overall AE Weight change	24 weeks	–

NR = Not Registered.

One of the most important adverse events experienced by diabetic patients is hypoglycemia. Hypoglycemia is related with poor clinical outcomes and increased mortality in older adults [48]. Consequently, minimizing the risk of hypoglycemia is very significant for a better clinical outcome and safety of the patient [10]. Our meta-analysis showed a significant reduction of hypoglycemia and severe hypoglycemic events in diabetic patients taking DPP-4 inhibitors in both comparisons with sulfonylureas, being more pronounced in combination with metformin. Several authors have stated that DPP-4 inhibitors cause less episodes of hypoglycemia when compared to sulfonylureas, independently of the combination or not with metformin [6,49,50]. In a specific population, Loh et al. (2016) compared both drugs during Ramadan period and also observed reduction of the risk of hypoglycemia and severe hypoglycemia in those patients [51]. A narrative review stated that sulfonylureas cause more hypoglycemia in T2DM patients and advised that both dose titration and dose timing, such as taking with meals, are important. Furthermore, it stated that sulfonylureas are not suitable for all patients and they should not be recommended to patients when there is an increased risk of hypoglycemia or to patients that may need special attention to minimize that risk, such as the elderly [2]. Colagiuri et al. (2018) state that the risk of hypoglycemia is significantly less with glipizide and gliclazide, therefore we performed a subanalysis only with studies with glipizide and gliclazide as intervention and still the risk of hypoglycemia was lower for DPP-4i without and with metformin combined (RR: 0·30; 95% CI, 0·20–0·44; $p < 0·00001$; $I^2 = 3\%$; RR: 0·13; 95% CI, 0·09–0·18; $p < 0·00001$; $I^2 = 67\%$, respectively)[52].

Both comparisons showed no weight gain in the patients taking DPP-4 inhibitors compared to those on sulfonylureas. This effect was more accentuated when metformin was combined. In fact, Azimova et al. (2014) reported that sulfonylureas combined with metformin are responsible for 2·06 kg mean weight gain when compared to placebo and metformin, and that with DPP-4 inhibitors there is no weight gain, except a study of saxagliptin that showed 0·4 kg weight loss [53]. Deacon et al. (2016) stated that DPP-4 inhibitors are weight neutral [2]. On the other hand, three meta-analyses of RCTs comparing DPP-4 inhibitors and sulfonylureas showed what the authors interpreted as a reduction of 1·94 kg, 1·62 kg, and 1·82 kg, favoring DPP-4 inhibitors, respectively [6,49,50]. However, in our meta-analysis, when the groups were analyzed separately, the results indicated that there was more of a weight gain in the sulfonylurea group than a weight loss in the DPP-4 inhibitors group. In this respect, DPP-4 inhibitors seem to be a better fit for overweight T2DM patients.

Although some authors consider the cardiovascular safety of sulfonylureas topic for ongoing debate, in our meta-analysis of RCTs, the risk of cardiovascular events was statistically lower for DPP-4 inhibitors plus metformin when compared to sulfonylureas plus metformin [54]. Two reviews state that DPP-4 inhibitors may have cardiovascular protective effects in DM patients, however, both cited observational studies or RCT comparing DPP-4 inhibitors to placebo or *versus* all therapeutic anti-hyperglycemic classes as control [53,55]. Yousefzadeh et al. (2013) and Scheen et al. (2013) listed that DPP-4 inhibitors may have some positive secondary

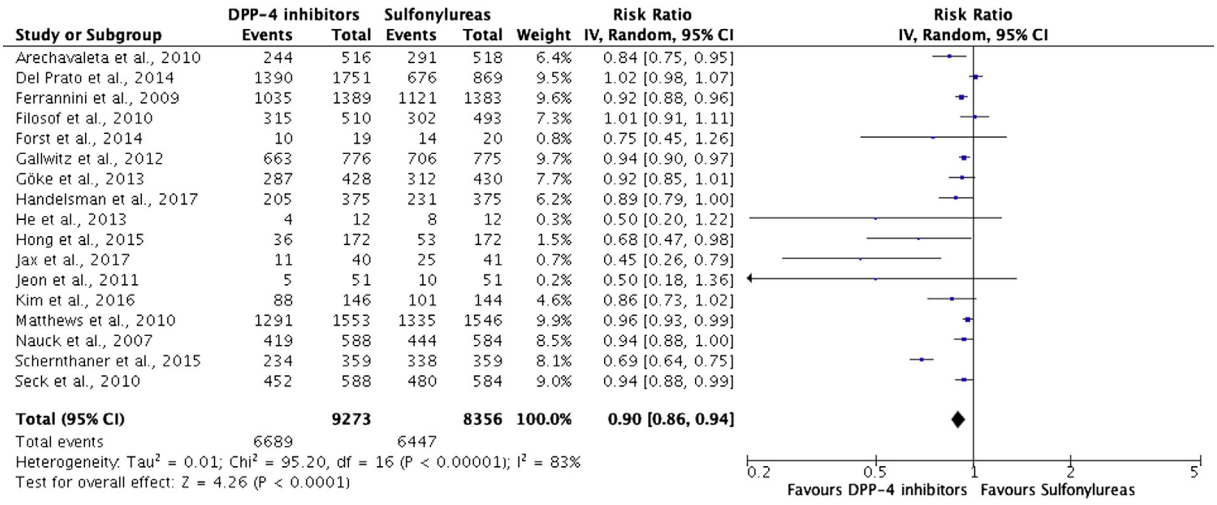


Fig. 6 – Forest plot of comparison between DPP-4 inhibitors *versus* sulfonylureas as add on to metformin for overall adverse events.

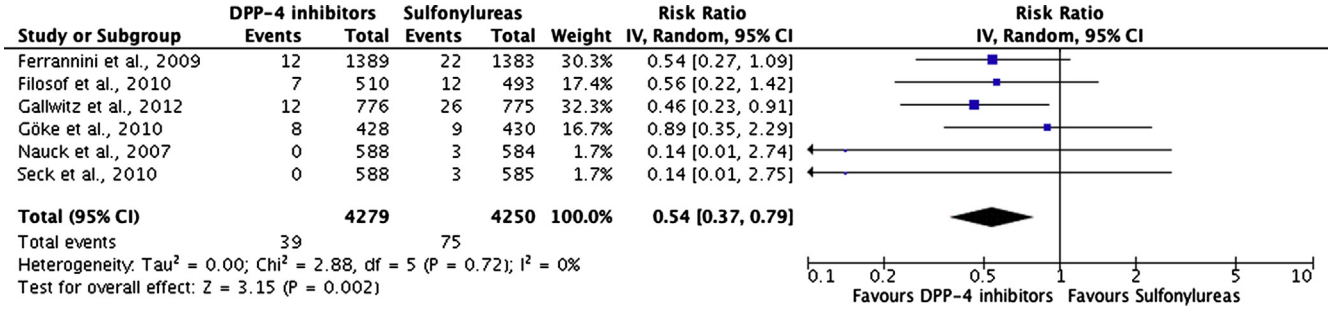


Fig. 7 – Forest plot of comparison between DPP-4 inhibitors *versus* sulfonylureas as add on to metformin for cardiovascular events.

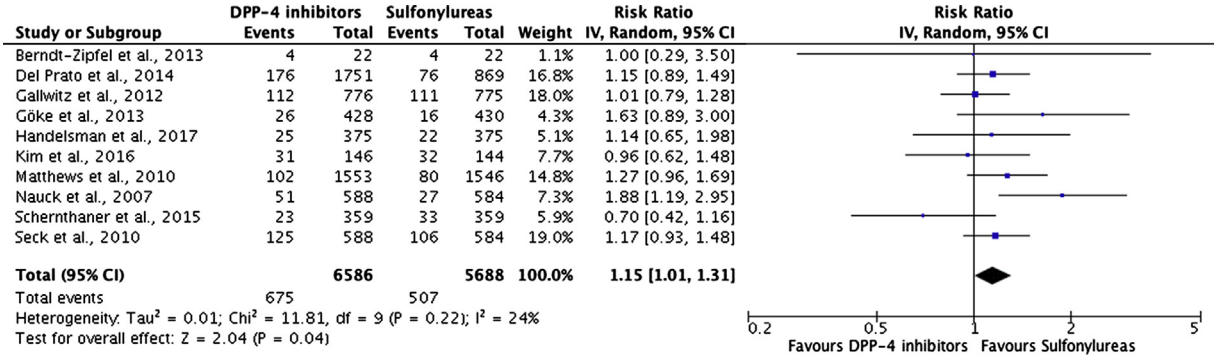
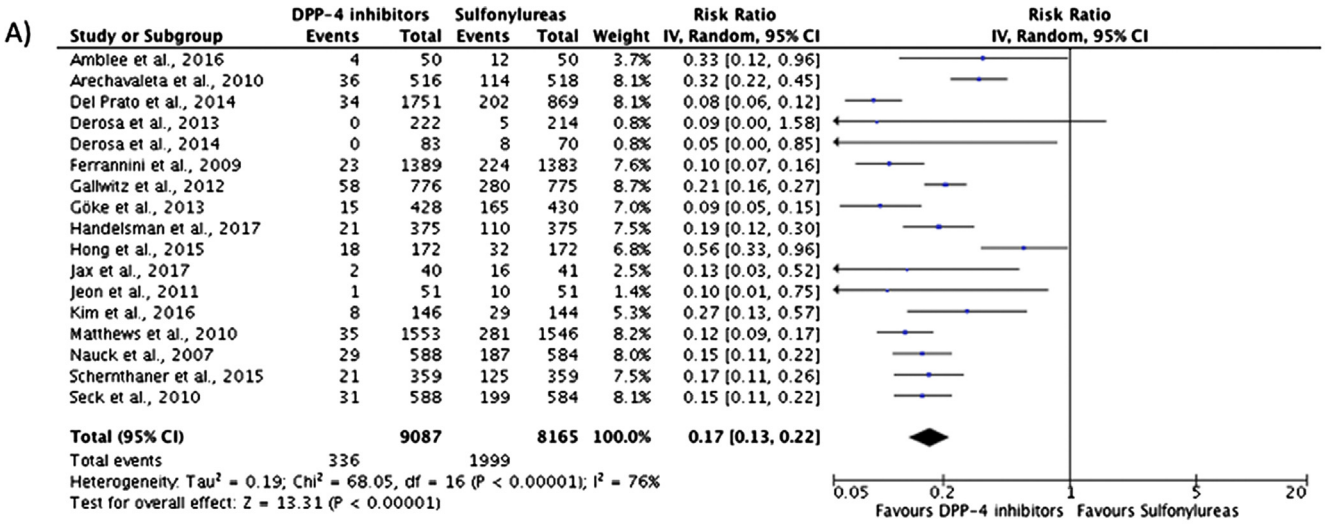


Fig. 8 – Forest plot of comparison between DPP-4 inhibitors *versus* sulfonylureas as add on to metformin for infections.

effects such as, reduce blood pressure, improve lipid profile and endothelial dysfunction, decrease the macrophage-mediated inflammatory response, and prevent myocardial injury [55,56]. Nevertheless, there is a large retrospective cohort study from South Korea which indicated a higher incidence of cardiovascular events in patients treated with sulfonylureas plus metformin when compared to subjects treated with DPP-4 inhibitors plus metformin [57]. In fact, there are three clinical trials that verified cardiovascular safety and possible benefits of DPP-4 inhibitors [58–60]. The SAVOR trial, which compared saxagliptin *versus* placebo, reported an increased heart failure hospitalization rate in the saxagliptin group, but no difference due to cardiovascular death, myocardial infarction, and stroke among treatments [58]. The EXAMINE trial compared alogliptin *versus* placebo and the TECOS trial compared sitagliptin *versus* placebo, and both trials showed no difference among treatments related to cardiovascular death, myocardial infarction, stroke and hospitalization for unstable angina and all evaluated outcomes [59,60]. One meta-analysis, with only twelve RCT stud-



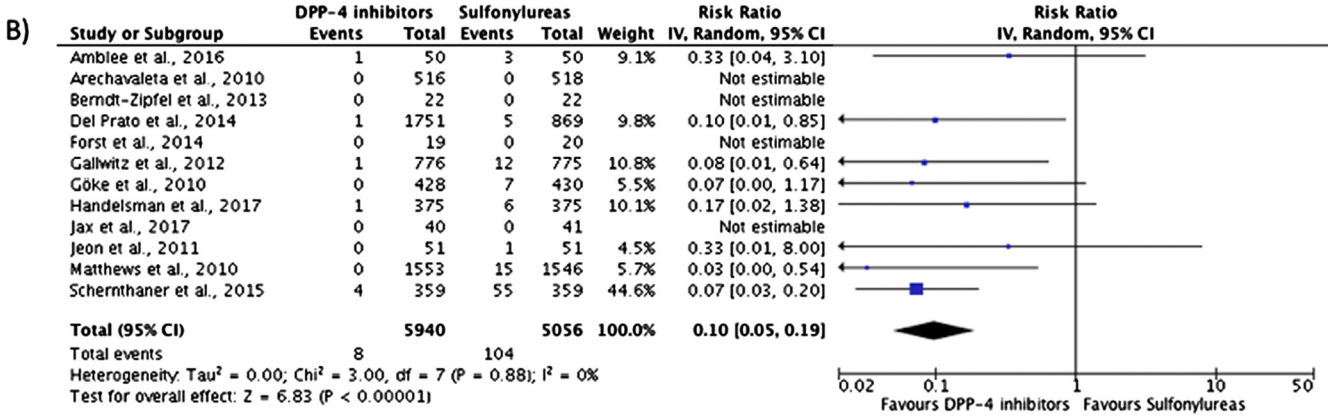


Fig. 9 – Forest plot of comparison between DPP-4 inhibitors *versus* sulfonylureas as add on to metformin for hypoglycemia and severe hypoglycemia.

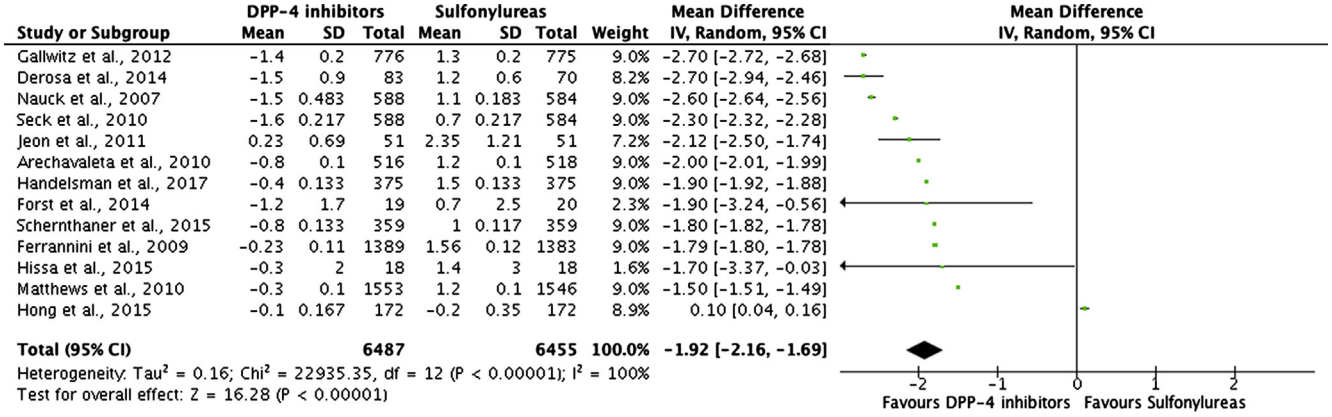


Fig. 10 – Forest plot of comparison between DPP-4 inhibitors *versus* sulfonylureas as add on to metformin for weight change.

ies, is in agreement with our results, reporting less cardiovascular events for DPP-4 inhibitors when compared to sulfonylureas (OR: 0·53; 95% CI 0·32 – 0·87)[50]. Some authors stated that gliclazide appears to have a more favorable cardiovascular profile than other sulfonylureas, but when we performed a subanalysis with only studies with gliclazide and glimepiride as intervention drug, no change of effect was seen (RR: 0·51; 95% CI, 0·33–0·79; p = 0·002; I^2 = 0%)[52,61,62]. In our meta-analysis, unfortunately, the comparison between both drug classes in monotherapy had only one study for this outcome, in which the author found no difference among treatments [25].

In this meta-analysis, we showed a reduced incidence of overall adverse events for patients treated with DPP-4 inhibitors in combination with metformin when compared to sulfonylureas with metformin. This effect was not observed for monotherapy comparison. In line with our results, two meta-analysis of RCTs observed a reduction in total adverse events in adult patients with DM when treated with DPP-4 inhibitors compared to sulfonylurea treatment [49,50]. However, in none of the studies, the authors separated monotherapy and dual-therapy with metformin during their analysis.

The risk of infection was lower for those patients in the sulfonylureas group combined with metformin, however this effect was not observed in the comparison without metformin. We can speculate that sulfonylureas have a protective effect concerning bacterial infections since there is some evidence that sulfonylureas can inhibit the biosynthesis of branched-chain amino acids by targeting acetohydroxyacid synthase (AHAS) and depleting BCAA supply to the bacteria and, thus making efficient bacteriostasis [63–65].

This meta-analysis has some strength. To the best of our knowledge, it is the largest meta-analysis including only RCTs and that compares two of the most used therapeutic classes of anti-hyperglycemic drugs for T2DM patients. Our study is the only one that separated monotherapy and dual therapy with metformin highlighting some important safety results to prescribers. Meanwhile, it also has several limitations. These include (1) some studies only reported adverse events that affected more than 5% of the subjects (2) the definition of severe hypoglycemia differed among studies, indeed "any hypoglycemic event" definition also varied in different studies (3) the mortality outcome is general, meaning that it is not specific to deaths related to the drugs.

Since DPP-4 inhibitors are still considered as a new drug class for T2DM treatment, it is necessary to wait for long-term efficacy and safety results of these drugs [2].

Deacon et al. (2016) suggests in their narrative review that DPP-4 inhibitors are probably a better clinical approach to T2DM patients since these drugs compared to sulfonylureas present less hypoglycemic events, neutral weight gain and do not increase cardiovascular risk [2].

Our data firmly supports the better clinical utility of DPP-4 inhibitors compared with sulfonylureas, however it should be considered that in poorer health economies, the lower headline cost of sulfonylurea may be taken into consideration, although the extra headline costs of DPP-4 inhibitors will probably be mitigated by reduction in hypoglycemia costs, and potentially better treatment satisfaction and quality of life [11].

5. Conclusion

This meta-analysis indicates that T2DM patients treated with DPP-4 inhibitors in combination with metformin have less overall adverse events compared to sulfonylureas in combination with metformin. Specifically, they also have less cardiovascular events, hypoglycemic episodes, severe hypoglycemic events, and do not gain weight, in comparison with sulfonylureas in combination with metformin. The monotherapy treatment indicates that DPP-4 inhibitors have lower impact on safety compared to sulfonylureas, showing better clinical outcomes concerning hypoglycemic events, severe hypoglycemia occurrences and not gaining weight. DPP-4 inhibitor monotherapy or in combination with metformin seems to be a better clinical option than sulfonylureas as they have a better safety profile with less hypoglycemic events, neutral weight gain, and lower cardiovascular risk.

Contributors

DF and MCMF were responsible for literature search, figures, study design, data analysis, data interpretation, and writing. DF, GML, FGE, and MCMF were responsible for the conception of the work, revising the draft critically for important intellectual content, final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Research in context

Evidence before this study

We systematically searched MEDLINE and EMBASE from inception until July 2017. Searches consisted of terms relating to "sulfonylureas", "dipeptidyl peptidase-4 inhibitors", "adverse events", and "safety", with no language restrictions. We only included data from randomized clinical trials comparing any sulfonylurea to dipeptidyl peptidase 4 inhibitors studied in human adults with type 2 diabetes mellitus (T2DM). We excluded studies that did not compare both drug classes, trials that did not report adverse events, and duplicate reports. A total of 36 RCTs were included, and were separated in DPP-4 inhibitors or sulfonylurea, both in monotherapy or combined with metformin. Several adverse events were reported in two recent large trials: one called START-J, in which Japanese patients with T2DM received sulfonylurea or DPP-4 inhibitors in monotherapy and the other, a US trial, where patients with T2DM received sulfonylurea or DPP-4 inhibitors combined with metformin. To our knowledge, no previous meta-analysis comparing these two classes of drugs has summarized the currently available evidence about safety outcomes.

Added value of this study

The meta-analysis showed a better safety profile for DPP-4 inhibitors when compared to sulfonylureas, and even better when treatment included metformin. A strong evidence for less overall hypoglycemic events and severe hypoglycemic events in patients treated with DPP-4 inhibitors and less risks for overall adverse events for DPP-4 inhibitors with metformin were demonstrated.

Implications of all the available evidence

The evidence suggests that DPP-4 inhibitors have less adverse events than sulfonylureas in patients with T2DM, and this evidence is more pronounced when DPP-4 inhibitors

are combined with metformin treatment. Considering that the efficacy of these two second-line treatments, DPP-4 inhibitors and sulfonylurea, is similar, it is interesting to the healthcare provider to know about the safety profile of these drugs, in order to guide his/her therapeutic decision.

Acknowledgment

We thank Takeda Pharmaceuticals for funding this publication.

Conflict of interest

DF reports grants from Takeda Distribuidora Ltda., during the conduct of the study. MCMF reports grants from Takeda Distribuidora Ltda. during the conduct of the study; he is scientific director from AxiaBio Life Sciences International, a consultancy company that provides various work to distinct healthcare stakeholders, including Takeda Distribuidora Ltda; and he is employed by Sao Paulo Federal University as professor, outside the submitted work. GML has nothing to disclosure. FGE has nothing to disclosure.

REFERENCES

[1] World Health Organization. Diabetes: fact sheet; 2017. http://www.who.int/mediacentre/factsheets/fs312/en/ [accessed Nov 6, 2017].
[2] Deacon CF, Lebovitz HE. Comparative review of dipeptidyl peptidase-4 inhibitors and sulphonylureas. DiabetesObes Metab 2016;18:333–47.
[3] Conlin PR, Colburn J, Aron D, Pries RM, Tschanz MP, Pogach L. Synopsis of the 2017 U.S. Department of Veterans Affairs/U.S. Department of Defense Clinical Practice Guideline: management of type 2 diabetes mellitus. Ann Intern Med 2017. https://doi.org/10.7326/M17-1362.
[4] Garber AJ, Abrahamson MJ, Barzilay JI, et al. consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2018 executive summary. Endocr Pract 2018;24:91–120.
[5] Hartley P, Shentu Y, Betz-Schiff P, et al. Efficacy and tolerability of sitagliptin compared with glimepiride in elderly patients with type 2 diabetes mellitus and inadequate glycemic control: a randomized, double-blind non-inferiority trial. Drugs Aging 2015;32:469–76.
[6] Hou L, Zhao T, Liu Y, Zhang Y. Efficacy and safety of sitagliptin compared with sulfonylurea therapy in patients with type 2 diabetes showing inadequately controlled glycosylated hemoglobin with metformin monotherapy: a Meta-Analysis. Exp Ther Med 2015;9:1528–36.
[7] Tamez-Perez HE. Efficacy and safety of initial treatment with glimepiride *versus* sitagliptin in type 2 diabetes. Rev Medica Inst Mex Seguro Soc 2015;53:142–8.
[8] Qaseem A, Barry MJ, Humphrey LL, Forciea MA. Oral Pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the american college of physicians. Ann Intern Med 2017;166:279–90.
[9] Optimal second- and third-line therapy in type 2 diabetes. In: CADTH report/project in Briefs. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2011. http://www.ncbi.nlm.nih.gov/books/NBK361996/ [accessed Nov 5, 2018].
[10] Jax T, Stirban A, Terjung A, et al. A randomised, active - and placebo - controlled, three – period crossover trial to investigate short – term effects of the dipeptidyl peptidase – 4 inhibitor linagliptin on macro – and microvascular endothelial function in type 2 diabetes. Cardiovasc Diabetol 2017:1–16.
[11] Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2018;61:2461–98.
[12] Sola D, Rossi L, Schianca GPC, et al. Sulfonylureas and their use in clinical practice. Arch Med Sci AMS 2015;11:840–8.
[13] Filozof C, Gautier J-F. A comparison of efficacy and safety of vildagliptin and gliclazide in combination with metformin in patients with Type 2 diabetes inadequately controlled with metformin alone: a 52-week, randomized study. Diabet Med 2010;27:318–26.
[14] Handelsman Y, Lauring B, Gantz I, et al. A randomized, double-blind, non-inferiority trial evaluating the efficacy and safety of omarigliptin, a once-weekly DPP-4 inhibitor, or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy. Curr Med Res Opin 2017;33:1861–8.
[15] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339. b2700-b2700.
[16] Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343. d5928-d5928.
[17] Vianna AGD, de Lacerda CS, Pechmann LM, et al. Vildagliptin has the same safety profile as a sulfonylurea on bone metabolism and bone mineral density in post-menopausal women with type 2 diabetes: a randomized controlled trial. Diabetol Metab Syndr 2017;9. https://doi.org/10.1186/s13098-017-0232-2.
[18] Terauchi Y, Yamada Y, Ishida H, et al. Efficacy and safety of sitagliptin as compared with glimepiride in Japanese patients with type 2 diabetes mellitus aged ≥ 60 years (START-J trial): TERAUCHI et al.. DiabetesObes Metab 2017;19:1188–92.
[19] Dei Cas A, Spigoni V, Cito M, et al. Vildagliptin but not glibenclamide, increases circulating endothelial progenitor cell number: a 12-month randomized controlled trial in patients with type 2 diabetes. Cardiovasc Diabetol 2017;16. https://doi.org/10.1186/s12933-017-0503-0.
[20] Park SE, Lee BW, Kim JH, et al. Effect of gemigliptin on glycaemic variability in patients with type 2 diabetes (STABLE study). DiabetesObes Metab 2017;19:892–6.
[21] Tahara N, Yamagishi S-I, Bekki M, et al. Anagliptin, a dipeptidyl peptidase-4 inhibitor ameliorates arterial stiffness in association with reduction of remnant-like particle cholesterol and alanine transaminase levels in type 2 diabetic patients. Curr Vasc Pharmacol 2016;14:552–62.
[22] The MAIKO Study group, Kondo Y, Harada N, et al. Sitagliptin monotherapy has better effect on insulinogenic index than glimepiride monotherapy in Japanese patients with type 2 diabetes mellitus: a 52-week, multicenter, parallel-group randomized controlled trial. Diabetol Metab Syndr 2016;8. https://doi.org/10.1186/s13098-016-0131-y.
[23] Shimoda S, Iwashita S, Sekigami T, et al. Comparison of the efficacy of sitagliptin and glimepiride dose-up in Japanese patients with type 2 diabetes poorly controlled by sitagliptin and glimepiride in combination. J DiabetesInvestig 2014;5:320–6.

[24] Rosenstock J, Wilson C, Fleck P. Alogliptin *versus* glipizide monotherapy in elderly type 2 diabetes mellitus patients with mild hyperglycaemia: a prospective, double-blind, randomized, 1-year study. DiabetesObes Metab 2013;15:906–14.
[25] Arjona Ferreira JC, Marre M, Barzilai N, et al. Efficacy and safety of sitagliptin *versus* glipizide in patients with type 2 diabetes and moderate-to-severe chronic renal insufficiency. Diabetes Care 2013;36:1067–73.
[26] Arjona Ferreira JC, Corry D, Mogensen CE, et al. Efficacy and safety of sitagliptin in patients with type 2 diabetes and ESRD receiving dialysis: a 54-week randomized trial. Am J Kidney Dis 2013;61:579–87.
[27] Foley JE, Sreenan S. Efficacy and safety comparison between the DPP-4 inhibitor vildagliptin and the sulfonylurea gliclazide after two years of monotherapy in drug-naïve patients with type 2 diabetes. Horm Metab Res 2009;41:905–9.
[28] Forst T, Anastassiadis E, Diessel S, Loffler A, Pfutzner A. Effect of linagliptin compared with glimepiride on postprandial glucose metabolism, islet cell function and vascular function parameters in patients with type 2 diabetes mellitus receiving ongoing metformin treatment. DiabetesMetab Res Rev 2014;30:582–9.
[29] Arechavaleta R, Seck T, Chen Y, et al. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. DiabetesObes Metab 2011;13:160–8.
[30] Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP, Sitagliptin Study 024 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. DiabetesObes Metab 2007;9:194–205.
[31] Kim SS, Kim IJ, Lee KJ, et al. Efficacy and safety of sitagliptin/metformin fixed-dose combination compared with glimepiride in patients with type 2 diabetes: a multicenter randomized double-blind study. J Diabetes 2017;9:412–22.
[32] Amblee A, Liousa D, Fogelfeld L. Combination of saxagliptin and metformin is effective as initial therapy in new-onset type 2 diabetes mellitus with severe hyperglycemia. J Clin Endocrinol Metab 2016;101:2528–35.
[33] Schernthaner G, Durán-Garcia S, Hanefeld M, et al. Efficacy and tolerability of saxagliptin compared with glimepiride in elderly patients with type 2 diabetes: a randomized, controlled study (GENERATION). DiabetesObes Metab 2015;17:630–8.
[34] Derosa G, Bonaventura A, Bianchi L, et al. Vildagliptin compared to glimepiride on post-prandial lipemia and on insulin resistance in type 2 diabetic patients. Metabolism 2014;63:957–67.
[35] He YL, Foteinos G, Neelakantham S, et al. Differential effects of vildagliptin and glimepiride on glucose fluctuations in patients with type 2 diabetes mellitus assessed using continuous glucose monitoring. DiabetesObes Metab 2013;15:1111–9.
[36] Del Prato S, Camisasca R, Wilson C, Fleck P. Durability of the efficacy and safety of alogliptin compared with glipizide in type 2 diabetes mellitus: a 2-year study. DiabetesObes Metab 2014;16:1239–46.
[37] Göke B, Gallwitz B, Eriksson JG, Hellqvist Å, Gause-Nilsson I. Saxagliptin vs. glipizide as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: long-term (52-week) extension of a 52-week randomised controlled trial. Int J Clin Pract 2013;67:307–16.
[38] Göke B, Gallwitz B, Eriksson J, Hellqvist Å, Gause-Nilsson I. Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. Int J Clin Pract 2010;64:1619–31.
[39] Berndt-Zipfel C, Michelson G, Dworak M, et al. Vildagliptin in addition to metformin improves retinal blood flow and erythrocyte deformability in patients with type 2 diabetes mellitus – results from an exploratory study. Cardiovasc Diabetol 2013;12:59.
[40] Derosa G, Cicero AFG, Franzetti IG, et al. A randomized, double-blind, comparative therapy evaluating sitagliptin *versus* glibenclamide in type 2 diabetes patients already treated with pioglitazone and metformin: a 3-year study. DiabetesTechnol Ther 2013;15:214–22.
[41] Gallwitz B, Rosenstock J, Rauch T, et al. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. The Lancet 2012;380:475–83.
[42] Jeon HJ, Oh TK. Comparison of vildagliptin-metformin and glimepiride-metformin treatments in type 2 diabetic patients. Diabetes Metab J 2011;35:529.
[43] Matthews DR, Dejager S, Ahren B, et al. Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study. Diabetes Obes Metab 2010;12:780–9.
[44] Seck T, Nauck M, Sheng D, et al. Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study. Int J Clin Pract 2010;64:562–76.
[45] Ferrannini E, Fonseca V, Zinman B, et al. Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. Diabetes Obes Metab 2009;11:157–66.
[46] Hong AR, Lee J, Ku EJ, et al. Comparison of vildagliptin as an add-on therapy and sulfonylurea dose-increasing therapy in patients with inadequately controlled type 2 diabetes using metformin and sulfonylurea (VISUAL study): a randomized trial. Diabetes Res Clin Pract 2015;109:141–8.
[47] Hissa MR, Cavalcante LL, Guimaraes SB, Hissa MN. A 16-week study to compare the effect of vildagliptin *versus* gliclazide on postprandial lipoprotein concentrations and oxidative stress in patients with type 2 diabetes inadequately controlled with metformin monotherapy. Diabetol Metab Syndr 2015;7:62.
[48] Perl S, Cook W, Wei C, Ohman P, Hirshberg B. Effects of glimepiride *versus* saxagliptin on beta-cell function and hypoglycemia: a post hoc analysis in older patients with type 2 diabetes inadequately controlled with metformin. Clin Ther 2016;38:2578–88.
[49] Zhou JB, Bai L, Wang Y, Yang JK. The benefits and risks of DPP4-inhibitors vs. sulfonylureas for patients with type 2 diabetes: accumulated evidence from randomised controlled trial. Int J Clin Pract 2016;70:132–41.
[50] Zhang Y, Hong J, Chi J, Gu W, Ning G, Wang W. Head-to-head comparison of dipeptidyl peptidase-IV inhibitors and sulfonylureas - a meta-analysis from randomized clinical trials. Diabetes Metab Res Rev 2014;30:241–56.
[51] Loh HH, Yee A, Loh HS, Sukor N, Kamaruddin NA. Comparative studies of dipeptidyl peptidase 4 inhibitor vs sulphonylurea among Muslim Type 2 diabetes patients who fast in the month of Ramadan: a systematic review and meta-analysis. Prim Care Diabetes 2016;10:210–9.
[52] Colagiuri S, Matthews D, Leiter LA, Chan SP, Sesti G, Marre M. The place of gliclazide MR in the evolving type 2 diabetes landscape: a comparison with other sulfonylureas and newer

oral antihyperglycemic agents. Diabetes Res Clin Pract 2018;143:1–14.
[53] Azimova K, San Juan Z, Mukherjee D. Cardiovascular safety profile of currently available diabetic drugs. Ochsner J 2014;14:616–32.
[54] Abdelmoneim AS, Eurich DT, Light PE, et al. Cardiovascular safety of sulphonylureas: over 40 years of continuous controversy without an answer. DiabetesObes Metab 2015;17:523–32.
[55] Yousefzadeh P, Wang X. The effects of dipeptidyl peptidase-4 inhibitors on cardiovascular disease risks in type 2 diabetes mellitus. J Diabetes Res 2013;2013:459821.
[56] Scheen AJ. Cardiovascular effects of gliptins. Nat RevCardiol 2013;10:73–84.
[57] Seong J-M, Choi N-K, Shin J-Y, et al. Differential cardiovascular outcomes after dipeptidyl peptidase-4 inhibitor, sulfonylurea, and pioglitazone therapy, all in combination with metformin, for type 2 diabetes: a population-based cohort study. PloS One 2015;10:e0124287.
[58] Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317–26.
[59] White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327–35.
[60] Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232–42.
[61] Scheen AJ. Cardiovascular safety of DPP-4 inhibitors compared with sulphonylureas: results of randomized controlled trials and observational studies. Diabetes Metab 2018;44:386–92.
[62] Khunti K, Chatterjee S, Gerstein HC, Zoungas S, Davies MJ. Do sulphonylureas still have a place in clinical practice? Lancet Diabetes Endocrinol 2018;6:821–32.
[63] Gokhale K, Tilak B. Mechanisms of bacterial acetohydroxyacid synthase (AHAS) and specific inhibitors of Mycobacterium tuberculosis AHAS as potential drug candidates against tuberculosis. Curr Drug Targets 2015;16:689–99.
[64] Wang D, Pan L, Cao G, et al. Evaluation of the in vitro and intracellular efficacy of new monosubstituted sulfonylureas against extensively drug-resistant tuberculosis. Int J Antimicrob Agents 2012;40:463–6.
[65] Liu Y, Bao P, Wang D, et al. Evaluation of the in vivo efficacy of novel monosubstituted sulfonylureas against H37Rv and extensively drug-resistant tuberculosis. Jpn J Infect Dis 2014;67:485–7.