META-ANALYSIS

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Effectiveness and safety of glimepiride and iDPP4, associated with metformin in second line pharmacotherapy of type 2 diabetes mellitus: systematic review and meta-analysis

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All authors are employed of the governmental institutions that have been indicated. Apart from Jorge Gonzalez-Canudas MD, which is part-time employed of Labs. Silanes, authors have not financial interest in any of the drugs discussed in this study.

SUMMARY

Objective: Our review analyses the studies that have specifically compared the association iDPP4/metformin with glimepiride/metformin, both in second line pharmacotherapy of type 2 diabetes mellitus (DM2). **Methods:** Systematic literature review with a meta-analysis of clinical trials comparing glimepiride with any iDPP4, both used together with metformin as a second line treatment of DM2. The effectiveness variables used were as follows: %HbA1c variation, fasting plasma glucose variation, patients achieving the therapeutic objective of HbA1c <7%, treatment dropouts due to lack of effectiveness and rescue treatments needed. The safety variables included were as follows: weight variation at the end of treatment; presentation of any type of adverse event; presentation of serious adverse events; patients who experienced any type of hypoglycaemia; patients who experienced severe hypoglycaemia; treatments suspended due to adverse effects; and deaths for any reason. **Results:** Four studies met the inclusion criteria. The group treated with glimepiride showed better results in all effectiveness variables. Regarding safety variables, the main differences observed were in the greater number of cases with hypoglycaemia in the group treated with glimepiride, and the serious adverse events or treatment discontinuations due to these which occurred in slightly over 2% more cases in this group compared to the iDPP4 group. The remaining adverse events, including mortality, did not show any differences between both groups. The variation in the weight difference between groups (2.1 kg) is not considered clinically relevant. **Conclusions:** A greater effectiveness is seen in the glimepiride/metformin association, which should not be diminished by slight differences in adverse effects, with absence of severe hypoglycaemia in over 98% of patients under treatment. The association of glimepiride/metformin, both due to cost as well as effectiveness and safety, may be the preferential treatment for most DM2 patients, and it offers a potential advantage in refractory hyperglycemic populations, tolerant to treatment.

Review criteria

- Systematic literature review of clinical trials comparing glimepiride/metformin vs. any iDPP4/metformin.
- Meta-analysis has been realized using a fixed-effects model according to basic criteria of Cochrane Handbook for Systematic Reviews of Interventions (V. 5.1.0). Sensibility analysis was carried out to explain statistical heterogeneity.
- There have been analyzed basic outcomes established by the European Medicines Agency according to efficacy and safety (5 outcomes of each category).

Message for the clinic

- All variables associated with effectiveness are consistently favourable to the combination of glimepiride with metformin.
- Treatment discontinuations due to serious adverse events only occurred in slightly over 2% more cases in the glimepiride group. No severe hypoglycaemic episode was observed in 98% patients.
- This treatment might be a preferential option for most DM2 patients who have not managed to achieve an adequate control with monotherapy

Introduction

The prevalence of type 2 diabetes mellitus (DM2) has been increasing in the last few decades, reaching pandemic proportions (1,2) that is already overwhelming industrialised countries and is spreading to low and medium income countries, where an 80% mortality can be attributed to this disease (3). At the same time, the progressive nature of diabetes and its associated complications carry an important economic impact, both because of the use of healthcare resources as well as loss of productivity, which are frequently undervalued (2,4–6).

Many, national and international, guidelines have been elaborated to standardise the complex management of this disease. Generally, and in addition to the permanent diet and physical exercise recommendations, the treatment guidelines suggest starting pharmacotherapy with metformin and, if the glycaemic objective (generally established at a glycosylated

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haemoglobin, HbA1c, concentration below 7% or even 6.5%) does not remain under control, then a second agent with a different action mechanism is added, among which a second generation sulfonylurea is usually recommended (7–12).

Among antihyperglycaemic agents used in second line pharmacotherapy, we find the inhibitors of dipeptylpeptidase 4 (iDPP4) and second generation sulfonylureas.

Sulfonylureas have been known for decades, but because of the differences seen among the different ones in the group, they cannot be considered homogeneous (13–17). However, in the case of glimepiride, perhaps because of their most recent appearance, its distinguishing characteristics are frequently masked by the class effect of the group as a whole.

In clinical practice, the doctor does not prescribe a pharmaceutical group but a specific drug. As a consequence, the specific information must be available to allow him to distinguish one in particular among the different agents of each pharmacological family to personalise the treatment, as required by a patient-centred approach (18). It is in this context which we consider that the assessment of the most used sulfonylureas requires individual studies to avoid confusion that could lead to an indiscriminate analysis of the drugs in the group. As a result, we have approached the study of glimepiride taking into account the growing interest this agent raises in the second line combination therapy (19) as well as the differences it presents compared to other drugs in the same group (20,21), its favourable balance between effectiveness and safety (17,22), together with its lower cost (23,24).

The objective of this study was, through a systematic literature review, to compare the effectiveness and safety of glimepiride with any iDPP4 agent when both are used together with metformin in second line treatment of DM2.

Material and methods

The selection of studies was carried out applying the following inclusion criteria: randomised or quasi-randomised clinical trials with a follow-up of at least 12 weeks that include pre-established variables on measures of effectiveness and safety, disaggregated by treatment group. Patients should be over 18 years of age and have a diagnosis of DM2, be on treatment with a stable dose of metformin for at least three months prior to the selection visit, and present an inadequate glycaemic control with HbA1C > 6.5%. Therefore, they should be considered for the second line pharmacotherapy and a second oral agent should be added, which could be either an inhibitor of dipeptylpeptidase 4 (iDPP4) or glimepiride. Included studies should compare an iDPP4 (alogliptin, linagliptin, saxagliptin, sitagliptin or vildagliptin) with glimepiride, both associated with metformin, as a second line pharmacotherapy. Non-randomised clinical trials were excluded, as well as those randomised trials which included patients with a diagnosis of type 1 diabetes mellitus without presenting separate results for DM2; clinically relevant cardiovascular disease; myocardial infarction; ischemic attack in the previous 6 months or with abnormal laboratory results.

A literature search was carried out in Medline (through PubMed) until 31 December 2013. In addition, a manual search of the references from the articles obtained was carried out, as well as a search in the Cochrane Library database.

The following MeSH terms were used in a Boolean query which combined each of the separately searched iDPP4 (OR): alogliptin, sitagliptin, saxagliptin, vildagliptin and linagliptin, with metformin, and then combining them (AND) with the combination of glimepiride and metformin. No restriction of language or publication date was applied.

The selection of abstracts was independently carried out by two different researchers, and disagreements were resolved through discussion with a third researcher. Next, a thorough reading of the complete text of the articles selected was carried out to decide on their eligibility. The references obtained were imported to a Reference Manager version 12 file and two authors independently reviewed the studies to select those which met the inclusion criteria. Differences between the two reviewers were resolved by consensus with a third reviewer. Methodological quality and bias risk was assessed according to the Cochrane Collaboration criteria (25).

The result variables analysed were selected according to the basic criteria developed by the European Medicines Agency (EMA) (26). Thus, to evaluate effectiveness, we chose the change in percentage of glycosylated haemoglobin as the main variable (% HbA1c), and the following were considered as secondary variables: patients who achieved the therapeutic objective of HbA1c < 7%; change in fasting plasma glucose level (FPG); patients achieving the therapeutic objective of HbA1c < 7%, treatment dropouts because of lack of effectiveness; and rescue treatments needed. Safety variables included: weight variation at the end of treatment; presentation of any type of adverse event; presentation of serious adverse events; patients who experienced any type of hypoglycaemia; patients who experienced severe hypoglycaemia, that is, those cases that required assistance

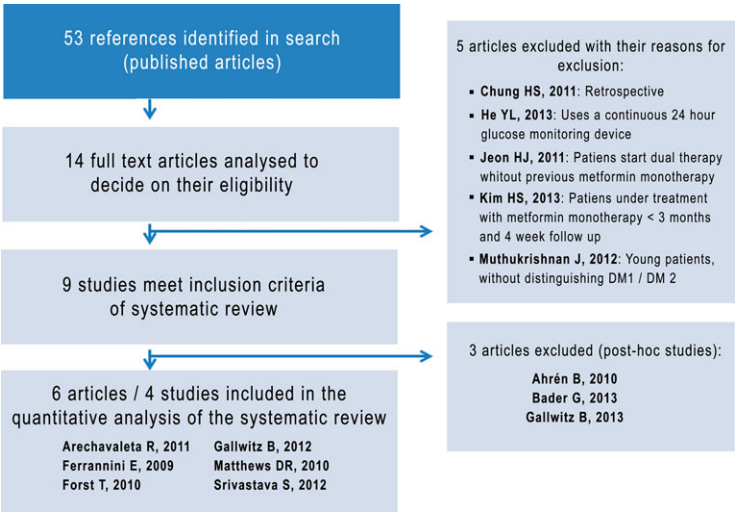

Figure 1 Bibliographic search diagram

by a third party, whether it be professional or non-professional assistance; treatments suspended because of adverse effects, and deaths for any reason.

The result variables were processed comparing their values at the end of the follow-up period to the basal levels. Meta-analysis was carried out using the statistics package STATA version 12 (StataCorp LP, College Station, TX, 1984–2007) comparing the intervention group, those using iDPP4, with the active comparator, glimepiride, using a fixed-effects model (27). Continuous variables were analysed using the difference in ponderated means (WMD), with the Mantel–Haenszel method and its corresponding 95% confidence interval. In the case of dichotomous variables, Odds ratio (OR) was calculated with its 95% confidence interval using the Peto method. The degree of inconsistency between study results was assessed using the I^2 statistic, using a value of $I^2 > 50\%$ as a limit for clinical relevance. Sensibility analysis was carried out to explain statistical heterogeneity. Given that the number of studies included in our review did not reach the minimum, 10, recommended in the Cochrane Manual (25) to carry out a funnel-plot, this possibility was not considered.

Results

The study selection process is shown in Figure 1. The initial bibliographic search generated 53 potentially relevant references. After reading the abstracts of these references, 14 articles were selected for a complete text reading, and a further five were discarded for not meeting inclusion criteria (28–32), making a total of nine articles selected for inclusion in the quantitative systematic review (33–41). Out of these, five articles corresponded to primary studies (34,37,38,40,41); another is an intermediate publication of the same study by Ferrannini et al. (36) and another three are *post-hoc* analyses of primary studies (33,35,39) which are excluded as they offer other *composite end-points* or outcome variables which are different to those established in our inclusion criteria.

The six selected articles correspond to five randomised, double blind, multi-centre clinical trials, with the exception of Srivastava et al. (41) which is a single-centre study and Forst et al. (37) which, although it is randomised in both arms, only the iDPP4 arm was blinded. The follow-up periods varied between 12 and 104 weeks and four studies (34,36,38,40) were funded by the pharmaceutical industry.

Quality of studies

All articles suffer from uncertainties which could be the cause of bias, thus: four articles do not mention how sample size was calculated to assure statistical power (34,36,38,41); two (37,38) do not mention if patients were receiving concomitant treatments or their description and another article (40) presents a dropout rate > 30% when 20% was estimated when sample size was calculated. Taking this into account, the methodological quality of the remaining six articles was assessed, as represented in Figure 2, after which we decided to exclude the high risk of bias articles (40,41) and replace Matthews 2010 (40) by the one by Ferrannini et al. (36) as it belonged to the same study but presented better quality indicators and provided results with a 52 week follow-up.

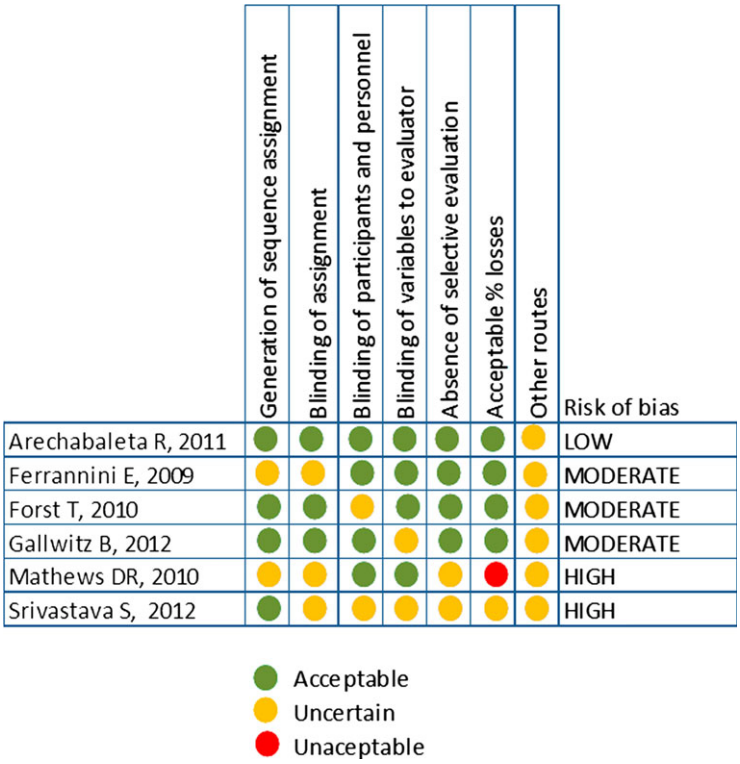

Figure 2 Assessment of the methodological quality of studies

All together, the selected articles included results from 5637 patients, mainly Caucasian (81%) and male (54%), with a mean age of 58 ± 9.4 years, a mean basal weight of 86.8 ± 17.1 kg, and an average BMI of 31.2 ± 4.9. The mean progression period of diabetes was 5.8 ± 4.5 years; mean basal HbA1c was 7.5% ± 0.7%, and the average FPG was 9.0 ± 2.2 mmol/l. The iDPP4 used in the studies was sitagliptin (34), vildagliptin (36) and linagliptin (37,38), the results of which are processed together to explore a class effect. The basal characteristics of the patients are described in Table 1 where, among the differences found between them, we would like to point out the following: three of the articles have a non/inferiority design (34,36,38,40) and two of them mention the possibility of introducing rescue medication (36,38,40).

The criteria defining a failure in glycaemic control of the previous treatment also varied between studies. In two studies (34,36), the treatment prior to inclusion consisted exclusively of metformin monotherapy, while in another two studies (37,38), patients were recruited after having received metformin treatment either as monotherapy or associated with another oral antidiabetic medication.

Finally, there are also differences in the maximum doses of glimepiride established which vary between 3 (37) and 6 mg/day (34,36)

Effectiveness

Reduction in HbA1c levels

The combined analysis of HbA1c variation after treatment in the four articles selected (34,36–38) includes the results of the observations after the different follow-up periods and shows that patients treated with glimepiride have a 12% greater reduction compared with those treated with iDPP4, WMD –0.12 (CI: −0.16, −0.07), as can be seen in Figure 3.

Proportion of patients achieving the objective of HbA1c < 7%

Three of the studies selected (34,36,38) use the proportion of patients who achieve the objective of HbA1c < 7% as a secondary effectiveness outcome, and two of them (34,38) also add those patients with HbA1c < 6.5%. The meta-analysis of the results from the first studies, shows a favourable result for glimepiride, OR: 1.14 (CI: 1.01, 1.28; I^2 = 13.5%).

FPG variation

The variation in FPG is studied in three studies (34,36,38) and its combined analysis shows that the association of glimepiride/metformin produces a

Table 1 Basal characteristics of articles and included patients

Author/Year/ Country/Study	Treatment groups	*N*	Study duration (weeks)	Age (years), mean ± SD)	Sex (% male)	T2DM duration (years), mean ± SD	Basal HbA1c (%), mean ± SD	FPG (mmol/l), mean ± SD	Basal weight (kg), mean ± SD	Basal BMI (kg/m^2), mean ± SD	a) Rescue medication (%) b) Concomitant medication c) Adherence
Arechabaleta, 2011 USA	Sitagliptin (100 mg/day)	516	30	56.3 ± 9.7	55	6.8 ± 4.6	7.5 ± 0.7	8.0 ± 1.8	80.6 ± 15.2	29.7 ± 4.5	a) No
Non-inferiority design	Glimepiride (1–6 mg/day)	519		56.2 ± 10.1	54	6.7 ± 4.8	(6.0–10.2)	8.1 ± 1.9	82.0 ± 16.7	30.2 ± 4.4	b) Yes
NCT00701090	Mean dose: 2.1 mg/day						7.5 ± 0.8				c) Yes (97%)
	Metformine (≥ 1500 mg/day)						(6.1–10.3)				
Ferrannini, 2009 France	Vildagliptin (50 mg bid)	1396	52	57.5 ± 9.06	53	5.7 ± 5.2	7.3 ± 0.6	9.2 ± 2.3	89.01	31.8 ± 5.3	a) 5.1 vs. 3.7
Non-inferiority design	Glimepiride (2–6 mg/day)	1393		57.46 ± 9.28	54	5.8 ± 5.0	7.3 ± 0.7	9.2 ± 2.2	88.62	31.7 ± 5.3	Pioglitazone if HbA1c>8%
NCT00106340	Mean dose: 4.5 mg/day										b) Yes (93%)
	Metformine										c) ND
	Mean dose: 1898 mg/day										
Forst 2010 Germany	Linagliptin (1 mg/day)	65	12	59.2 ± 8.4	55	7.5 ± 6.8	8.2 ± 0.7	10.1 ± 2.3	92.5 ± 16.9	32.3 ± 4.3	a) No
NCT00309608	Linagliptin (5 mg/day)	66		59.6 ± 9.8	63	6.7 ± 5.9	8.5 ± 0.8	10.5 ± 2.4	90.7 ± 14.2	31.7 ± 4.5	b) ND
	Linagliptin (10 mg/day)	66		61.8 ± 8.8			8.4 ± 0.7	10.5 ± 2.4	89.9 ± 16.3	31.7 ± 4.5	c) ND
	Glimepiride (1–3 mg/day)	65		59.4 ± 9.9			8.2 ± 0.7	10.0 ± 2.2	90.5 ± 15	31.5 ± 4.2	
	Metformine (≥ 1500 mg/day)										
Gallwitz 2012 Germany	Linagliptin (5 mg qd)	776	104	59.8 ± 9.4	60	≤ 1 year:	7.7 ± 0.9	9.1 ± 2.4	86.0 ± 17.6	30.2 ± 4.8	a) 25 vs. 21
Non-inferiority design	Glimepiride (1–4 mg qd)	775		59.8 ± 9.4	61	50 (7%)*^{L}	7.7 ± 0.9	9.2 ± 2.3	87.0 ± 16.7	30.3 ± 4.6	p = 0.117;
NCT00622284	Metformine (≥ 1500 mg/day)					58 (8%)*^{G}					Pioglitazone if HbA1c > 8.5%
						1 ≤ years ≤ 5:					b) Yes (< 91%)
						316 (41%)*^{L}					c) Yes (98%)
						291 (39%)*^{G}					
						≥ 5 years:					
						398 (52%)*^{L}					
						406 (54%)*^{G}					

bid, twice at day; BMI, body mass index; FPG, fasting plasma glucose; *N*, number of patients; ND, Not described in the study; SD: standard deviation. *Number and (%) of patients under such condition (L = Linagliptin; G = Glimepiride).

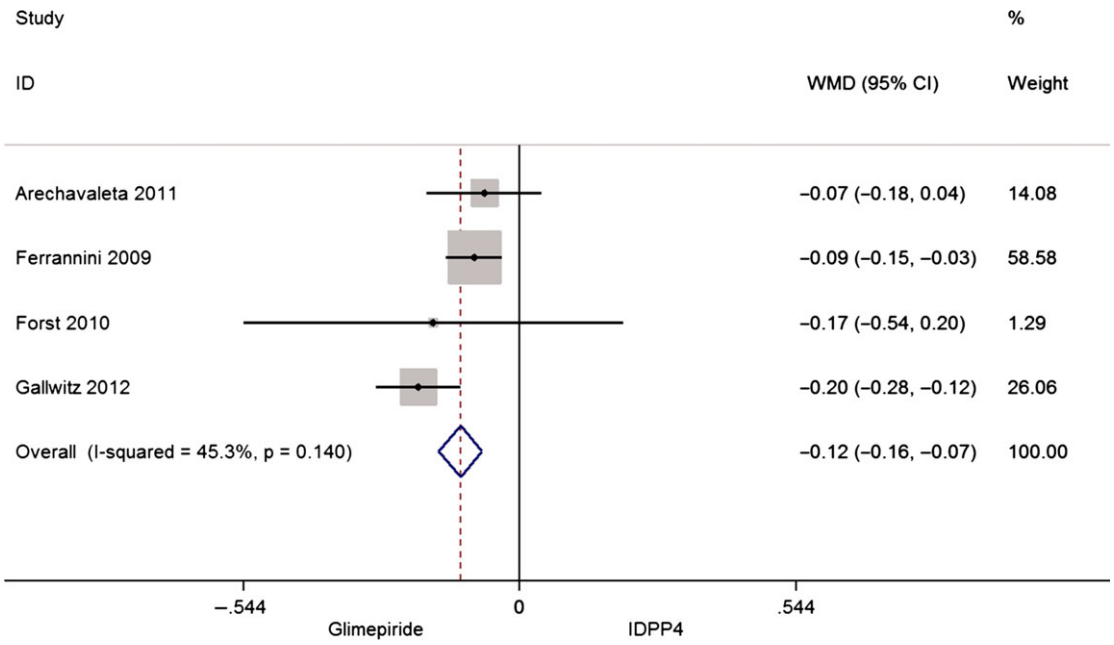

Figure 3 Meta-analysis of HbA1c (%) reduction after treatment

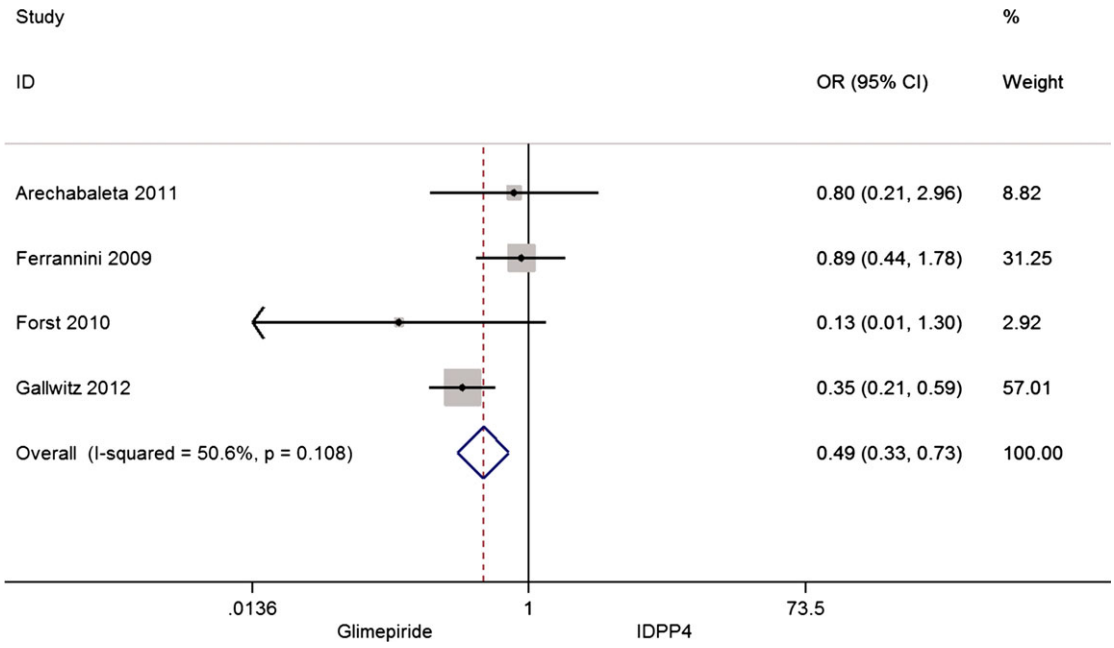

Figure 4 Risk of dropout because of the lack of effectiveness

reduction 0.21 mmol/l greater than with iDPP4/metformin (I^2 = 17.4%).

Dropouts because of lack of effectiveness

Four studies (34,36–38) analysed the number of dropouts in each group because of the lack of effectiveness. Results show that there are significantly fewer dropouts, 50%, in the glimepiride group compared with the iDPP4 group, as can be seen in Figure 4.

Need for rescue treatments

Two studies (36,38) analyse the number of rescue treatments needed with another drug, because of lack of effectiveness of the treatments under study. The combined analysis of this variable shows that in the

Table 2 Weight variation (△) in the different treatment groups with basal BMI and weight

	Glimepiride					iDPP4			
Author	Treatment (weeks)	BMI (kg/m^2)	Weight (kg)	ΔWeight (kg)	ΔWeight (%)	BMI (kg/m^2)	Weight (kg)	ΔWeight (kg)	ΔWeight (%)
Forst (2010)	12	31.5	91 ± 15	0.73	0.81	31.7	91 ± 14	−0.57	−0.63
Arechavaleta (2011)	30	30.2	82 ± 17	1.2	1.46	29.7	81 ± 15	−0.8	−1
Ferrannini (2009)	52	31.7	89	1.56	1.76	31.8	89	−0.23	−0.26
Gallwitz (2012)	104	30.3	86 ± 18	1.3	1.49	30.2	87 ± 17	−1.4	−1.63

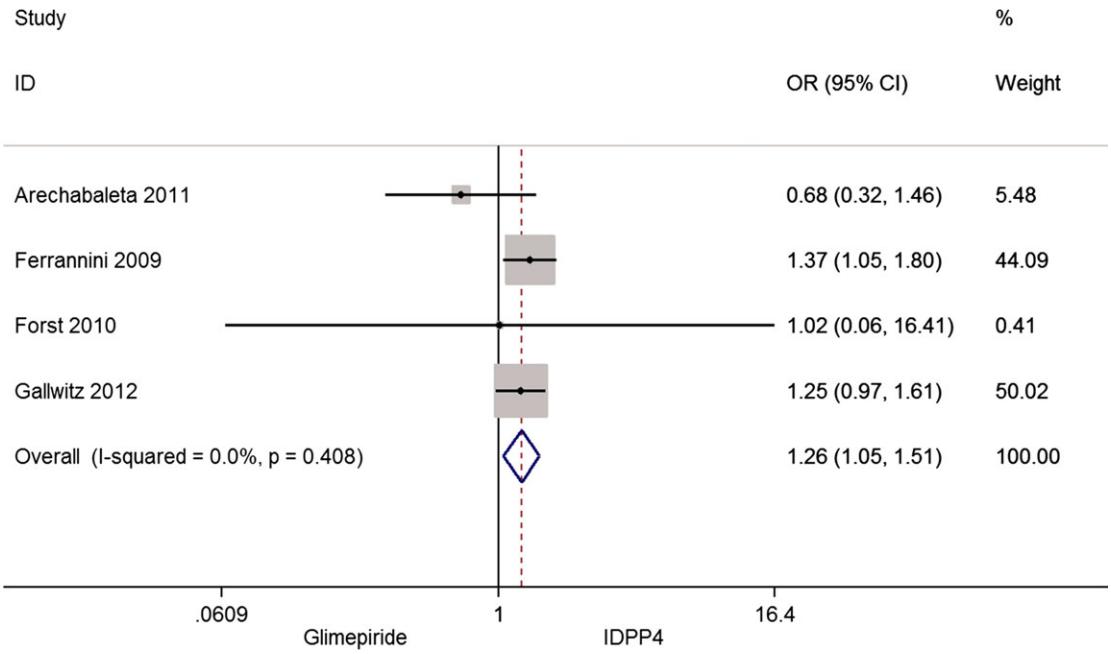

Figure 5 Risk of serious adverse effects

group treated with glimepiride/metformin, the risk of needing rescue treatments is 20% less than in the iDPP4/metformin group (OR: 0.80, 95% CI: 0.65, 0.99; I^2 = 0.0%).

Safety

Weight variation

Table 2 summarizes basal body mass index (42) and weight in the different treatment groups, together with the variations in weight experienced in each group, expressed as an absolute value (kg) and as a proportion (%). The greatest weight reduction, that corresponds to a difference of 1.63% from the basal level, is seen with the treatment of linagliptine after 104 weeks, while the greatest increase, which is 1.76% compared with the basal weight, is observed after 52 weeks of treatment with glimepiride.

Given that weight variation can occur in both directions: increase and decrease, in the combined analysis of this variable, the differences produced between both treatment groups have been processed. The overall difference between the increase in weight experienced in the groups treated with glimepiride and the decrease in weight observed in those treated with iDPP4 is 2.1 kg (95% CI: 1.78, 2.24; I^2 = 74.3%).

Adverse effects

Four studies (34,36–38) analysed the number of adverse effects in each group. The combined analysis of the number of patients experiencing adverse effects of any severity shows a high proportion. Over 70%, is seen in both groups: 71.9% in patients treated with iDPP4 and 78.3% in those treated with glimepiride, which means that out of one hundred patients who receive each of these treatments, in the glimepiride group there are six cases more experiencing adverse events than in the iDPP4 group (95% CI: 1.29, 1.67; I^2 = 14.0%).

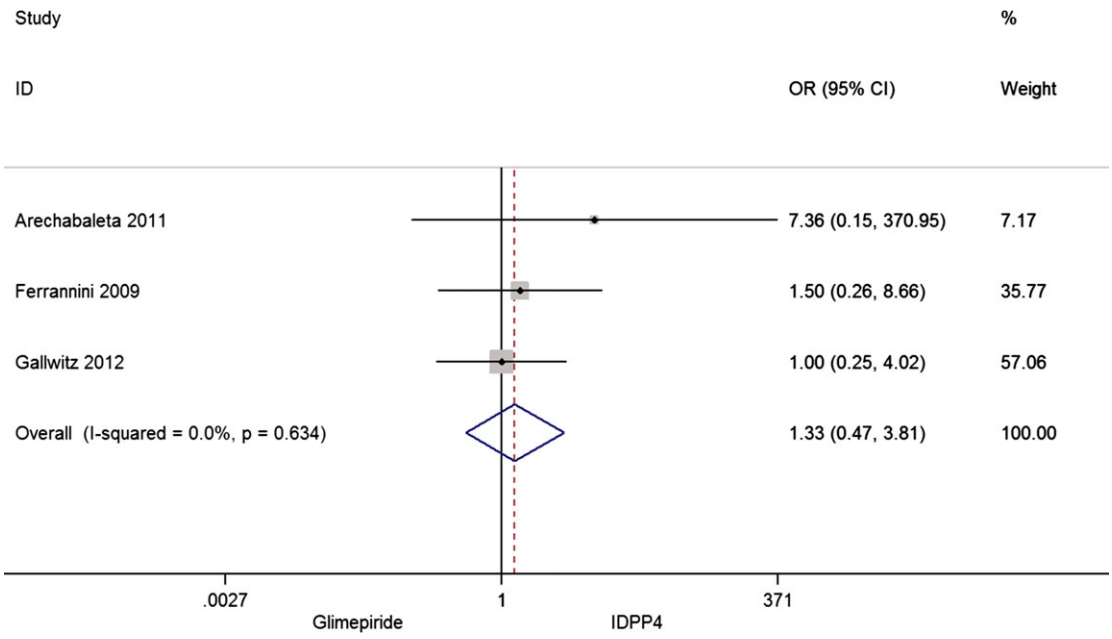

Figure 6 Risk of death for any season

As indicated, these figures include all type of adverse effects, including the severe ones which are examined later on. However, the articles analysed mention several adverse effects which are produced with a frequency ≥ 5%, and include the following: headaches, cough, nasofaringitis, urinary infection, musculoskeletal and gastrointestinal disorders, flu and hypoglycaemia. Except this last one, the others do not show differences between both treatment groups.

The same articles (34,36–38) include also information about the number of patients who present serious adverse effects including episodes of severe hypoglycaemia. The combined analysis shows greater proportion in the group treated with glimepiride, as can be seen in Figure 5. However, analysis of the crude figures reflects a much smaller difference: 9.1% in the group treated with iDPP4 and 11.2% in the group treated with glimepiride.

Hypoglycaemia

Four articles (34,36–38) analyse this variable and results show that in patients treated with glimepiride there are more cases of patients suffering from any type of hypoglycaemia than in those treated with IDPP4: OR: 5.07 (95% CI: 4.33, 5.93; I^2 = 59.2%), although this difference is mainly due to the cases of mild or moderate hypoglycaemia, as can be seen by the next analysis of severe hypoglycaemia.

Three of the articles (34,36,38) have separately analysed the hypoglycaemic episodes according to their severity. According to the combined analysis of this variable, the magnitude of the effect is greater in the glimepiride group: OR: 5.57 (95% CI: 2.79, 10.34; I^2= 0.0%) and corresponds to 0.1% of patients treated with iDPP4 who suffer some episode compared to 1.2% in the group treated with glimepiride.

Discontinuation caused by adverse events

Discontinuation caused by adverse events is analysed in four studies (34,36–38) and their combined analysis shows greater proportion in the group treated with glimepiride, OR: 1.45 (95% CI: 1.17, 1.81; I^2 = 69.2%). This variable is important in reflecting the effective clinical relevance of adverse events in each of the treatments analysed as, without undermining the combined analysis, the proportion of discontinuations because of adverse events show only a difference of two more patients suffering from these out of every hundred patients treated with glimepiride: 7.3% compared to 5.2% in cases treated with iDPP4.

Deaths for any reason

The combined analysis does not show any difference in the number of deaths because of any cause between both groups (Figure 6), with 0.2% deaths in the treatment with iDPP4 and 0.3% with glimepiride.

Discussion

Composite end-points

The clinical application of composite end-points is discussed due to the heterogeneity among their components and the relative influence of each of

them on treatment (43–47), which is the reason why in our review we have picked articles that express their results in simple primary variables, excluding those that were extension studies or those expressing their results as composite end-points (33,35,39), that can offer an excessive simplification of evidence and result in mistakes in clinical practice, where the individual needs of each patient, defined by their specific characteristics such as age, glycaemic level, response and tolerance to treatment or associated morbidities, prevail (18,48).

Glycaemic control

The main effectiveness variable presented in the four studies analysed is the variation in HbA1c with respect to basal levels. In those studies with greater number of patients, the average values of HbA1c in each treatment group, vary between 7.30 ± 0.65 in the group treated with glimepiride by Ferrannini et al. (36) and 7.7 ± 0.9 in both groups treated with linagliptine and glimepiride by Gallwitz et al. (38). However, this value increases to 8.5 ± 0.8 in the 66 patients treated with 5 mg/day of linagliptine by Forst et al. (37). The weight of this work in the overall analysis of this end-point, is only 1.29%, and it studies the effects after only 12 weeks of treatment with three different doses of linagliptine, which may explain the amplitude of the range.

As can be seen in fig. 3, the study by Gallwitz, with a 2 year follow-up and significant adherence, is the one to offer a greater magnitude of effect (20%) in the reduction in HbA1c concentration in favour of glimepiride treatment. Together with the proven effectiveness of the medication, we can also relate this result to the favourable adherence of patients treated that is a result of the careful therapeutic approach taken.

The percentage of patients achieving the therapeutic objective of HbA1c < 7% also shows a favourable global effect estimator in favour of glimepiride, despite the selection bias that can be attributed to the small basal concentration in the three studies analysed, as all included great proportions of patients with values of HbA1c between 6.5% and 7%, that are only quantified by Arechavaleta et al. (34) and Gallwitz et al. (38), as 22% and 23% in the groups treated with iDPP4 and 24% and 21% in the glimepiride treated groups.

Fasting plasma glucose levels offer an analogous reflection on possible biases as, except for the small study by Forst et al. (37), most patients treated in the different groups present FPG levels around 9 mmol/l and have had diabetes for approximately 6 years. In any case, the combined analysis, which is quite consistent, shows a significantly greater global estimator for glimepiride in 0.21 mmol/l, compared with iDPP4.

The cases of treatment discontinuation resulting from the lack of effectiveness, 1.2% vs. 2.4%, as well as the need to start rescue treatments, 11% vs. 13.1%, offer a favourable result for glimepiride treatment.

Effect on weight

The study of oral antidiabetics has paid significant attention to their effect on patient′s weight. In our study, we see that weight variations, in both directions, seen in the different groups are small, and clinically not relevant as, although there are no totally accepted thresholds to define a minimum weight change that can be considered significant, the published literature estimates decreases between 5% and 10% (7,49), very far from those seen in our review, where the combined analysis of weight reductions observed with iDPP4 and the increases observed with glimepiride only show a difference of 2 kg between both treatment groups.

Ethnic differences are not always well reflected in the international weight classification based on Body Mass Index (42), as has been proposed in different populations such as the Asian (50). In the German population, an increase in mortality risk by any cause has been observed in obese people (BMI $\geq$ 36), both in the general population and in the diabetic one, but not in the overweight population (51). This trend in diabetic population has recently been confirmed, with the observation of a decrease in HbA1c concentration and decreased mortality risk in overweight states ($25 \leq$ BMI ≤ 35), defining what has been called 'U figure' (42,52,53).

The controversy arisen by the so-called 'obesity paradox' has not yet reached an unanimous conclusion (54,55) and still brings up methodological discussions which even suggest that the current obesity classification criteria are not enough (56–60). In addition, the differences between the effective weight variation and that perceived by patients were added to this controversy (61).

Hypoglycaemia

Hypoglycaemia has an important impact in the management of DM2 patients, and the complexity of this phenomenon itself requires careful assessment for several reasons such as: the scarce consistency in its definition; the continuous changes that have taken place in defining therapeutic objectives, as well as the duration itself of diabetes and the degree of insulin deficiency, in addition to the inter-individual variability itself, as some patients experience repetitive hypoglycaemic episodes and others only occasionally (62). At the same time, hypoglycaemic episodes are related to the HbA1c objective which, together with

the overall treatment, needs to be personalised as a function of the patient's characteristics and risk factors such as: intensive control and duration of diabetes, hypoglycaemia history, cognitive state, comorbidities or poli-medication (12,63,64). To this, we must add the fact that patients more vulnerable to a repetition of these episodes are more prone to loss of adherence (65) which, in any case, must be fought against with greater personalisation in patient training and care (66,67) or ultimately, with treatment revision, as adequate glycaemia monitoring and subsequent adjustment of medication, diet, and physical activity, substantially contributes to the prevention of hypoglycaemic episodes (12).

In our analysis, the main safety variable used is the number of patients who have suffered a severe hypoglycaemia episode, defined as an episode which requires assistance by another person, be it professional or not (68), allowing us to manage more standardised data and with a greater healthcare impact.

However, when analysing overall hypoglycaemia, mild or moderate hypoglycaemia was also included, despite the ambiguity that can arise in declaring symptomatic episodes of varying intensity and frequency. Although more frequent in glimepiride treatment, it has proven to be of little clinical relevance, given the small number of treatment discontinuations because of adverse effects.

In the articles analysed, numerous patients have basal HbA1c levels which are under 7% that is the basic glycaemic objective of the studies themselves and the one proposed in general in the main guidelines, which also often suggest objectives such as HbA1c $< 6.5\%$ or HbA1c $< 8\%$, depending on the specific characteristics of each patient (7,10,18,69–72), accepting the difficulty, in general, of achieving a HbA1c $< 7\%$ (18).

In any case, we must emphasise that the number of patients who experience severe hypoglycaemic episodes only reaches 1.2% of all patients treated with glimepiride.

On the other hand, the fact that longer treatments present severe hypoglycaemic episodes in 0.72% (36) and 1.55% (38) of subjects treated with glimepiride through 52 and 104 weeks, respectively, compared with the 2.12% seen in the study by Arechavaleta et al. (34), of only 30 weeks, suggests a possible effect of patient adaptation to treatment

The combined analysis of patients who experience adverse effects, of any type or any severity, is greater in the group treated with glimepiride, resulting from the episodes of hypoglycaemia. However, when these are excluded, the mild or moderate adverse effects with a frequency of ≥ 5, do not show differences between groups.

As the combined analysis has revealed, the number of patients who experience serious adverse effects, including serious hypoglycaemia, is greater in the group treated with glimepiride. However, crude data show this greater incidence is limited, in practice, to 2 of every 100 patients treated: 9.1% in the iDPP4 group and 11.2% in the glimepiride group. This similarity is maintained when the number of treatments discontinued because of adverse effects is assessed: 5.2% in the iDPP4 group and 7.3% in the glimepiride one.

Mortality

Significant differences between the groups have not been observed.

Study limitations

This study presents the limitations associated with, to a large degree, the lack of original articles and their objectives themselves, directed at showing a better tolerance of iDPP4, without a decrease in effectiveness. Thus, apart from the work by Forst et al. (37), which only has a 12 week follow-up and with low weight in the meta-analysis, the studies analysed have a non-inferiority design, with margins of HbA1c established at 4% (34) in one of them and 3.5% in another (38), both above the 3% margin considered acceptable by the EMA (26), which is why we believe the initial assertion of 'non-inferiority' must be interpreted with caution. In any case, the analysis has been done on outcome variables which are clearly quantified in the original studies, without carrying out any assignments or estimation approaches.

Conclusions

Our review on effectiveness and safety analyses the studies that have specifically compared the association glimepiride/metformin with iDPP4/metformin, both in second line pharmacotherapy of DM2 because of the distinguishing characteristics of this sulfonylurea, which, perhaps because of their most recent appearance, are frequently masked by the class effect of the group as a whole.

The association of iDPP4 or sulfonylureas with metformin has generally been compared on a non-inferiority basis and greater tolerance of the first. We believe the results from non-inferiority studies which apply margins above those considered acceptable by EMA must be interpreted with caution. In any case, the response to all effectiveness variables related to antihyperglycaemic treatment effect such as: reduction in HbA1c, proportion of patients who achieve HbA1c $< 7\%$, and decrease in FPG, are consistently favourable to glimepiride. These results are complementary to those of treatment discontinuation because of the lack

of effectiveness and start of rescue treatment with other drugs, which at the same time are also favourable to the association glimepiride/metformin.

The differences in weight variation, in both directions, experienced in the treatments with each of the agents studied is 2 kg, very far from magnitudes found in the literature to show clinical relevance, thus we do not consider these differences to be clinically important.

The analysis of adverse effects with a frequency of ≥ 5%, do not show differences between groups, except for mild or moderate hypoglycaemia, more common in those treated with glimepiride. In both treatment groups, general adverse effects are observed in more than 70% of patients treated: 71.9% with iDPP4 and 78.3% with glimepiride. This difference is reduced when analysing the serious adverse effects, which only occur in two patients more out of every 100 patients treated with glimepiride. Severe hypoglycaemia, despite being greater in the group treated with glimepiride, only occurs in 1.2% of patients with this treatment. The clinical relevance of the overall effects can be seen in the number of patients who had to discontinue treatment because of the adverse effects, which only shows a difference between treatments of two patients for every one hundred: 7.3% with glimepiride compared to 5.2% with iDPP4.

The fact that no severe hypoglycaemic episode was observed in over 98% patients offers a broad margin for use of glimepiride /metformin which, as occurs with any type of treatment, does not mean that treatment should not be checked and revised in those patients who show intolerance.

In summary, there is a greater effectiveness in the glimepiride/metformin association which should not be undermined by slight differences in adverse effects. The glimepiride/metformin association, both because of effectiveness and safety as well as cost, could be the preferential treatment for most DM2 patients who have not managed to achieve an adequate control with monotherapy, and it offers a potential advantage in refractory hyperglycaemic populations, tolerant to treatment.

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Author contributions

J.M. Amate, was involved in the concept, design, data interpretation, the resolution of differences between reviewers and coordination of the study. T. López-Cuadrado, was involved in the quality assessment and review of articles, data extraction and statistical analysis. N. Almendro-Motos, was involved in the bibliographic search, quality assessment of articles, review of articles and data extraction. C. Bouza, was involved in the study design, the resolution of differences between reviewers and data interpretation. Z. Saz-Parkinson, was involved in the critical review of the text and its translation into English. R. Rivas-Ruiz and J. Gonzalez-Canudas were involved in the study design. All authors participated in the drafting of this manuscript and its final approval.

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