Risk of hypoglycaemia related to the addition of DPP-4 inhibitors to sulphonylureas: systematic review and meta-analysis

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Medline Search terms

((DPP-4[All Fields] AND ("inhibitors and inhibitors"[Subheading] OR ("inhibitors"[All Fields] AND "inhibitors"[All Fields]) OR "inhibitors and inhibitors"[All Fields] OR "inhibitors"[All Fields])) OR ("sitagliptin"[Supplementary Concept] OR "sitagliptin"[All Fields]) OR ("vildagliptin"[Supplementary Concept] OR "vildagliptin"[All Fields]) OR ("saxagliptin"[Supplementary Concept] OR "saxagliptin"[All Fields]) OR ("alogliptin"[Supplementary Concept] OR "alogliptin"[All Fields]) OR ("Linagliptin"[Supplementary Concept] OR "Linagliptin"[All Fields] OR "linagliptin"[All Fields])) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomised clinical trials"[All Fields] OR "randomized clinical trials"[All Fields]

Studies excluded after full-text review: reasons for exclusion

Forty-seven studies were excluded after the full text analysis: nine because included ≤50 patients in DPP4-i + SU group [1-9], seven because they were not RCTs,[10-16] one because there was no placebo group,[17] five because the patients were not treated with DPP4-i + SU,[18-22] three because they were extension studies,[23-25] two because they were sub-analyses or post-hoc analyses,[26, 27] 15 because they were pooled analyses without new data,[28-42] two because they were not assessable,[43, 44] and three because they did not report data on hypoglycaemia in patients treated with DPP4-i + SU and, after having e-mailed authors or study contacts, we did not received the requested data.[45-47]

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eTable 1. Low and full daily dose of DPP4 inhibitors.

	Low daily dose, mg	Full daily dose, mg
Alogliptin	6·5 or 12·5	25
Linagliptin	N/A	5
Saxagliptin	2·5	5
Sitagliptin	N/A	100
Vildagliptin	50	100

N/A: not applicable

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eTable 2. Trial data used to calculate the Assumed Control Risk (ACR) of hypoglycaemia; from Hemmingsen *et al.*[48]

First author	Year	Patients with hypoglycaemia, n	Total patients, n	Treatment duration, months
Feinbock *et al.*[49]	2003	20	111	6
Hermann *et al.*[50]	1991	12	34	6
Rosenthal & Mauersberger [51]	2002	0	37	6
Segal *et al.*[52]	1997	6	69	6
Shihara *et al.*[53]	2011	7	95	6
Spengler *et al.*[54]	1992	0	36	6
Tosi *et al.*[55]	2003	2	22	6
DeFronzo *et al.*[56]	1995	6	209	7
Charbonnel *et al.*[57]	2005	63	626	12
Hanefeld *et al.* [58]	2011	25	207	12
Kaku *et al.*[59]	2011	55	139	12
Nakamura *et al.*[60]	2006	6	18	12
Nathan *et al.*[61]	1988	0	16	9
St John Sutton *et al.*[62]	2002	7	99	12
Tan *et al.*[63]	2004	32	109	12
van de Laar *et al.*[64]	2004	1	50	7
ADOPT Study [65]	2006	557	1447	48
Alvarsson *et al.* [66]	2010	7	26	72
APPROACH Study [67]	2010	96	339	19
Birkeland *et al.*[68]	1994	0	30	15
Birkeland *et al.*[69]	2002	0	18	42
Derosa *et al.*[70]	2004	0	81	14
Foley & Sreenan [71]	2009	14	546	24
Jain *et al.*[72]	2006	61	251	13
LEAD-3 *et al.*[73]	2006	60	248	45
UKPDS 33 Study[74]	1998	177	1234	120
UKPDS 34 Study [75]	1998	52	277	128

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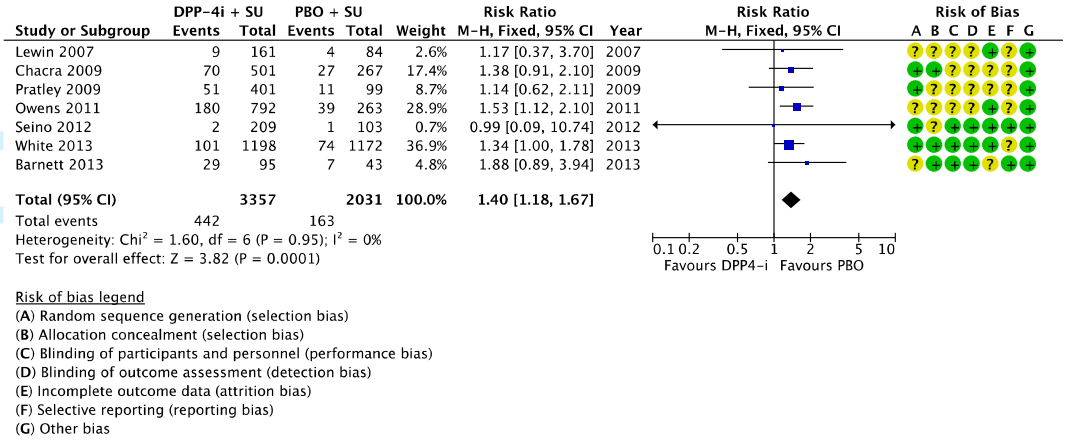

eFigure 1. Forest plot of the risk of hypoglycaemia in patients treated with DPP4-i + SU in comparison with those treated with placebo + SU and included in studies with low or unknown risk of bias. Risk ratios (RR) calculated for individual randomized controlled trials (RCTs) with 95% confidence intervals (CI) are presented. Arrows indicate the CI exceeding the limits of the graph. Pooled RR is also presented (black diamond). Statistical heterogeneity among studies was evaluated with the Q statistic ($p<0.10$ considered significant), and the proportion of total variation contributed by between-study variance was estimated by using the I^2 index. The risk of bias for each included study is presented as different coloured circles: green represents a low risk of bias, and yellow an unclear risk of bias.

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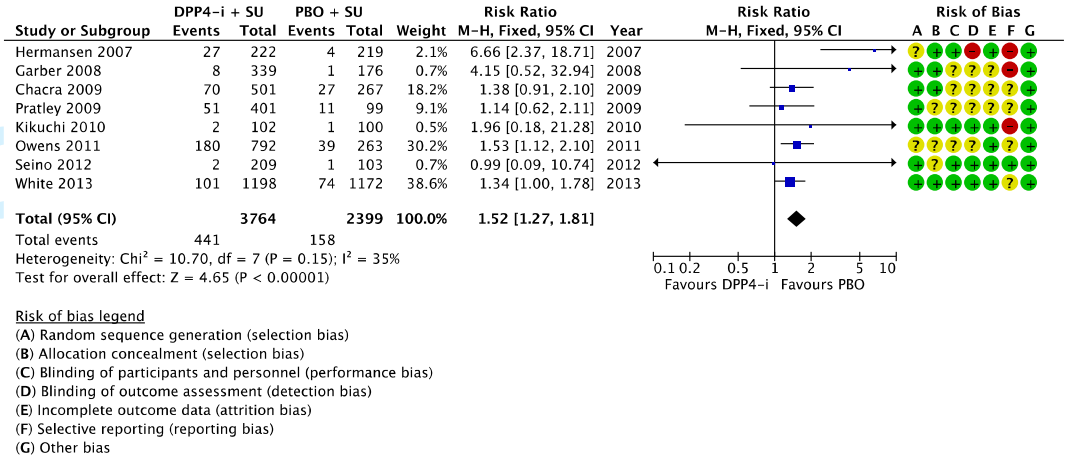

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

eFigure 2. Forest plot of the risk of hypoglycaemia in patients treated with DPP4-i + SU in comparison with those treated with placebo + SU including RCTs with a well-balanced sex ratio among groups. Risk ratios (RR) calculated for individual randomised controlled trials (RCTs) with 95% confidence intervals (CI) are presented. Arrows indicate the CI exceeding the limits of the graph. Pooled RR is also presented (black diamond). Statistical heterogeneity among studies was evaluated with the Q statistic ($p<0.10$ considered significant), and the proportion of total variation contributed by between-study variance was estimated by using the I^2 index. The risk of bias for each included study is presented as different coloured circles: green represents a low risk of bias, red a high risk of bias, and yellow an unclear risk of bias.

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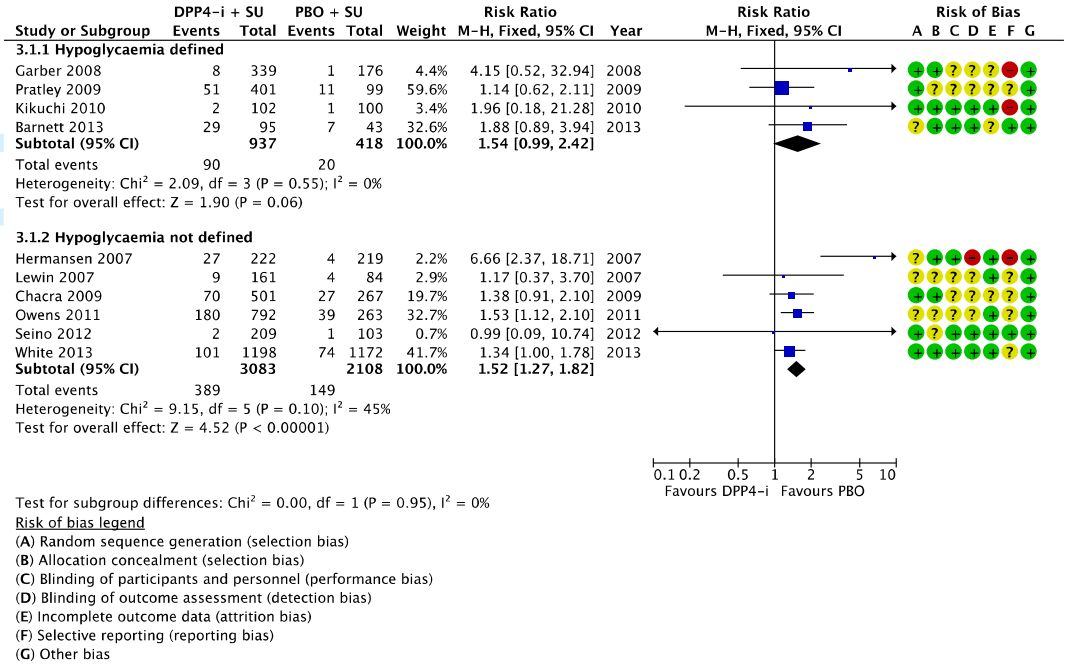

eFigure 3. Forest plot of the risk of hypoglycaemia in patients treated with DPP4-i + SU in comparison with those treated with placebo + SU according to the presence of a definition of hypoglycaemia in the included RCTs. Risk ratios (RR) calculated for individual randomized controlled trials (RCTs) with 95% confidence intervals (CI) are presented. Arrows indicate the CI exceeding the limits of the graph. Pooled RR is also presented (black diamond). Statistical heterogeneity among studies was evaluated with the Q statistic ($p<0.10$ considered significant), and the proportion of total variation contributed by between-study variance was estimated by using the I^2 index. The risk of bias for each study included is presented as different coloured circles: green represents a low risk of bias, red a high risk of bias, and yellow an unclear risk of bias.

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Risk of hypoglycaemia related to the addition of DPP-4 inhibitors to sulphonylureas: systematic review and meta-analysis

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ABSTRACT

Objective: Quantify the risk of hypoglycaemia associated with the concomitant use of dipeptidyl peptidase-4 inhibitors (DPP4-i) and sulphonylureas (SU) in comparison with placebo (PBO) and SU.

Design: Systematic review and meta-analysis. The Cochrane Collaboration tool for assessing risk of bias in randomized trials was used for quality assessment. The Risk Ratio (RR) of hypoglycaemia with 95% confidence intervals (95%CI) was computed for each study and then pooled. The Number Needed to Treat for one person to be Harmed, NNT(H), was estimated.

Data source: Medline, ISI Web of Science, SCOPUS, Cochrane Central Register of Controlled Trials, and clinicaltrial.gov were searched without any language restriction.

Eligibility criteria for selecting studies: PBO-controlled randomized trials with at least 50 Type II diabetic patients treated with DPP4-i + SU.

Results: The 10 studies included represented a total of 6,546 patients (4,020 received DPP4-i + SU, 2,526 PBO + SU). The RR of hypoglycaemia was 1.52 (95% confidence interval 1.29 to 1.80) with a corresponding NNT(H) of 10 (6 to 17). The subgroup analysis by dose did not reveal any difference between full and low DPP4-i doses: the RR related to full dose DPP4-i was 1.66 (1.34 to 2.06), with a corresponding NNT(H) of 8 (5 to 15). The increased RR related to low dose DPP4-i did not reach significance (RR 1.33; 0.92 to 1.94).

Conclusions: Addition of DPP4-i to SU in patients with type II diabetes would lead to about a 50% increase in risk of hypoglycaemia and to a supplementary case of this for every 10 patients treated. This highlights the need to respect recommendations for a decrease in SU dose when initiating DPP4-i and to assess the effectiveness of this risk minimization strategy.

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What this paper adds

What is already known on this subject

Hypoglycaemia is a serious event that could be related to increased morbidity and mortality in Type II diabetic patients. The risk of hypoglycaemia is known to increase when DPP4 inhibitors are used concomitantly with sulphonylureas. However, the magnitude of this risk has not yet been measured.

What this study adds

We found about a 50% increase in risk of hypoglycaemia and a supplementary case for every 10 patients treated with DPP4 inhibitors and sulphonylureas in comparison with patients treated only with SU. Thus, the recommendations for a decrease in SU dose when initiating DPP4 inhibitors must be followed, even though the effectiveness of this risk minimization strategy has not yet been assessed.

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INTRODUCTION

Hypoglycaemia is a potentially life-threatening event associated with an increased risk of hospital admission,[1] cardiovascular disease and mortality.[2, 3] This is illustrated in the ACCORD (Action to Control Cardiovascular Disease in Diabetes) trial that evaluated intensive glucose lowering in Type II diabetic patients in whom a 2.5-fold increase in hypoglycaemic events was found. That trial was prematurely stopped for reasons of increased mortality possibly related to the unfavourable effect of hypoglycaemia in susceptible patients, such as those with underlying coronary diseases.[4, 5]

Hypoglycaemia has emerged as a leading complication of diabetes in older adults with a longer history of disease. It is the second cause of hospitalisation in type II diabetic patients,[6] it can cause falls and fractures in the elderly,[7] and it accounts for 20%-25% of hospital admissions for adverse drug reactions.[1, 8] More generally, hypoglycaemia has a negative impact on patient quality of life,[9, 10] and, in the long-term, may impair the maintenance of euglycaemia and the full benefit of treatments.[11] Moreover, the importance of mild-to-moderate (iatrogenic) hypoglycaemia should not be neglected as this may lead to hypoglycaemia unawareness (through altered adrenergic response to hypoglycaemia).[12] This may compromise behavioural defences (hunger resulting in carbohydrate ingestion), and increase the risk of recurrent episodes and severe hypoglycaemia.[13, 14] Therefore, hypoglycaemia is a serious adverse event that must be considered when studying the safety of glucose-lowering drugs.

Dipeptidyl peptidase 4-inhibitors (DPP4-i) are a recently marketed class of oral anti-diabetic drugs indicated as a second line treatment in patients with Type II diabetes mellitus not adequately responsive or intolerant to metformin, or in whom treatment with other glucose-lowering drugs (such as sulphonylureas, SU, or thiazolidinediones) is insufficient to achieve glycaemic control. The mechanisms of action of these anti-diabetic drugs are different. For

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instance, target tissue sensitivity to insulin is increased by thiazolidinediones,[15] hepatic gluconeogenesis is suppressed by metformin,[16] and insulin secretion is increased indirectly by DPP4-i (via the inhibition of incretin catabolism[17]) and directly by SU.[18, 19]

A number of randomised clinical trials (RCTs) have studied DPP4-i both in monotherapy and, more frequently, in patients treated with other glucose-lowering drugs, metformin in particular, but also thiazolidinediones and SU.[20] When used in monotherapy, DPP4-i has shown an incidence of hypoglycaemia comparable to that related to placebo or metformin (around 5%),[21, 22] and a number of RCTs indicate that this risk is not increased when DPP4-i are used in patients treated with metformin or thiazolidinediones, thus confirming their acceptable safety profile.[20, 23]

Conversely, when DPP4-i are used in association with SU, an increased frequency of hypoglycaemia has been noted.[24, 25] This could be related to the higher frequency of hypoglycaemia among SU-treated patients (about 20% and increases as a function of treatment duration)[26] that is further increased when patients are treated by a second drug acting on insulin secretion. While the summaries of the product characteristics (SmPCs) of DPP4-i acknowledge the increased risk of hypoglycaemia due to this association,[27-31] this risk remains insufficiently assessed and has yet to be quantified. Thus, a meta-analysis to quantify the risk of hypoglycaemia associated with the use of DPP4-i and SU in patients with Type II diabetes mellitus was performed.

METHODS

Eligibility criteria

Clinical trials eligible for this meta-analysis were those: i) that studied the effect of adding one DPP4-i to SU, with or without other oral antidiabetic drug(s), in Type II diabetics; ii) that studied one DPP4-i used at daily doses approved in clinical practice, namely alogliptin (trade

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name Nesina® in the US, and Vipidia® in Europe), linagliptin (trade name Tradjenta® or Trajenta®), saxagliptin (trade names Onlgyza®, or Kombiglyze® when in fixed combination with metformin), sitagliptin (Januvia®, Ristaben®, Tesavel®, Xelevia®, and Efficib®, or Janumet®, Ristfor® and Velmetia® when in fixed combination with metformin), and vildagliptin (Jalra®, Xiliarx®, Galvus®, and Eucreas®, or Icandra® and Zomarist® when in fixed combination with metformin); iii) that were randomized; iv) that were placebo-controlled; v) that included at least 50 patients treated with DPP4-i. Reports concerning RCT extension phases were not eligible.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Search strategy

Medline, ISI Web of Science, SCOPUS and Cochrane Central Register of Controlled Trials databases were searched on 15 October 2013 using keywords related to *DPP-4 inhibitors* and *randomised controlled trials*. The detailed list of keywords used to search the Medline database is provided in the Supplement. In addition, articles in the "Related citations in PubMed" were screened and a snowballing procedure was conducted to examine the references cited in systematic reviews and meta-analyses retrieved through the systematic search. *Clinicaltrials.gov* was also periodically investigated in order to identify and include hitherto unpublished but eligible RCTs. The last search in *clinicaltrials.gov* was performed in

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November 2014. No time or language restriction was applied to the searches. EndNote X6 for Macintosh (Thomson Reuters) was used to compile the bibliography.

Study selection

Two authors (FS and AP) independently reviewed and screened the title and abstract of potentially relevant RCTs and determined final eligibility through examination of full texts. Disagreements were resolved through discussion. Each eligible RCT was checked for the presence of the number of patients treated with DPP4-i + SU, with PBO + SU, and for the number of patients with at least one episode of hypoglycaemia in each treatment group. If part of these data were unavailable in the full text, missing information was requested by email to the study authors or study contacts.

Data extraction

Two authors (FS and AP) independently extracted the following information: i) methods: study design, study duration, and allowed use of other glucose-lowering drugs; ii) participants: age, gender, country, setting, and baseline mean glycated haemoglobin A_{1C} (HbA_{1c}); iii) intervention: DPP4-i and SU international non-proprietary names, daily doses, and number of treated patients; iv) hypoglycaemia: definition of hypoglycaemia used in the study. Disagreements were resolved through discussion and/or revision of the full text.

Quality assessment and evidence quality

Study quality assessment was performed using the Cochrane Collaboration tool for assessing risk of bias in randomized trials through examination of the full text or the original study protocol (as published or reported in *clinicaltrial.gov*) of the included studies.[32] The quality assessment considered the following items: i) random sequence generation; ii) allocation

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concealment; iii) blinding of participants, personnel, and outcome assessors; iv) incomplete outcome data; v) selective outcome reporting; vi) other potential biases. The risk of bias for each of these items was assessed as high, low or unknown. The GRADE framework was used to determine the strength of evidence of the meta-analysis.[33] This approach is used to contextualize or justify recommendations; it grades the quality of evidence resulting from a meta-analysis from very low to high, which corresponds to how likely further research might alter conclusions drawn from the current evidence. "High quality" suggests that it is very unlikely for conclusions about effect estimates to change, whereas "very low quality" means very likely for conclusions about effect estimates to change.[34]

The study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (see research checklist supplement).[35]

Statistical analysis

The risk of hypoglycaemia in patients treated with DPP4-i + SU was estimated in comparison with that in patients treated with PBO + SU. All studies meeting the inclusion criteria were included in the quantitative analysis, irrespective of their quality.[32]

The risk ratio (RR) of hypoglycaemia and its 95% confidence of intervals (95%CI) were computed for each study. The pooled RR was computed using fixed-effect models (Mantel-Haenszel method)[36] or, in the event of significant heterogeneity between estimates, using random-effect models.[37] Mantel-Haenszel method was used as it has been shown to have better statistical properties than inverse variance methods when included studies report few events [38], which is the case in a meta-analysis investigating the risk of hypoglycaemia in RCTs investigating primarily the efficacy of glucose-lowering drugs. Statistical heterogeneity among studies was evaluated using the Q-statistic ($p<0.10$ considered significant), and the

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proportion of total variation contributed by between-study variance was estimated using the I^2 index.[39] All P values were two-sided.

The primary analysis concerned all studies meeting the inclusion criteria; secondary analyses were performed classifying the DPP4-i doses into full and low daily dose (as mentioned in the corresponding SmPC, the latter are mostly recommended in patients with renal impairment; see eTable 1 in Supplement), and according to the presence of a clear definition of hypoglycaemia. The forest plot of each analysis presents the subgroups which were compared using the Cochrane Q test and the I_2 index.[38] Moreover, sensitivity analyses were conducted by excluding studies with a high risk of bias (i.e. at least one item), studies allowing the use of insulin, or studies for which one or more patients characteristics were imbalanced among groups.

Publication bias was evaluated by using a funnel plot and Egger's regression test ($p<0.05$ considered significant).[40] The number of patients needed to be treated to observe a harmful outcome (Number Needed to Treat for one person to be Harmed, NNT(H)) was estimated according to the Cochrane recommendations.[41] The Assumed Control Risk (ACR) of hypoglycaemia in SU-treated patients was calculated from a meta-analysis reported by Hemmingsen *et al.* that included 27 clinical trials from which the incidence of hypoglycaemia was calculated.[26] On the assumption that the prevalence of hypoglycaemia is related to the length of follow-up, different follow-up scenarios were created: any duration (ACR 19.9%, 23 studies), ≤6 months (ACR 11.6%, 7 studies), from 6.1 to 12 months (ACR: 13.3%, 9 studies), more than 12 months (ACR 22.8%, 11 studies) (see eTable 2 in the Supplement for study details).

The analyses were conducted with Review Manager software (RevMan version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration) and R software (version 2.15.3).

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All relevant aspects related to search strategy, study selection, data extraction and quality assessment, and data analysis were specified in a synopsis protocol detailing the meta-analysis objective and context, and the principles and modalities of the literature search and the data analysis were developed.

RESULTS

Study selection

The literature search identified 2,379 records from the literature databases used, 687 of which were duplicates and were thus removed. Eleven records were retrieved through other sources. Thus, the title and abstract of 1,708 individual study records were assessed, 1,650 of which were found to be irrelevant and were excluded. The remaining 57 records underwent full text examination (results detailed in the Supplement); 10 were finally included in this meta-analysis (Figure 1).[24, 42-50]

Study characteristics

The 10 selected RCTs included a total of 6,456 patients of whom 4,020 received DPP4-i + SU, and 2,526 PBO + SU. All studies were randomized and used double-blind procedures. The study reported by Barnett *et al.* included only patients aged ≥70 years.[24] The planned follow-up of the included studies ranged from 12 to 76 weeks. The associated SU varied across the selected RCTs (Table 1). Drug therapy also included metformin in four RCTs.[24, 44, 47, 50] Use of insulin was allowed in two RCTs.[24, 50] Baseline key patient characteristics (namely mean glycated haemoglobin A_{1C}, mean age, and gender) were well balanced among the patients included in each group of included RCTs, with the exception of two studies[24, 46] in which there was a notable difference in sex ratio between the groups (Table 1).

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Three RCTs studied linagliptin 5 mg/day for a total of 1,038 patients.[24, 46, 47] Vildagliptin 100 mg/day was studied in two RCTs,[43, 45] and vildagliptin 50 mg/day in one[43] for a total of 271 patients with 100 mg/day, and 170 with 50 mg/day. Alogliptin was studied once at 12.5 mg/day and once at 25 mg/day[48, 49] for a total of 308 patients with 12.5 mg/day and 302 with 25 mg/day. White *et al.* studied alogliptin at different doses (from 6.5 mg/day to 25 mg/day) in 1,198 patients receiving SU.[50] Saxagliptin (248 patients with 2.5 mg/day, and 253 with 5 mg/day)[42] and sitagliptin 100 mg/day (222 patients)[44] were each studied once. Overall, a total of 2,526 patients receiving PBO + SU were identified in the included RCTs (Table 1).

Six of the ten included RCTs did not clearly report the definition of hypoglycaemia (Table 1).[42, 44, 46, 47, 49, 50] There was a high risk of reporting bias in three of the included studies.[43-45] One RCT also presented a high risk of detection bias (Figure 2).[44]

Overall, 4,020 patients received DPP4-i (2,096 at full dose, 726 at low dose, and 1,198 at undefined dose) + SU, of whom 479 patients developed hypoglycaemia (311 at full dose, 67 at low dose, and 101 at undefined dose) corresponding to an absolute risk of 11.9%; 2,526 received PBO + SU, of whom 169 developed hypoglycaemia, corresponding to an absolute risk of 6.7%.

Meta-analysis

The RR of hypoglycaemia for DPP4-i any dose + SU versus PBO + SU was 1.52 (95%CI 1.29 to 1.80), with no evidence of heterogeneity across RCTs ($Q = 11.2$, $p = 0.26$, $I^2 = 20\%$; Figure 3). For any DPP4-i +SU duration of use, the corresponding NNT(H) was 10 (6 to 17); it was 17 (11 to 30) for a treatment duration $\leq$6 months, 15 (9 to 26) for 6.1 to 12 months, and 8 (5 to 15) for a treatment duration longer than one year.

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The pooled RR did not markedly change when RCTs with a high risk of detection bias and reporting bias (1.40; 1.18 to 1.67; eFigure 1 in the Supplement), or when the RCTs which allowed the use of insulin (1.61; 1.30 to 2.00), were excluded from the analysis. The RR was similar to that of the principal analysis when RCTs in which a notable imbalance in sex ratio were excluded (1.52; 1.27 to 1.81; Q = 10.70, p = 0.15; I^2 = 35%; eFigure 2 in the supplement). The pooled RR was also similar for RCTs in which a definition of hypoglycaemia was reported (1.54; 0.99 to 2.42; Q = 2.1, p = 0.5, I^2 = 0%), and in those in which a definition was not reported (1.52; 1.27 to 1.82; Q = 9.1, p = 0.10, I^2 = 45%), without any evidence of heterogeneity between these two groups (Q = 0.0, p = 0.95, I^2 = 0%; eFigure 3 in the supplement).

According to the dose of DPP4-i evaluated, the subgroup analysis showed no difference between low and full DPP4-i dose with regard to the risk of hypoglycaemia (Q = 0.99, p = 0.32, I^2 = 0%; Figure 4). The risk remained significantly increased for DPP4-i full dose (1.66; 1.34 to 2.06) but was not significantly increased for DPP4-i low doses (1.33; 0.92 to 1.94; Figure 5). For DPP4-i full dose+SU, the NNT(H) was 8 (5 to 15) for any treatment duration; it was 13 (8 to 25) for a treatment duration ≤6 months, 11 (7 to 22) for a treatment duration between 6.1 to 12 months, and 7 (4 to 13) for a treatment duration longer than one year.

Visual inspection of the funnel plot did not show any clear evidence of publication bias (Figure 5), and the Egger test did not find any asymmetry (z=1.3; p=0.2). The strength of evidence of this meta-analysis was evaluated as high with regards to the GRADE framework (Table 2).

DISCUSSION

Principal findings

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This meta-analysis found about a 50% increase in the risk of hypoglycaemia when DPP4-i and SU were associated in Type II diabetic patients, leading to one supplementary case of hypoglycaemia for every 10 treated patients. This risk was confirmed for full doses of DPP4-i, while it could not be excluded for lower doses.

DPP4-i act indirectly on insulin levels by enforcing the incretin effect, which is a response to high oral intake of carbohydrates and fatty acids.[17] Such drugs should therefore act on glycaemia only in response to such intakes, thereby protecting patients from hypoglycaemia. However, in patients treated with SU, insulin secretion is already stimulated independently of glycaemia and the addition of a reinforced incretin effect on insulin levels leads to an increase in the risk of hypoglycaemia. Given the frequency of this event in Type II diabetic patients treated with SU, the risk associated with the addition of DPP4-i would lead to a huge number of cases of induced hypoglycaemia, some of which could be severe.[51] The present meta-analysis did not allow investigation of the threshold of dose combination (DPP4-i + SU) associated with an increased risk of hypoglycaemia; an individual patient meta-analysis could be helpful in this regard.

The risk of hypoglycaemia related to the addition of a DPP4-i to SU is acknowledged in the SmPCs for DPP4-i; most recommend using full-dose DPP4-i but a reduced SU dose in patients taking such combinations, although the magnitude of reduction is not stated.[27-31] Currently, to what extent this recommendation would lower the number of excess cases of induced hypoglycaemia is unknown. It is also of note that the suggested individual patient meta-analysis would not fill this knowledge gap as the effect of SU dose reduction has not been investigated in trials studying DPP4-i.

For low doses of DPP4-i (half the full dose when applicable), the increase in hypoglycaemia risk was not significant. However, the existence of this risk cannot be fully ruled out by the present results and a larger sample would be required to increase the precision of the

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estimates. Furthermore, although the point estimate was lower (RR 1.33 vs. 1.66 for full-doses), which suggests a potential dose-effect, no heterogeneity was found between low and full doses of DPP4-i, yet this could result from a lack of power in the heterogeneity test (low-dose group was half the size of the high-dose group).

Strengths and limitations of study

The present analysis has important strengths. Firstly, it is based on a large sample of patients; over 4,000 treated with a combination of DPP4-i and SU, and over 2,500 treated with PBO and SU. Secondly, the overall quality of the included studies seems high according to the Cochrane Collaboration tool for risk of bias assessment, which was confirmed by the GRADE framework evaluation of the meta-analysis that considers that the strength of evidence provided is high. The present meta-analysis used data concerning all currently marketed DPP4-i (alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin), and results were consistent within studies with no heterogeneity being found among estimates. Thirdly, there was no evidence of publication bias; the funnel plot was balanced and the Egger test was not significant.

Nevertheless, the meta-analysis does have certain limitations. Firstly, certain studies that presented a high risk for detection and reporting bias were included in the main analysis,[43-45] but exclusion of these studies did not change the estimates significantly. Secondly, three studies could not be included as data were not available for the risk of hypoglycaemia in patients receiving SU.[52-54] However, in view of the GRADE framework, including results from these studies would be unlikely to change the results significantly owing to the size of the present meta-analysis, the high number of hypoglycaemia cases, and the confidence intervals of the pooled RR that clearly do not cross the line of no effect.[33] The absence of heterogeneity in estimates found from the 10 included studies further supports this hypothesis.

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Thirdly, the results of this meta-analysis are dominated by the results of three studies that account for more than 80% of the pooled results of the principal analysis;[42, 47, 50] a sensitivity analysis without these studies did not substantially change the results of the meta-analysis (data not shown). Fourthly, the definition of hypoglycaemia varied among the included RCTs and was not reported in five. Other authors did not perform a meta-analysis on hypoglycaemia risk on the basis of this lack of homogeneity in its definition across the RCTs;[20] nevertheless, this could be considered as a minor limitation, as in the present analysis the risk did not differ between RCTs with or without a clear definition of hypoglycaemia. The incidence of hypoglycaemia also differed among studies, mainly because of different durations of follow-up. However, this did not have any impact on the estimation of the pooled risk (no statistical heterogeneity was found) nor on the NNT(H) calculation, which was based on an external Assumed Control Risk of hypoglycaemia retrieved from 27 clinical studies included in a meta-analysis of the Cochrane library.[26]

Clinical importance

It is important to underline that hypoglycaemia is the most frequent adverse reaction related to anti-diabetic treatments and that, even when not directly life-threatening, it is associated with an increased risk of all-cause mortality, cardiovascular disease, and cardiovascular mortality and hospital admission.[2, 3, 6] In addition, it should not be neglected that hypoglycaemia and its related symptoms (e.g. nervousness, sweating, trembling, weakness, palpitations) impact negatively on patient quality of life and disrupt many daily activities such as driving, work performance and leisure activities.[9, 10] More importantly, mild-to-moderate iatrogenic hypoglycaemia can decrease the usual adrenergic response to hypoglycaemia.[12] This may cause hypoglycaemia unawareness and compromise behavioural defences (hunger resulting in sugar ingestion), which in turn can lead to severe hypoglycaemia.[13, 14] It is thus an

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important to lower the risk of mild-to-moderate hypoglycaemia, which remains a serious adverse event. Adequate information regarding the risk of hypoglycaemia, whatever its severity, should thus be considered of primary importance for patients and all health professionals involved in the management of diabetic patients. Reaching good glycated haemoglobin levels should not be at the expense of hypoglycaemic events, which could outweigh the benefit of preventing risks associated with elevated blood glucose concentrations. Thus, the risk demonstrated herein for all-type hypoglycaemia should not be minimized by considering that only severe episodes would be of clinical concern.

Conclusions

In conclusion, this meta-analysis found about a 50% increase in the risk of hypoglycaemia associated with the addition of DPP4-i to SU in patients with type II diabetes. For this adverse event commonly experienced by treated diabetic patients, this would lead to the occurrence of one supplementary hypoglycaemic event in every 10 treated patients. This potentially represents a huge number of attributable cases worldwide. These results clearly highlight the need to respect existing recommendations for SU dose reduction when initiating a DPP4-i treatment, and the urgency to determine the efficacy of this measure in minimizing the risk of hypoglycaemia.

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The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Francesco Salvo (corresponding author) and Antoine Pariente (manuscript's guarantor) affirm that the manuscript is an honest, accurate, and transparent, and that no important aspects of the study have been omitted.

Authors' contributions

FS: conception and design; acquisition, analysis and interpretation of data; drafting the article and revising it critically for important intellectual content; final approval of the version to be published. FS gives 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.

NM: conception and design; analysis and interpretation of data; revising the article critically for important intellectual content; final approval of the version to be published. NM gives 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.

MA: analysis and interpretation of data; revising the article critically for important intellectual content; final approval of the version to be published. MA gives agreement to be accountable

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for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

PR: analysis and interpretation of data; revising the article critically for important intellectual content; final approval of the version to be published. PR agrees to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ER: conception and design; interpretation of data; revising the article critically for important intellectual content; final approval of the version to be published. ER agrees to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FDP: conception and design; interpretation of data; revising the article critically for important intellectual content; final approval of the version to be published. FDP agrees to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

BB: conception and design; analysis and interpretation of data; revising the article critically for important intellectual content; final approval of the version to be published. BB agrees to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

AP conception and design; acquisition and interpretation of data; drafting the article and revising it critically for important intellectual content; investigating accuracy and integrity of any part of the work; final approval of the version to be published. AP agrees to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AP is the guarantor.

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Declaration of interests

The corresponding author ensures that the manuscript is complete and that the conflict of interest disclosures are accurate, up-to-date, and consistent with the information provided in each author's ICMJE Form for Disclosure of Potential Conflicts of Interest.

All authors have read and understood BMJ policy on declaration of interests; all authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work. FS, MA, ER, FdP, and BB, and have no with any organisations that might have an interest in the submitted work in the previous three years. NM and PR have had specified relationships on other matters with Novartis and Takeda, which might have an interest in the submitted work. AP has had specified relationships on other matters with Novartis, which might have an interest in the submitted work. BB, NM and AP have had specified relationships on other matters with public regulatory agencies and with health care insurance systems that might have an interest in the submitted work. All authors declare no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

This type of study does not require ethical approval.

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Data sharing

No additional data available.

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Figure legends

Figure 1. Flow diagram of study identification, selection, and inclusion. The search strategy identified 2,379 records of which 687 were duplicates and removed. Fifteen references were retrieved by other sources, thus a total of 1,707 individual titles and abstracts were assessed, leading to the exclusion of 1,650 records. After evaluation of 57 full texts, 13 studies were eligible for this meta-analysis. Data from three studies were not available so 10 studies were included.

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Figure 2. Risk of bias graph. Review authors' judgments for each 'Risk of bias' item presented as percentages across all included studies. The risk of bias of the included studies is presented in different colours: green represents a low risk of bias, red represents a high risk of bias, yellow represents an unclear risk of bias.

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Figure 3. Forest plot of the risk of hypoglycaemia in patients treated with DPP4-i + SU in comparison with those treated with PBO + SU. Risk ratios (RR) calculated for individual randomized controlled trials (RCTs) with 95% confidence intervals (CI) are presented. Arrows indicate the CI exceeding the limits of the graph. Overall RR is also presented (black diamond). An estimate of the weight of each RCT on overall RR is reported as a percentage and graphically (blue square size). Statistical heterogeneity among studies was evaluated with the Q statistic ($p<0.10$ considered significant), and the proportion of total variation contributed by between-study variance was estimated by using the I^2 index. The risk of bias for each study included is presented as different coloured circles: green represents a low risk of bias, red represents a high risk of bias, yellow represents an unclear risk of bias.

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Figure 4. Forest plot of the risk of hypoglycaemia in patients treated with full or low DPP4-i doses + SU in comparison with those treated with PBO + SU. Risk Ratios (RR) calculated for individual randomized controlled trials (RCTs) with 95% confidence interval (CI) are presented. Arrows indicate the CI exceeding the limits of the graph. For each subgroup, an estimate of the weight of each RCT on pooled RRs is reported as a percentage and graphically (black square size). Pooled RRs for low and full doses are also presented (black diamonds). Statistical heterogeneity among studies was evaluated with the Q statistic ($p<0.10$ considered significant), and the proportion of total variation contributed by between-study variance was estimated by using the I^2 index. The risk of bias for each included study is presented as different coloured circles: green represents a low risk of bias, red represents a high risk of bias, yellow represents an unclear risk of bias.

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Figure 5. Funnel plot for publication bias. Scatter plot reporting risk ratio of the studies testing DPP4-i +SU in comparison with those treated with PBO + SU (horizontal axis) against their standard error (vertical axis).

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TABLES

Table 1. Study characteristics

	Study duration, weeks	Intervention, daily dose (n)	Associated SU	Mean HbA_{1c} at baseline, %	Mean age of participants, years	Male, %	Definition of hypoglycaemia
Barnett *et al.*[24]	24	Linagliptin 5 mg (95 pts) or PBO (43 pts)	SU, not specified	DPP4-i: 7.8 PBO: 7.7*	DPP4-i: 75 PBO: 75*	DPP4-i: 72 PBO: 62*	PG of 3.9 mmol/l or less, with or without symptoms
Chacra *et al.*[42]	24	Saxagliptin 2.5 mg (248 pts), saxagliptin 5 mg (253 pts), or PBO (267 pts)	Glyburide	DPP4-i: 8.4-8.5 PBO: 8.4	DPP4-i: 55 PBO: 55	DPP4-i: 45 PBO: 46	Not reported
Garber *et al.*[43]	24	Vildagliptin 50 mg (170 pts) or 100 mg (169 pts), or PBO (176 pts)	Glimepiride	DPP4-i: 8.5-8.6 PBO: 8.5	DPP4-i: 58-59 PBO: 58	DPP4-i: 59 PBO: 58	Symptomatic hypoglycaemia confirmed by self-monitored BG <3.1 mmol/l
Hermansen *et al.*[44]	24	Sitagliptin 100 mg (222 pts) or PBO (219 pts)	Glimepiride	DPP4-i: 8.3 PBO: 8.3	DPP4-i: 56 PBO: 56.5	DPP4-i: 53 PBO: 53	Not reported, but hypoglycaemia is included in the AEs of special interest
Kikuchi *et al.*[45]	12	Vildagliptin 100 mg (102 pts) or PBO (100 pts)	Glimepiride	DPP4-i: 7.8 PBO: 8.0	DPP4-i: 59 PBO: 60	DPP4-i: 73.5 PBO: 69	Symptomatic hypoglycaemia, confirmed by self-monitored BG <3.1 mmol/l
Lewin *et al.*[46]	18	Linagliptin 5 mg (161 pts) or PBO (84 pts)	SU, not specified	DPP4-i: 8.6 PBO: 8.6	DPP4-i: 57 PBO: 56	DPP4-i: 48 PBO: 62	Not reported, but hypoglycaemia were recorded and analyzed separately from other AEs.
Owens *et al.*[47]	24	Linagliptin 5 mg (792 pts) or PBO (263 pts)	SU, not specified	DPP4-i: 8.1 PBO: 8.1	DPP4-i: 58 PBO: 58	DPP4-i: 48 PBO: 47	Not reported
Pratley *et al.* [48]	26	Alogliptin 12.5 mg (203 pts), alogliptin 25 mg (198 pts), or PBO (99 pts)	Glyburide	NR	DPP4-i: 56.5 PBO: 57	DPP4-i: 52 PBO: 51.5	Symptomatic hypoglycaemia with BG <3.3 mmol/l or BG <2.8 mmol/l without symptoms
Seino *et al.*[49]	12	Alogliptin 12.5 mg (105 pts), alogliptin 25 mg (104 pts), or PBO (103 pts)	Glimepiride	DPP4-i: 8.5% PBO: 8.6%	DPP4-i: 60 PBO: 60	DPP4-i: 66 PBO: 69	Not reported
White *et al.*[50]	76**	Alogliptin any doses (1,198), or PBO (1,172 pts)	SU, not specified	DPP4-i: 8.0 PBO: 8.0*	DPP4-i: 61 PBO: 61***	DPP4-i: 68 PBO: 69*	Not reported

HbA_{1c} Glycated hemoglobin A_{1C}; NR: not reported; PBO: placebo; Pts: patients; SU: sulphonylureas; y=years old. PG: Plasma Glucose; mmol/l: millimols/liter BG: Blood Glucose; AEs: adverse events.

* Data refer to overall study population, not only to SU treated patients.

** Median exposure weeks for alogliptin treated patients.

*** Median age (years).

Table 2.Summary of findings according to GRADE framework

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All studies	Placebo	Relative (95% CI)	Absolute (95% CI)		
Hypoglycaemia												
10	randomized trials	not serious [1]	not serious [2]	not serious	not serious [3]	dose response gradient	479/4,020 (11.9%)	169/2,526 (6.7%)	RR 1.52 (1.29 to 1.80)	35 more per 1,000 (from 19 more to 54 more)	⊕⊕⊕⊕ HIGH	CRITICAL [4]

RR – relative risk

1. Only three studies were judged to have a high risk of detection bias. Among them, a high risk of reporting bias was found in one study. Nevertheless, when these studies were excluded from the analysis the result did not change substantially.
2. No heterogeneity among estimates was found.
3. The sample size is large (n=6,526), the number of the events high (648), and the confidence intervals of the pooled RR clearly do not cross the line of no effect (lower bound of 95%CI = 1.29)
4. Hypoglycaemia is the most frequent adverse reaction related to anti-diabetic treatment. It increases the risk of all-cause mortality and cardiovascular events. Symptoms related to hypoglycaemia (e.g. nervousness, sweating, trembling, weakness, palpitations) reduce the quality of life of affected patients.

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Risk of hypoglycaemia related to the addition of DPP-4 inhibitors ~~plus~~to sulphonylureas: systematic review and meta-analysis~~.~~

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ABSTRACT

Objective: Quantify the risk of hypoglycaemia associated with the concomitant use of dipeptidyl peptidase-4 inhibitors (DPP4-i) and sulphonylureas (SU) in comparison with ~~those treated with~~ placebo (PBO) and SU.

Design: Systematic review and meta-analysis. The Cochrane ~~Collaboration's~~Collaboration tool for assessing risk of bias in randomized trials was used for quality assessment. The Risk Ratio (RR) of hypoglycaemia with 95% confidence intervals (95%CI) was computed for each study and ~~the~~then pooled. The ~~number of patients needed to be treated to observe a harmful outcome (~~Number Needed to ~~Harm, NNH)~~Treat for one person to be Harmed, NNT(H), was estimated ~~and presented in forest plot~~.

Data source: Medline, ISI Web of Science, SCOPUS, Cochrane Central Register of Controlled Trials, and clinicaltrial.gov were searched without any language restriction.

Eligibility criteria for selecting studies: PBO-controlled randomized trials with at least 50 Type II diabetic patients treated with DPP4-i + SU.

Results: The ~~ten~~10 studies included represented a total of 6,546 patients (4,020 received DPP4-i + SU, 2,526 PBO + SU). The RR of hypoglycaemia was 1.52 (95% confidence interval 1.29 to 1.80) with a corresponding ~~NNH~~NNT(H) of ~~26.9 (19.5 to 43.3). The~~10 (6 to 17). The subgroup analysis by dose did not reveal any difference between full and low DPP4-i doses: the RR related to full dose DPP4-i was 1.66 (1.34 to 2.06), with a corresponding ~~NNH~~NNT(H) of ~~19.4 (13.98~~ (5 to ~~32.2~~15). The increased RR related to low dose DPP4-i did not reach significance (RR 1.33; 0.92 to 1.94).

Conclusions: ~~Associating~~Addition of DPP4-i ~~with~~to SU in patients with type II diabetes would lead to about a 50% increase in risk of hypoglycaemia and to a supplementary case of this for every ~~27 treated~~10 patients treated. This highlights the need to ~~strictly~~ respect

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recommendations for a decrease in SU dose when initiating DPP4-i, and to urgently assess the effectiveness of this risk minimization strategy.

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What this paper adds

What is already known on this subject

Hypoglycaemia is a serious event that could be related to ~~an~~ increased morbidity and mortality in Type II diabetic patients. ~~It is known the~~ The risk of hypoglycaemia is ~~increased~~known to increase when DPP4 ~~i~~ inhibitors are used concomitantly with ~~SU~~ sulphonylureas. However, ~~its~~the magnitude of this risk has not yet been measured.

What this study adds

~~A~~We found about a 50% ~~of~~ increase in risk of hypoglycaemia and a supplementary case for every ~~27~~10 patients treated with DPP4 ~~i~~ inhibitors and ~~SU~~sulphonylureas in comparison with patients treated only with SU ~~was found~~. Thus, the recommendations for a decrease in SU dose when initiating DPP4 ~~i~~ inhibitors must be followed, even though the effectiveness of this risk minimization strategy has not yet been assessed.

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INTRODUCTION

Hypoglycaemia is a potentially life-threatening event associated with an increased risk of hospital admission,[1] cardiovascular disease~~,~~ and mortality.[2, 3] ~~In~~ This is illustrated in the ACCORD (Action to Control Cardiovascular Disease in Diabetes) trial ~~evaluating~~that evaluated intensive glucose lowering in Type II diabetic patients~~,~~ in whom a 2.5-fold increase in hypoglycaemic events was ~~noted. This~~found. That trial was prematurely stopped for reasons of increased mortality~~,~~ possibly related to the unfavourable effect of hypoglycaemia in susceptible patients, such as those with underlying coronary diseases.[4, 5] ~~Studies conducted within US hospitals found that hypoglycaemia accounted for 20% of hospital admissions attributed to adverse drug reactions,[1] with a median four days of hospital stay.[6]~~

Hypoglycaemia has emerged as a leading complication of diabetes in older adults with a longer history of disease. It is the second cause of hospitalisation in type II diabetic patients,[6] it can cause falls and fractures in the elderly,[7] and it accounts for 20%-25% of hospital admissions for adverse drug reactions.[1, 8] More generally, hypoglycaemia has a negative impact on patient quality of life,[9, 10] and, in the long-term, may impair the maintenance of euglycaemia and the full benefit of treatments.[11] Moreover, the importance of mild-to-moderate (iatrogenic) hypoglycaemia should not be neglected as this may lead to hypoglycaemia unawareness (through altered adrenergic response to hypoglycaemia).[12] This may compromise behavioural defences (hunger resulting in carbohydrate ingestion), and increase the risk of recurrent episodes and severe hypoglycaemia.[13, 14] Therefore, hypoglycaemia is a serious adverse event that must be considered when studying the safety of glucose-lowering drugs.

Dipeptidyl peptidase 4-inhibitors (DPP4-i) are a recently marketed class of oral ~~antidiabetic~~anti-diabetic drugs indicated as a second line treatment in patients with Type II

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diabetes mellitus not adequately responsive or intolerant to metformin, or in whom treatment with other glucose-lowering ~~-~~ drugs (such as sulphonylureas, SU, or thiazolidinediones) is insufficient to achieve glycaemic control. ~~Notably, the~~The mechanisms of action of these ~~hypoglycaemic~~anti-diabetic drugs are different. For instance, target tissue sensitivity to insulin is increased by thiazolidinediones,[~~7~~15] hepatic gluconeogenesis is suppressed by metformin,[~~8~~16] and insulin secretion is increased indirectly by DPP4-i (via the inhibition of incretin catabolism[~~9~~17]) and directly by SU.[~~10, 11~~18, 19]

A number of randomised clinical trials (RCTs) have studied DPP4-i both in monotherapy and, more frequently, in patients treated with other glucose ~~-~~ lowering drugs~~:~~, metformin in particular, but also thiazolidinediones ~~or~~and SU.[~~12] These~~20] When used in monotherapy, DPP4-i has shown an incidence of hypoglycaemia comparable to that related to placebo or metformin (around 5%).[21, 22] and a number of RCTs indicate ~~an acceptable safety profile~~ that this risk is not increased when DPP4-i are used in patients treated with metformin or thiazolidinediones ~~[12, 13]~~, thus confirming their acceptable safety profile.[20, 23] Conversely, when DPP4-i are used in association with SU, an increased frequency of hypoglycaemia ~~was~~has been noted.[~~14, 15] The~~24, 25] This could be related to the higher frequency of hypoglycaemia among SU-treated patients (about 20% and increases as a function of treatment duration)[26] that is further increased when patients are treated by a second drug acting on insulin secretion. While the summaries of the product characteristics (SmPCs) of DPP4-i acknowledge the increased risk of hypoglycaemia due to this association ~~[16-20] however,~~[27-31] this risk remains insufficiently assessed and ~~it was never~~has yet to be quantified. Thus, a meta-analysis to quantify the risk of hypoglycaemia associated with the use of DPP4-i and SU in patients with Type II diabetes mellitus was performed.

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METHODS

Eligibility criteria

~~Placebo (PBO)-controlled RCTs that studied the effect of adding DPP4-i to SU for the management of Type II diabetes mellitus were selected thorough a systematic review. RCTs~~Clinical trials eligible for this meta-analysis were those: i) that ~~were performed in adults with Type-2 diabetes mellitus~~studied the effect of adding one DPP4-i to SU, with or without other oral antidiabetic drug(s), in Type II diabetics; ii) that studied ~~the effect of~~one DPP4-i used at daily doses approved in clinical practice, ~~in addition to SU, with or without other oral antidiabetic drug(s~~namely alogliptin (trade name Nesina® in the US, and Vipidia® in Europe), linagliptin (trade name Tradjenta® or Trajenta®), saxagliptin (trade names Onlgyza®, or Kombiglyze® when in fixed combination with metformin), sitagliptin (Januvia®, Ristaben®, Tesavel®, Xelevia®, and Efficib®, or Janumet®, Ristfor® and Velmetia® when in fixed combination with metformin), and vildagliptin (Jalra®, Xiliarx®, Galvus®, and Eucreas®, or Icandra® and Zomarist® when in fixed combination with metformin); iii) that were randomized; iv) that were placebo-controlled; v) that included at least 50 patients treated with DPP4-i. Reports concerning RCT extension phases were not eligible.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Search strategy

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Medline, ISI Web of Science, SCOPUS, and Cochrane Central Register of Controlled Trials databases were searched in on 15 October 2013 using keywords related to *DPP-4 inhibitors* and *randomised controlled trials*. The detailed list of keywords used to search the Medline database is provided in supplement the Supplement. In addition, articles in the "Related citations in PubMed" were screened, and a snowballing procedure was conducted to examine the references cited in systematic reviews and meta-analyses retrieved through the systematic search. *Clinicaltrials.gov* was also periodically investigated in order to identify and include not yet publishedhitherto unpublished but eligible RCTs. The last search in *clinicaltrials.gov* was performed in November 2014. No time or language restriction was applied to the searches. EndNote X6 for Macintosh (Thomson Reuters) was used to compile the bibliography.

Study selection

Two authors (FS and AP) independently reviewed and screened independently the title and abstract of the potentially relevant RCTs, and performed their determined final eligibility through examination of full- texts. Disagreements were solvedresolved through discussion. Each eligible RCT was checked for the presence of the number of patients treated with DPP4-i + SU, with PBO + SU, and for the number of patients with at least one episode of hypoglycaemia in each treatment group. If part of these data were unavailable in the full-text, missing information was requested by email to the principalstudy authors or study contacts.

Data extraction

Two authors (FS and AP) extracted independently extracted the following information: i) methods: study design, study duration, and allowed use of metformin and dosesother glucose-lowering drugs; ii) participants: age, gender, country, setting, and baseline mean glycated

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haemoglobin A_{1C} (HbA_{1c}); iii) intervention: DPP4-i and SU international non-proprietary names, daily doses, and number of treated patients; iv) hypoglycaemia: definition of hypoglycaemia used in the study~~; v) allowed insulin treatment~~. Disagreements were ~~solved~~resolved through discussion and/or revision of the full-text.

Quality assessment and evidence quality

Study quality assessment was performed using the Cochrane ~~Collaboration's~~Collaboration tool for assessing risk of bias in randomized trials through ~~the~~ examination of the full-text or the original study protocol (as published or reported in *clinicaltrial.gov*) of the included studies.[~~21~~32] The quality assessment considered the following items: i) random sequence generation; ii) allocation concealment; iii) blinding of participants, personnel, and outcome assessors; iv) incomplete outcome data; v) selective outcome reporting; vi) other potential ~~bias~~biases. The risk of bias for each of these items was assessed as high, low~~,~~ or unknown. The GRADE framework was used to determine the strength of evidence of the meta-analysis.[~~22~~33] This approach is used to contextualize or justify recommendations; it grades the quality of evidence resulting from a meta-analysis from very low to high, which corresponds to how likely further research might ~~to~~ alter conclusions drawn from the current evidence. ~~"~~"High ~~quality"~~quality" suggests that it is very unlikely for conclusions about effect estimates to change, whereas ~~"~~" very low ~~quality"~~quality" means very likely for conclusions about effect estimates to change.[~~23~~34]

~~This~~The study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (see research checklist supplement).[~~24~~35]

Statistical analysis

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The risk of hypoglycaemia in patients treated with DPP4-i + SU was estimated in comparison with that in patients treated with ~~placebo~~PBO + SU. All studies meeting the inclusion criteria were included in the quantitative analysis~~ irrespectively~~, irrespective of their quality.[~~21~~32] The risk ratio (RR) of hypoglycaemia and its 95% confidence of intervals (95%CI) were computed for each study. The pooled RR was computed using fixed-effect models (Mantel-Haenszel method)[~~25~~36] or, in ~~case~~the event of significant heterogeneity between estimates, using random-effect models.[~~26~~]37] Mantel-Haenszel method was used as it has been shown to have better statistical properties than inverse variance methods when included studies report few events [38], which is the case in a meta-analysis investigating the risk of hypoglycaemia in RCTs investigating primarily the efficacy of glucose-lowering drugs. Statistical heterogeneity among studies was evaluated using the Q-statistic ($p<0.10$ considered significant), and the proportion of total variation contributed by between-study variance was estimated using the I^2 index.[~~27~~39] All P values were two-sided.

The primary analysis concerned all studies meeting the inclusion criteria; secondary analyses were performed classifying the DPP4-i doses into full and low daily dose (as mentioned in the corresponding SmPC, the latter are mostly recommended in patients with renal impairment; see eTable 1 in ~~supplement),~~Supplement), and according to the presence of a clear definition of hypoglycaemia. The forest plot of each analysis presents the subgroups which were compared using the Cochrane Q test and the I_2 index.[38] Moreover, sensitivity analyses were conducted by excluding studies with a high risk of bias (i.e. at least one item), ~~or~~ studies allowing the use of insulin, or studies for which one or more patients characteristics were imbalanced among groups.

Publication bias was evaluated by using a funnel plot and Egger's regression test.~~[28~~ ($p<0.05$ considered significant).[40] The number of patients needed to be treated to observe a harmful outcome (Number Needed to ~~Harm (NNH)~~Treat for one person to be Harmed, NNT(H)) was

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estimated according to the Cochrane recommendations.[41] The Assumed Control Risk (ACR) of hypoglycaemia in SU-treated patients was calculated ~~for each~~from a meta-analysis reported by Hemmingsen *et al.* that included 27 clinical trials from which the incidence of hypoglycaemia was calculated.[26] On the assumption that the prevalence of hypoglycaemia is related to the length of follow-up, different follow-up scenarios were created: any duration (ACR 19.9%, 23 studies), <6 months (ACR 11.6%, 7 studies), from 6.1 to 12 months (ACR: 13.3%, 9 studies), more than 12 months (ACR 22.8%, 11 studies) (see eTable 2 in the Supplement for study ~~and pooled in a forest plot.[29] The~~ details).

The analyses were conducted ~~using~~with Review Manager software (RevMan version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration) and R software (version 2.15.3).

All relevant aspects related to search strategy, study selection, data extraction and quality assessment, and data analysis were specified in a synopsis protocol ~~specifying~~detailing the meta-analysis objective and context, and the principles and modalities of the literature search and the data analysis ~~was~~were developed.

RESULTS

Study selection

The literature search identified 2,379 records from the literature databases used, 687 of which were duplicates and were thus removed. Eleven records were retrieved through other sources. Thus, the title and abstract of 1,708 individual study records were assessed, 1,650 of which were found to be irrelevant and were excluded. The remaining 57 records underwent full~~-~~text examination (results detailed in the ~~supplement); ten~~Supplement); 10 were finally included in this meta-analysis (Figure 1).[~~14, 30-38~~24, 42-50]

Study characteristics

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The 10 selected RCTs included a total of 6,456 patients~~.~~ of whom 4,020 received DPP4~~-~~i + SU, and 2,526 PBO + SU. All studies were randomized~~.~~ and used double-blind procedures~~.~~ ~~the.~~ The study reported by Barnett *et al.* included only patients aged ≥70 years.[~~14~~24] The planned follow-up of the included studies ranged from 12 to 76 weeks. The associated SU varied across the selected RCTs (Table 1~~); drug~~). Drug therapy also included metformin in four RCTs~~.[14, 32, 35 , 38] use~~.[24, 44, 47, 50] Use of insulin was allowed in two RCTs.[~~14, 38~~24, 50] Baseline key patient characteristics (namely mean ~~(standard deviation)~~ glycated haemoglobin A_{1C} ~~(HbA$_{1c}$) of~~, mean age, and gender) were well balanced among the patients included in ~~these~~each group of included RCTs ~~ranged from 7.8% (0.8) to 8.6% (0.8~~, with the exception of two studies[24, 46] in which there was a notable difference in sex ratio between the groups (Table 1).

Three RCTs studied ~~in~~ linagliptin 5 mg/day~~.~~ for a total of 1,038 patients.[~~14, 34, 35~~24, 46, 47] Vildagliptin 100 mg/day was studied in two RCTs,[~~31, 33~~43, 45] and vildagliptin 50 mg/day in one.[~~31~~43] for a total of 271 patients with 100 mg/day, and 170 with 50 mg/day. Alogliptin was studied once at 12.5 mg/day and once at 25 mg/day.[~~36, 37~~48, 49] for a total of 308 patients with 12.5 mg/day~~.~~ and 302 with 25 mg/day. White *et al.* studied alogliptin at different doses (from 6.5 mg/day to 25 mg/day) in 1,198 patients receiving SU.[~~38~~50] Saxagliptin (248 patients with 2.5 mg/day, and 253 with 5 mg/day)[~~30~~42] and sitagliptin 100 mg/day (222 patients)[~~32~~44] were each studied once. Overall, a total of 2,526 patients receiving PBO + SU were identified in the included RCTs (Table 1).

Six of the ten included RCTs did not clearly report the definition of hypoglycaemia (Table ~~2)~~ [~~30, 32, 34, 35, 37, 38~~1) [42, 44, 46, 47, 49, 50] There was a high risk of reporting bias in three of the included studies.[~~31-33~~] ~~one~~.[43-45] One RCT also presented a high risk of detection bias (Figure 2).[~~32~~44]

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Overall, 4,020 patients received DPP4-i (2,096 at full dose, 726 at low dose, and 1,198 at undefined dose) + SU, of whom 479 patients developed hypoglycaemia (311 at full dose, 67 at low dose, and 101 at undefined dose) corresponding to an absolute risk of 11.9%; 2,526 received PBO + SU, of whom 169 developed hypoglycaemia, corresponding to an absolute risk of 6.7%.

Meta-analysis

The RR of hypoglycaemia for DPP4-i any dose + SU versus PBO + SU was 1.52 (95%CI 1.29 to 1.80), with no evidence of heterogeneity across RCTs (Q = 11.2, p = 0.26, I^2 = 20%; Figure 3). ~~The correspondent NNH~~For any DPP4-i +SU duration of use, the corresponding NNT(H) was 10 (6 to 17); it was 17 (11 to 30) for a treatment duration <6 months, 15 (9 to 26~~9 (19;~~) for 6.1 to 12 months, and 8 (5 to ~~43.3; Figure 4)~~ 15) for a treatment duration longer than one year.

The pooled RR did not markedly change when RCTs with a high risk of detection bias and reporting bias (1.40; 1.18 to 1.67; eFigure 1 in the ~~supplement~~Supplement), or when the RCTs which allowed the use of insulin (1.61; 1.30 to 2.00), were excluded from the analysis. The RR was similar to that of the principal analysis when RCTs in which a notable imbalance in sex ratio were excluded (1.52; 1.27 to 1.81; Q = 10.70, p = 0.15; I^2 = 35%; eFigure 2 in the supplement). The pooled RR was also similar for RCTs in which a definition of hypoglycaemia was reported (1.54; 0.99 to 2.42; Q = 2.1, p = 0.5, I^2 = 0%), and ~~for~~in those in which a definition was not reported (1.52; 1.27 to 1.82; Q = 9.1, p = 0.10, I^2 = 45%), without any evidence of heterogeneity between these two groups (Q = 0.0, p = 0.95, I^2 = 0%; eFigure ~~2 in the supplement). According to the dose of DPP4-i evaluated, the RR of hypoglycaemia remained significantly increased for DPP4-i full dose (1.66; 1.34 to 2.06), but not for DPP4-i low doses (1.33; 0.92 to 1.94; Figure 5). The NNH for DPP4-i full dose was 19.4 (13.9 to~~

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~~32.2; Figure 6). Funnel plot did not show clear evidence of publication bias, (Figure 7) and the Egger test did not find asymmetry (z=1.3; p=0.2). The strength of evidence of this meta-analysis was evaluated as high with regards to the GRADE framework (Table 3~~3 in the supplement).

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According to the dose of DPP4-i evaluated, the subgroup analysis showed no difference between low and full DPP4-i dose with regard to the risk of hypoglycaemia (Q = 0.99, p = 0.32, I^2 = 0%; Figure 4). The risk remained significantly increased for DPP4-i full dose (1.66; 1.34 to 2.06) but was not significantly increased for DPP4-i low doses (1.33; 0.92 to 1.94; Figure 5). For DPP4-i full dose+SU, the NNT(H) was 8 (5 to 15) for any treatment duration; it was 13 (8 to 25) for a treatment duration <6 months, 11 (7 to 22) for a treatment duration between 6.1 to 12 months, and 7 (4 to 13) for a treatment duration longer than one year. Visual inspection of the funnel plot did not show any clear evidence of publication bias (Figure 5), and the Egger test did not find any asymmetry (z=1.3; p=0.2). The strength of evidence of this meta-analysis was evaluated as high with regards to the GRADE framework (Table 2).

DISCUSSION

Principal findings

This meta-analysis found about a 50% increase in the risk of hypoglycaemia when DPP4-i and SU were associated in Type II diabetic patients, leading to one supplementary case of hypoglycaemia for every ~~27~~10 treated patients. This risk was confirmed for full doses of DPP4-i, while it ~~cannot~~could not be excluded for lower doses.

DPP4-i act indirectly on insulin levels by enforcing the incretin effect, which is a response to high oral intake of carbohydrates and fatty acids.[~~9~~17] Such drugs should therefore act on glycaemia only in response to such intakes, thereby protecting patients from hypoglycaemia.

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However, in patients treated with SU, insulin secretion is already stimulated independently of glycaemia and the addition of a reinforced incretin effect on insulin levels leads to an increase in the risk of hypoglycaemia. Given the frequency of this event in Type II diabetic patients treated with SU, the risk associated with the addition of DPP4-i would lead to a ~~tremendous~~huge number of cases of induced ~~hypoglycaemias~~hypoglycaemia, some of which could be severe.[~~39~~51] The present meta-analysis did not allow ~~the~~ investigation ~~as to~~of the threshold of dose combination (DPP4-i + SU) associated with an increased risk of hypoglycaemia; an individual patient meta-analysis could be helpful in this regard. ~~This~~ The risk of hypoglycaemia related to the addition of a DPP4-i to SU is~~, however,~~ acknowledged in the SmPCs for DPP4-i; most recommend using full-dose DPP4-i but a reduced SU dose in patients taking such combinations, although the magnitude of reduction is not stated.[~~16-20~~27-31] Currently, to what extent this recommendation would lower the number of excess cases of induced hypoglycaemia is unknown. ~~The~~It is also of note that the suggested individual patient meta-analysis would not fill this knowledge gap as the effect of SU dose reduction has not been investigated in trials studying DPP4-i.

For low doses of DPP4-i (half the full-dose when applicable), the increase in hypoglycaemia risk was not significant. ~~The~~However, the existence of this risk cannot ~~however~~ be fully ruled-out by the present results~~;~~ and a larger sample would be required to increase the precision of the estimates. Furthermore, although the point estimate was lower (RR 1.33 vs. 1.66 for full-doses), which suggests a potential dose-effect, no heterogeneity was found between low~~-~~ and full-doses of DPP4-i~~–~~, yet this could result from a lack of power in the heterogeneity test (low-dose group was half the size of the high-dose group).

Strengths and limitations of study

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The present analysis has important strengths. Firstly, it is based on a large sample of patients; over 4,000 treated with a combination of DPP4-i and SU, and over 2,500 treated with PBO and SU. Secondly, the overall quality of the included studies ~~appeared~~seems high ~~overall~~ according to the Cochrane ~~Collaboration's~~Collaboration tool for risk of bias assessment, which was confirmed by the GRADE framework evaluation of the meta-analysis that considers that the strength of evidence provided is high. The present meta-analysis used data concerning all currently marketed DPP4-i (alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin), and results were consistent within studies with no heterogeneity being found among estimates. Thirdly, there was no evidence of publication bias; the funnel plot was balanced and the Egger test was not significant. ~~The~~ Nevertheless, the meta-analysis does~~, however,~~ have certain limitations. Firstly, certain studies that presented ~~with~~a high risk for detection and reporting bias ~~risk of bias~~ were included in the main analysis,[~~31-33~~43-45] but exclusion of these ~~from~~studies did not change the estimates significantly. Secondly, three studies could not be included as data were not available for the risk of hypoglycaemia in patients ~~under~~receiving SU.[~~40-42~~52-54] However, in view of the GRADE framework, including results from these studies would be unlikely to ~~significantly~~ change the results significantly owing to the size of the present meta-analysis, the high number of hypoglycaemia cases, and the confidence intervals of the pooled RR that clearly do not cross the line of no effect.[~~22~~33] The absence of heterogeneity in estimates found from the ~~ten~~10 included studies further supports this hypothesis. Thirdly, the results of this meta-analysis are dominated by the results of three studies that account for more than 80% of the pooled results of the principal analysis:[42, 47, 50] a sensitivity analysis without these studies did not substantially change the results of the meta-analysis (data not shown). Fourthly, the definition of hypoglycaemia varied among the included RCTs~~,~~ and was not reported in five. Other authors ~~have~~did not ~~performed~~perform a meta-analysis on

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hypoglycaemia risk on the basis of this lack of homogeneity in its definition across the RCTs;[~~12~~20] nevertheless, this could be considered as a minor limitation, as in the present analysis the risk did not differ between RCTs with or without a clear definition of hypoglycaemia. The incidence of hypoglycaemia also differed among studies, mainly because of different durations of follow-up. However, this did not have any impact on the estimation of the pooled risk (no statistical heterogeneity was found) nor on the NNT(H) calculation, which was based on an external Assumed Control Risk of hypoglycaemia retrieved from 27 clinical studies included in a meta-analysis of the Cochrane library.[26]

Clinical importance

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It is important to underline that hypoglycaemia is the most frequent adverse reaction related to anti-diabetic treatments and that, even when not directly life-threatening, it is associated with an increased risk of all-cause mortality, cardiovascular disease, and cardiovascular mortality and hospital admission.[2, 3, ~~4~~36] In addition, it should not be neglected that ~~these frequent events~~hypoglycaemia and ~~their~~its related symptoms (e.g. nervousness, sweating, trembling, weakness, palpitations) impact negatively on patient quality of life~~, and disrupt many daily activities such as driving, work performance, and leisure pursuits.[44, 45] The risk herein demonstrated for all-type hypoglycaemia should thus~~ and disrupt many daily activities such as driving, work performance and leisure activities.[9, 10] More importantly, mild-to-moderate iatrogenic hypoglycaemia can decrease the usual adrenergic response to hypoglycaemia.[12] This may cause hypoglycaemia unawareness and compromise behavioural defences (hunger resulting in sugar ingestion), which in turn can lead to severe hypoglycaemia.[13, 14] It is thus an important to lower the risk of mild-to-moderate hypoglycaemia, which remains a serious adverse event. Adequate information regarding the risk of hypoglycaemia, whatever its severity, should thus be considered of primary importance for patients and all health

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professionals involved in the management of diabetic patients. Reaching good glycated haemoglobin levels should not be at the expense of hypoglycaemic events, which could outweigh the benefit of preventing risks associated with elevated blood glucose concentrations. Thus, the risk demonstrated herein for all-type hypoglycaemia should not be minimized by considering that only severe episodes would be of clinical concern.

Conclusions

In conclusion, this meta-analysis found about a 50% increase in the risk of hypoglycaemia associated with the addition of DPP4-i to SU in patients with type II diabetes. For this adverse event commonly experienced by treated diabetic patients, this would lead to the occurrence of one supplementary hypoglycaemic event ~~of hypoglycaemia for~~in every ~~27~~10 treated patients. This ~~has the potential to represent~~potentially represents a ~~tremendous~~huge number of attributable cases worldwide. These results clearly highlight the need to respect existing recommendations for SU dose reduction when initiating a DPP4-i treatment, and the urgency to determine the efficacy of this measure in minimizing the risk of hypoglycaemia.

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The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Francesco Salvo (corresponding author) and Antoine Pariente (manuscript's guarantor) affirm that the manuscript is an honest, accurate, and transparent, and that no important aspects of the study have been omitted.

Authors' contributions

FS: conception and design; acquisition, analysis and interpretation of data; drafting the article and revising it critically for important intellectual content; final approval of the version to be published. FS gives 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.

NM: conception and design; analysis and interpretation of data; revising the article critically for important intellectual content; final approval of the version to be published. NM gives 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.

MA: analysis and interpretation of data; revising the article critically for important intellectual content; final approval of the version to be published. MA gives agreement to be accountable

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for all aspects of the work ~~in~~by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

PR: analysis and interpretation of data; revising the article critically for important intellectual content; final approval of the version to be published. PR ~~gives agreement~~agrees to be accountable for all aspects of the work ~~in~~by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ER: conception and design; interpretation of data; revising the article critically for important intellectual content; final approval of the version to be published. ER ~~gives agreement~~agrees to be accountable for all aspects of the work ~~in~~by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FDP: conception and design; interpretation of data; revising the article critically for important intellectual content; final approval of the version to be published. FDP ~~gives agreement~~agrees to be accountable for all aspects of the work ~~in~~by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

BB: conception and design; analysis and interpretation of data; revising the article critically for important intellectual content; final approval of the version to be published. BB ~~gives agreement~~agrees to be accountable for all aspects of the work ~~in~~by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

AP conception and design; acquisition and interpretation of data; drafting the article and revising it critically for important intellectual content; investigating accuracy and integrity of any part of the work; final approval of the version to be published. AP ~~gives agreement~~agrees to be accountable for all aspects of the work ~~in~~by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AP is the guarantor.

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Declaration of interests

The corresponding author ensures that the manuscript is complete and that the conflict of interest disclosures are accurate, up-to-date, and consistent with the information provided in each author's ICMJE Form for Disclosure of Potential Conflicts of Interest.

All authors have read and understood BMJ policy on declaration of interests; all authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work ~~the following interests: in the previous 3~~three ~~years;~~ FS, MA, ER, FdP, and BB, and have no with any organisations that might have an interest in the submitted work in the previous three years~~relationships with companies that might have an interest in the submitted work~~; NM and PR ~~has~~have had specified relationships on other matters with Novartis and Takeda, which might have an interest in the submitted work~~;~~ AP has had specified relationships on other matters with Novartis, which might have an interest in the submitted work. BB, NM~~;~~ and AP have had specified relationships on other matters with public regulatory agencies and with health care insurance systems that might have an interest in the submitted work. All authors declare ~~that~~ no other relationships or activities that could appear to have influenced the submitted work~~their spouses, partners, or children do not have nogny financial relationships that may be relevant to the submitted work; and that they do not have noany non-financial interests that may be relevant to the submitted work~~.

Ethical approval

This type of study does not require ethical approval.

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Data sharing

No additional data available.

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Figure legends

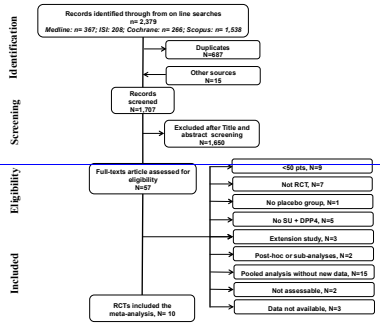

Figure 1. Flow diagram of study identification, selection, and inclusion. The search strategy identified 2,379 records~~,~~ of which 687 were duplicates and removed. Fifteen references were retrieved by other sources, thus a total of 1,707 individual titles and abstracts were assessed, leading to the exclusion of 1,650 records. After evaluation of 57 full~~-~~ texts, 13 studies ~~could have been~~ were eligible for this meta-analysis~~; data were~~. Data from ~~four~~three studies were not available~~, thus nine~~ so 10 studies were included.

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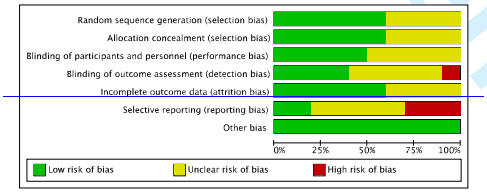

Figure 2. Risk of bias graph. Review authors' judgments for each 'Risk of bias' item presented as percentages across all included studies. The risk of bias of the included studies is presented in different ~~colors~~colours: green represents a low risk of bias, red represents a high risk of bias, yellow ~~represent~~represents an unclear risk of bias.

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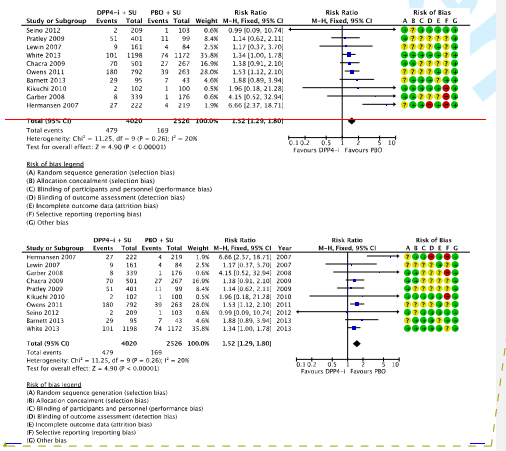

Figure 3. Forest plot of the risk of hypoglycaemia in patients treated with DPP4-i + SU in comparison with those treated with PBO + SU. Risk ratios (RR) calculated for individual randomized controlled trials (RCTs) with 95% confidence intervals (CI) are presented~~:~~ ~~arrows.~~ Arrows indicate the CI exceeding the limits of the graph. Overall RR is also presented (black diamond). An estimate of the weight of each RCT on overall ~~risk ratio~~RR is reported as a percentage and graphically (blue square size). Statistical heterogeneity among studies was evaluated ~~using~~with the Q statistic ($p<0.10$ considered significant), and the proportion of total variation contributed by between-study variance was estimated by using the I^2 index. The risk of bias for each study included ~~study~~ is presented as different coloured circles: green

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represents a low risk of bias, red represents a high risk of bias, yellow ~~represent~~represents an unclear risk of bias.

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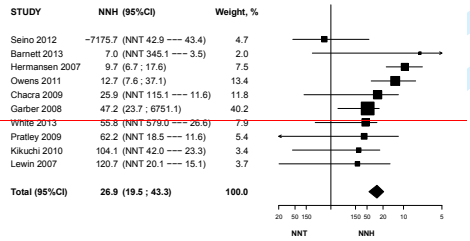

Figure 4. Forest plot of the Number Needed to Harm (NNH) of hypoglycaemia in patients treated with DPP4 i + SU in comparison with those treated with PBO + SU. NNH calculated for individual randomized controlled trials (RCTs) with 95% confidence intervals (CI) are presented; arrows indicate the CI exceeding the limits of the graph. Protective estimates (or CI) are reported as Number Needed to Treat (NNT, left side of the forest plot). An estimate of the weight of each RCT on overall NNH is reported as a percentage and graphically (black square size). Overall NNH is also presented (black diamond).

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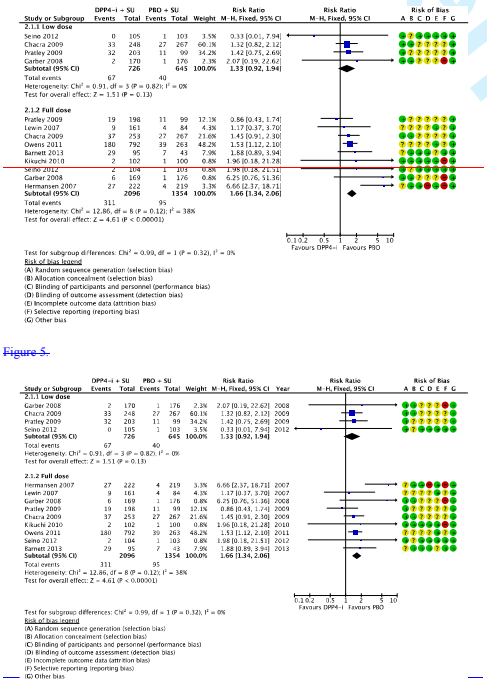

~~Figure 5.~~

Figure 4. Forest plot of the risk of hypoglycaemia in patients treated with full or low DPP4-i doses + SU in comparison with those treated with PBO + SU. Risk ~~Ratio~~Ratios (RR)

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calculated for individual randomized controlled trials (RCTs) with 95% confidence interval (CI) ~~is~~are presented~~, arrows~~. Arrows indicate the CI exceeding the limits of the graph. For each subgroup, an estimate of the weight of each RCT on pooled RRs is reported as a percentage and graphically (black square size~~), pooled~~). Pooled RRs for low and full doses are also presented (black diamonds~~), statistical~~). Statistical heterogeneity among studies was evaluated ~~using~~with the Q statistic ($p<0.10$ considered significant), and the proportion of total variation contributed by between-study variance was estimated by using the I^2 index. The risk of bias for each included study is presented as different coloured circles: green represents a low risk of bias, red represents a high risk of bias, yellow ~~represent~~represents an unclear risk of bias.

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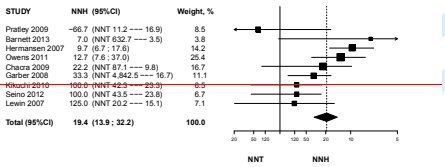

Figure 6. Forest plot of the Number Needed to Harm (NNH) of hypoglycaemia in patients treated with full DPP4 i dose + SU in comparison with those treated with PBO + SU. NNH calculated for individual randomized controlled trials (RCTs) with 95% confidence intervals (CI) are presented, arrows indicate the CI exceeding the limits of the graph. Protective estimates (or CI) are reported as Number Needed to Treat (NNT, left side of the forest plot). An estimate of the weight of each RCT on overall NNH is reported as a percentage and graphically (black square size). Overall NNH is also presented (black diamond).

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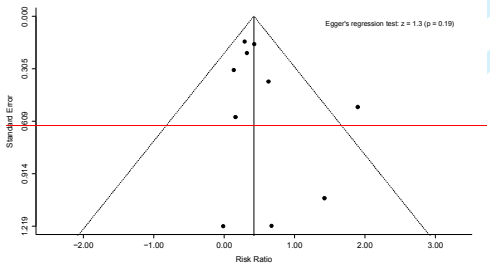

~~Figure 7.~~

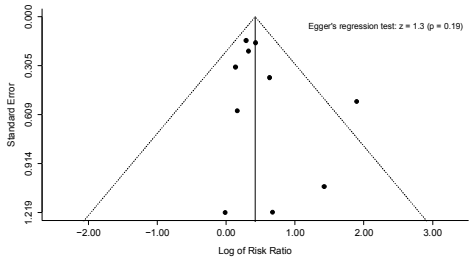

Figure 5. Funnel plot for publication bias. Scatter plot reporting risk ratio of the studies testing DPP4-i +SU in comparison ~~in comparison~~ with those treated with PBO + SU (horizontal ~~axes)~~axis) against their standard error (vertical ~~axes~~axis).

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TABLES

Table 1. Study characteristics

	Study duration, weeks	Intervention, daily dose (n)	Associated SU	Mean HbA_{1c} at baseline, %	Mean age of participants (, years)	Male, %	Definition of hypoglycaemia
Barnett *et al.*[14]	24	Linagliptin 5 mg (95 pts) or PBO (43 pts)	SU, not specified	DPP4-i: 7.8% PBO: 7.7*	DPP4-i: 75 PBO: 75*	DPP4-i: 72 PBO: 62*	PG of 3.9 mmol/l or less, with or without symptoms
Chacra *et al.*[30]	24	Saxagliptin 2.5 mg (248 pts), saxagliptin 5 mg (253 pts), or PBO (267 pts)	Glyburide	DPP4-i: 8.4%–8.5* PBO: 8.4	DPP4-i: 55 PBO: 55	DPP4-i: 45 PBO: 46	Not reported
Garber *et al.*[31]	24	Vildagliptin 50 mg (170 pts) or 100 mg (169 pts), or PBO (176 pts)	Glimepiride	DPP4-i: 8.5%–8.6 PBO: 8.5	58 DPP4-i: 58–59 PBO: 58	DPP4-i: 59 PBO: 58	Symptomatic hypoglycaemia confirmed by self-monitored BG <3.1 mmol/l
Hermansen *et al.*[32]	24	Sitagliptin 100 mg (222 pts) or PBO (219 pts)	Glimepiride	DPP4-i: 8.3% PBO: 8.3	NR DPP4-i: 56 PBO: 56.5	DPP4-i: 53 PBO: 55	Not reported, but hypoglycaemia is included in the AEs of special interest
Kikuchi *et al.*[33]	12	Vildagliptin 100 mg (102 pts) or PBO (100 pts)	Glimepiride	7.9% DPP4-i: 7.8 PBO: 8.0	DPP4-i: 59 PBO: 60	DPP4-i: 73.5 PBO: 69	Symptomatic hypoglycaemia confirmed by self-monitored BG <3.1 mmol/l
Lewin *et al.*[34]	18	Linagliptin 5 mg (161 pts) or PBO (84 pts)	SU, not specified	DPP4-i: 8.6% PBO: 8.6	DPP4-i: 57 PBO: 56	DPP4-i: 48 PBO: 62	Not reported, but hypoglycaemia were recorded and analyzed separately from other AEs.
Owens *et al.*[35]	24	Linagliptin 5 mg (792 pts) or PBO (263 pts)	SU, not specified	DPP4-i: 8.1% PBO: 8.1	DPP4-i: 58 PBO: 58	DPP4-i: 48 PBO: 47	Not reported
Pratley *et al.*[36]	26	Alogliptin 12.5 mg (203 pts), alogliptin 25 mg (198 pts), or PBO (99 pts)	Glyburide	NR	57 DPP4-i: 56.5 PBO: 57	DPP4-i: 52 PBO: 51.5	Symptomatic hypoglycaemia with BG <3.3 mmol/l or BG <2.8 mmol/l without symptoms
Seino *et al.*[37]	12	Alogliptin 12.5 mg (105 pts), alogliptin 25 mg (104 pts), or PBO (103 pts)	Glimepiride	DPP4-i: 8.5%–8.6% PBO: 8.6%	DPP4-i: 60 PBO: 60	DPP4-i: 66 PBO: 69	Not reported
White *et al.*[38]	76***	Alogliptin any doses (1,198), or PBO (1,172 pts)	SU, not specified	DPP4-i: 8.0% PBO: 8.0*	61 DPP4-i: 61 PBO: 69*	DPP4-i: 68	Not reported

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PBO: 61***

HbA_{1c}: Glycated hemoglobin A_{1C}; NR: not reported; PBO: placebo; Pts: patients; SU: sulphonylureas; y=years old. PG: Plasma Glucose; mmol/l: millimols/liter BG; Blood Glucose; AEs: adverse events.

*Data for group with saxagliptin 2.5 mg/day and in placebo group; in saxagliptin 5 mg/day HbA_{1c} was 8-5%.

** Data for group with alogliptin; in placebo group HbA_{1c} was 8-6%.

*** Data refer to overall study population, not only to SU treated patients.

** Median exposure weeks for alogliptin treated patients.

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*** Median age (years).

Table 2 ~~Definition of hypoglycaemia among the included RCTs.~~

	Definition of hypoglycaemia
~~Barnett *et al.*[14]~~	~~PG of 3.9 mmol/l or less, with or without symptoms~~
~~Chacra *et al.*[30]~~	~~Not reported~~
~~Garber *et al.*[31]~~	~~Symptomatic hypoglycaemia confirmed by self-monitored BG <3.1 mmol/l~~
~~Hermansen *et al.*[32]~~	~~Not reported, but hypoglycaemia is included in the AEs of special interest~~
~~Kikuchi *et al.*[33]~~	~~Symptomatic hypoglycaemia, confirmed by self-monitored BG <3.1 mmol/l~~
~~Lewin *et al.*[34]~~	~~Not reported, but hypoglycaemia were recorded and analyzed separately from other AEs.~~
~~Owens *et al.*[35]~~	~~Not reported~~
~~Pratley *et al.*[36]~~	~~Symptomatic hypoglycaemia with BG <3.3 mmol/l or BG <2.8 mmol/l without symptoms~~
~~Seino *et al.*[37]~~	~~Not reported~~
~~White *et al.*[38]~~	~~Not reported~~

~~PG: Plasma Glucose; mmol/l: millimols/liter BG: Blood Glucose; AEs: adverse events~~

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~~Table 3.~~ Summary of findings according to ~~the~~ GRADE framework~~.~~

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	All studies	Placebo	Relative (95% CI)	Absolute (95% CI)		
Hypoglycaemia												
10	randomized trials	not serious [1]	not serious [2]	not serious	not serious [3]	dose response gradient	479/4,020 (11.9%)	169/2,526 (6.7%)	RR 1.52 (1.29 to 1.80)	35 more per 1,000 (from 19 more to 54 more)	⊕⊕⊕⊕ HIGH	CRITICAL [4]

RR – relative risk

1. Only three studies were judged to have a high risk of detection bias. Among them, a high risk of reporting bias was found in one study. Nevertheless, when these studies were excluded from the analysis the result did not change substantially.
2. No heterogeneity among estimates was found.
3. The sample size is large (n=6,526), the number of the events high (648), and the confidence intervals of the pooled RR clearly do not cross the line of no effect (lower bound of 95%CI = 1.29)
4. Hypoglycaemia is the most frequent adverse reaction related to anti-diabetic treatment. It increases the risk of all-~~causes~~cause mortality and ~~of~~ cardiovascular events. Symptoms related to hypoglycaemia (e.g. nervousness, sweating, trembling, weakness, palpitations) reduce the quality of life of affected patients.

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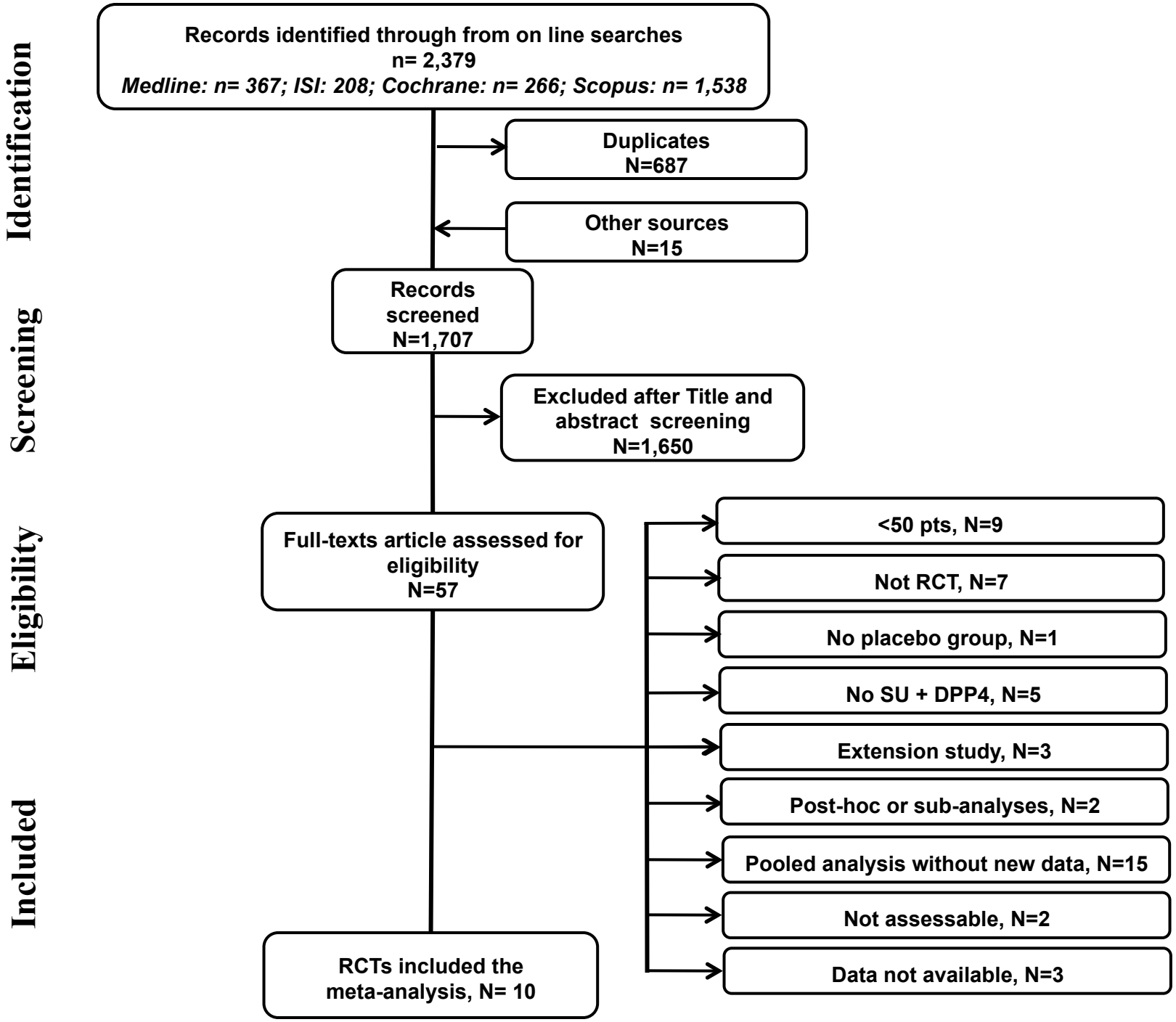
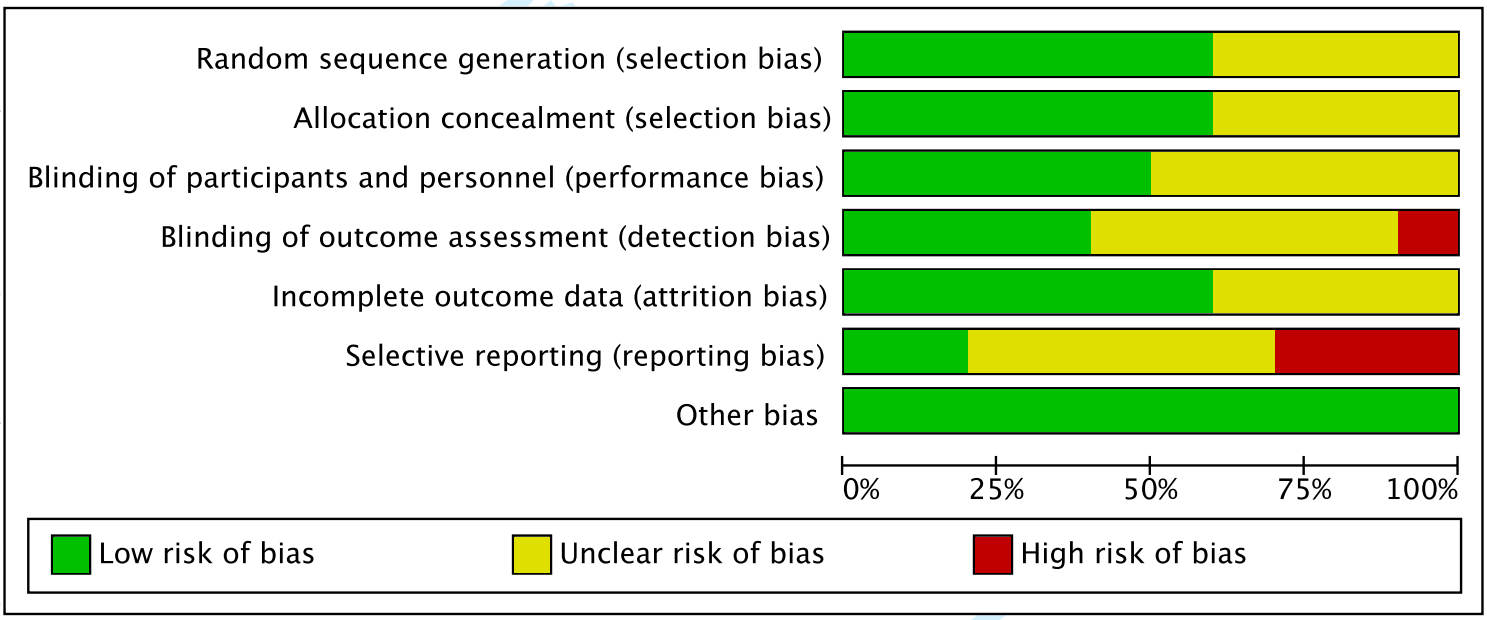

Identification
Records identified through from on line searches
n= 2,379
Medline: n= 367; ISI: 208; Cochrane: n= 266; Scopus: n= 1,538
Duplicates
N=687
Other sources
N=15
Screening
Records screened
N=1,707
Excluded after Title and abstract screening
N=1,650
Eligibility
Full-texts article assessed for eligibility
N=57
<50 pts, N=9
Not RCT, N=7
No placebo group, N=1
No SU + DPP4, N=5
Extension study, N=3
Post-hoc or sub-analyses, N=2
Pooled analysis without new data, N=15
Not assessable, N=2
Data not available, N=3
Included
RCTs included the meta-analysis, N= 10



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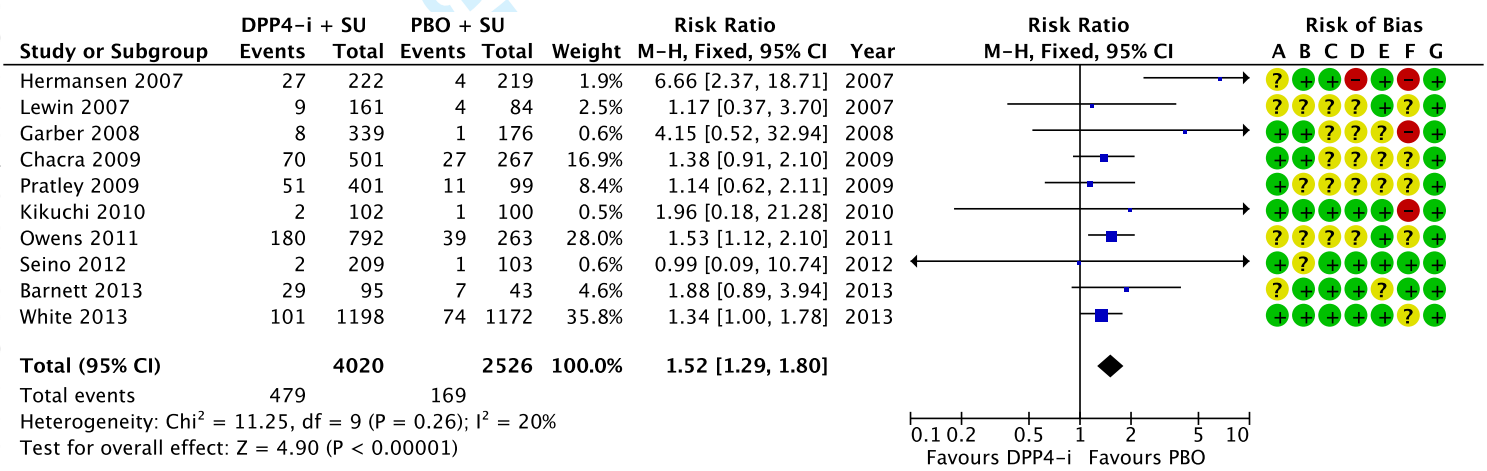

Study or Subgroup	DPP4-i + SU Events	Total	PBO + SU Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Hermansen 2007	27	222	4	219	1.9%	6.66 [2.37, 18.71]	2007
Lewin 2007	9	161	4	84	2.5%	1.17 [0.37, 3.70]	2007
Garber 2008	8	339	1	176	0.6%	4.15 [0.52, 32.94]	2008
Chacra 2009	70	501	27	267	16.9%	1.38 [0.91, 2.10]	2009
Pratley 2009	51	401	11	99	8.4%	1.14 [0.62, 2.11]	2009
Kikuchi 2010	2	102	1	100	0.5%	1.96 [0.18, 21.28]	2010
Owens 2011	180	792	39	263	28.0%	1.53 [1.12, 2.10]	2011
Seino 2012	2	209	1	103	0.6%	0.99 [0.09, 10.74]	2012
Barnett 2013	29	95	7	43	4.6%	1.88 [0.89, 3.94]	2013
White 2013	101	1198	74	1172	35.8%	1.34 [1.00, 1.78]	2013
Total (95% CI)		**4020**		**2526**	**100.0%**	**1.52 [1.29, 1.80]**	
Total events	479		169				

Heterogeneity: $Chi^2 = 11.25$, df = 9 (P = 0.26); $I^2 = 20\%$

Test for overall effect: Z = 4.90 (P < 0.00001)

Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

(**C**) Blinding of participants and personnel (performance bias)

(**D**) Blinding of outcome assessment (detection bias)

(**E**) Incomplete outcome data (attrition bias)

(**F**) Selective reporting (reporting bias)

(**G**) Other bias

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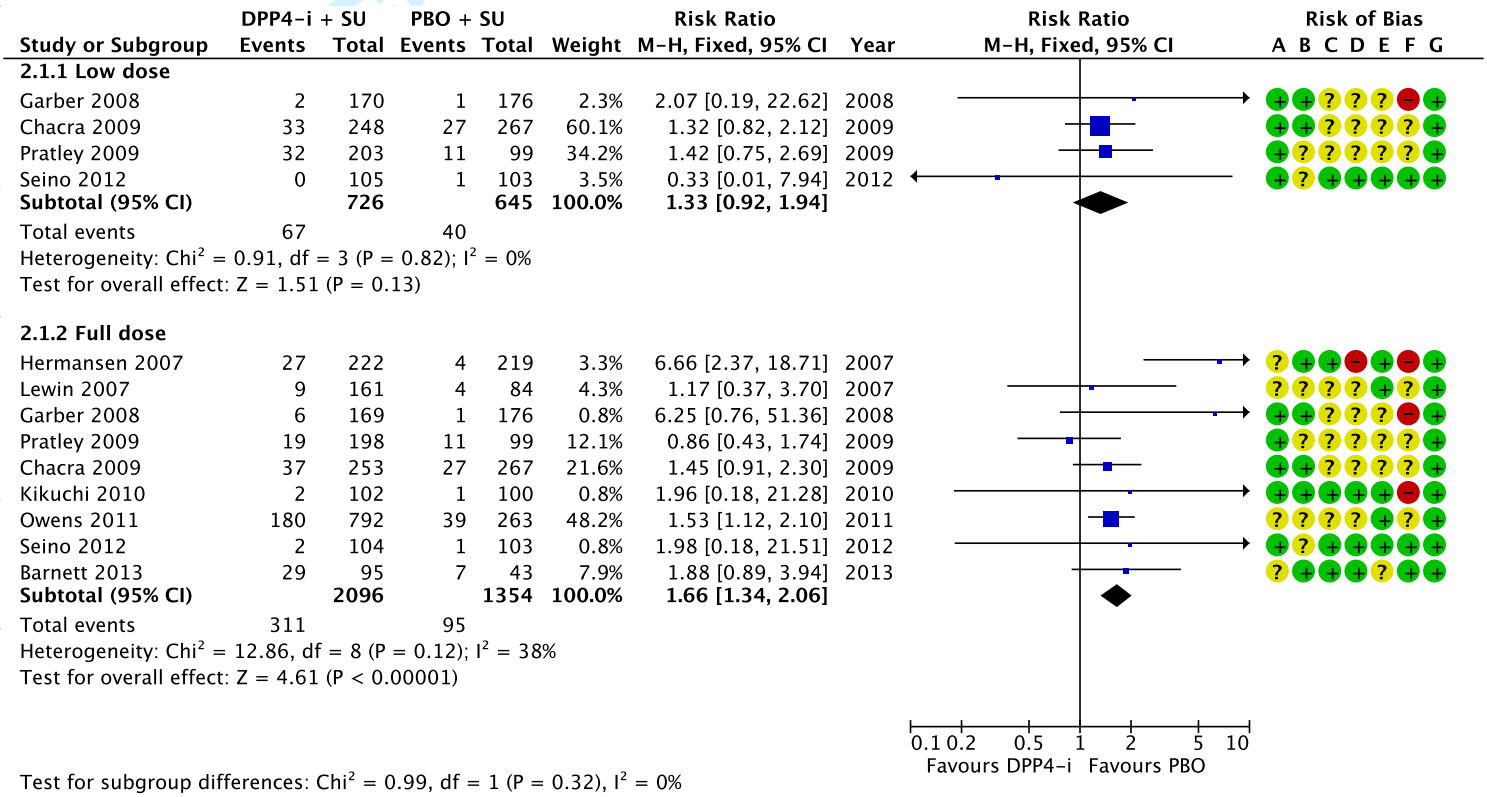

Test for subgroup differences: Chi² = 0.99, df = 1 (P = 0.32), I² = 0%

Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
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(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

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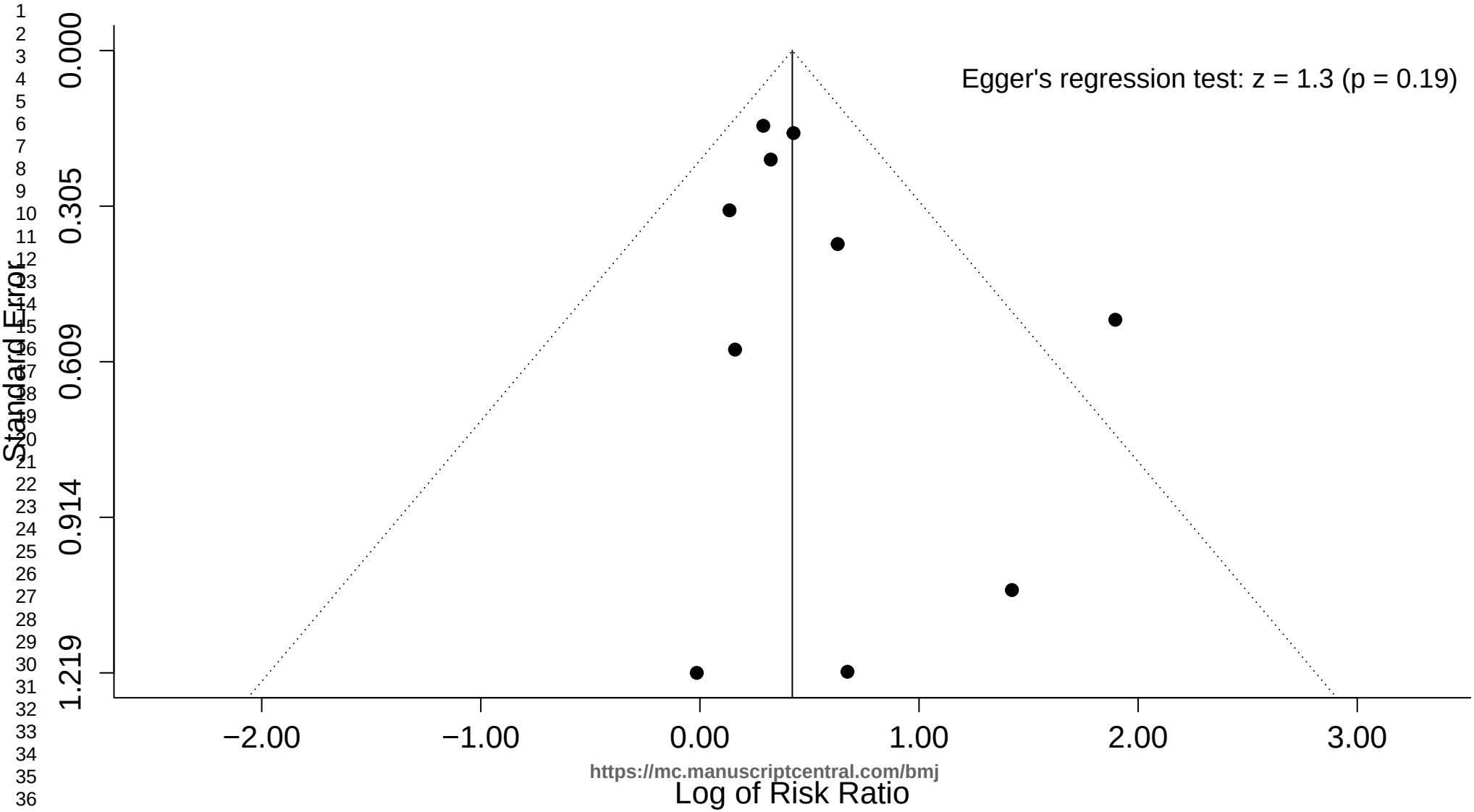
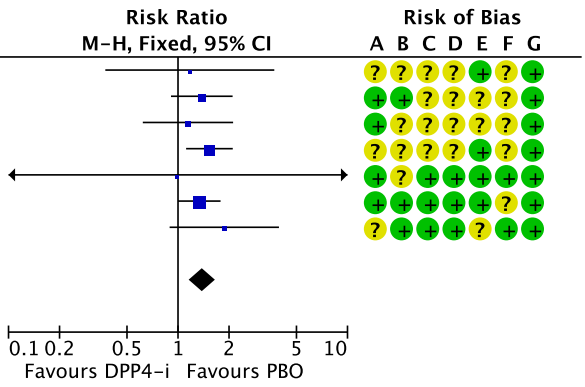

Egger's regression test: z = 1.3 (p = 0.19)
Standard Error
0.000
0.305
0.609
0.914
1.219
−2.00
−1.00
0.00
1.00
2.00
3.00
Log of Risk Ratio

Study or Subgroup	DPP-4i + SU Events	Total	PBO + SU Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Lewin 2007	9	161	4	84	2.6%	1.17 [0.37, 3.70]	2007
Chacra 2009	70	501	27	267	17.4%	1.38 [0.91, 2.10]	2009
Pratley 2009	51	401	11	99	8.7%	1.14 [0.62, 2.11]	2009
Owens 2011	180	792	39	263	28.9%	1.53 [1.12, 2.10]	2011
Seino 2012	2	209	1	103	0.7%	0.99 [0.09, 10.74]	2012
White 2013	101	1198	74	1172	36.9%	1.34 [1.00, 1.78]	2013
Barnett 2013	29	95	7	43	4.8%	1.88 [0.89, 3.94]	2013
Total (95% CI)		**3357**		**2031**	**100.0%**	**1.40 [1.18, 1.67]**	
Total events	442		163				

Heterogeneity: Chi^2 = 1.60, df = 6 (P = 0.95); I^2 = 0%

Test for overall effect: Z = 3.82 (P = 0.0001)



Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

(**C**) Blinding of participants and personnel (performance bias)

(**D**) Blinding of outcome assessment (detection bias)

(**E**) Incomplete outcome data (attrition bias)

(**F**) Selective reporting (reporting bias)

(**G**) Other bias

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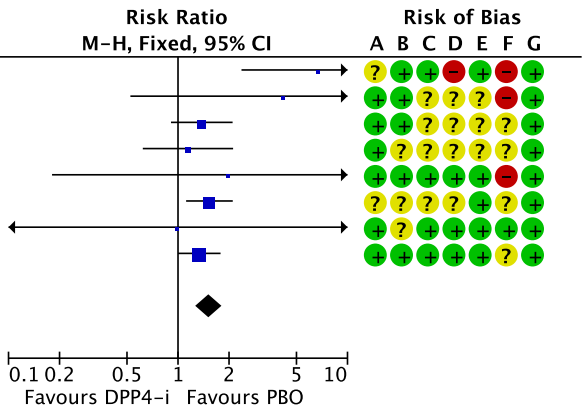
Study or Subgroup	DPP4-i + SU Events	Total	PBO + SU Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Hermansen 2007	27	222	4	219	2.1%	6.66 [2.37, 18.71]	2007
Garber 2008	8	339	1	176	0.7%	4.15 [0.52, 32.94]	2008
Chacra 2009	70	501	27	267	18.2%	1.38 [0.91, 2.10]	2009
Pratley 2009	51	401	11	99	9.1%	1.14 [0.62, 2.11]	2009
Kikuchi 2010	2	102	1	100	0.5%	1.96 [0.18, 21.28]	2010
Owens 2011	180	792	39	263	30.2%	1.53 [1.12, 2.10]	2011
Seino 2012	2	209	1	103	0.7%	0.99 [0.09, 10.74]	2012
White 2013	101	1198	74	1172	38.6%	1.34 [1.00, 1.78]	2013
Total (95% CI)		**3764**		**2399**	**100.0%**	**1.52 [1.27, 1.81]**	
Total events	441		158				

Heterogeneity: $Chi^2 = 10.70$, df = 7 (P = 0.15); $I^2 = 35\%$

Test for overall effect: Z = 4.65 (P < 0.00001)



Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

(**C**) Blinding of participants and personnel (performance bias)

(**D**) Blinding of outcome assessment (detection bias)

(**E**) Incomplete outcome data (attrition bias)

(**F**) Selective reporting (reporting bias)

(**G**) Other bias

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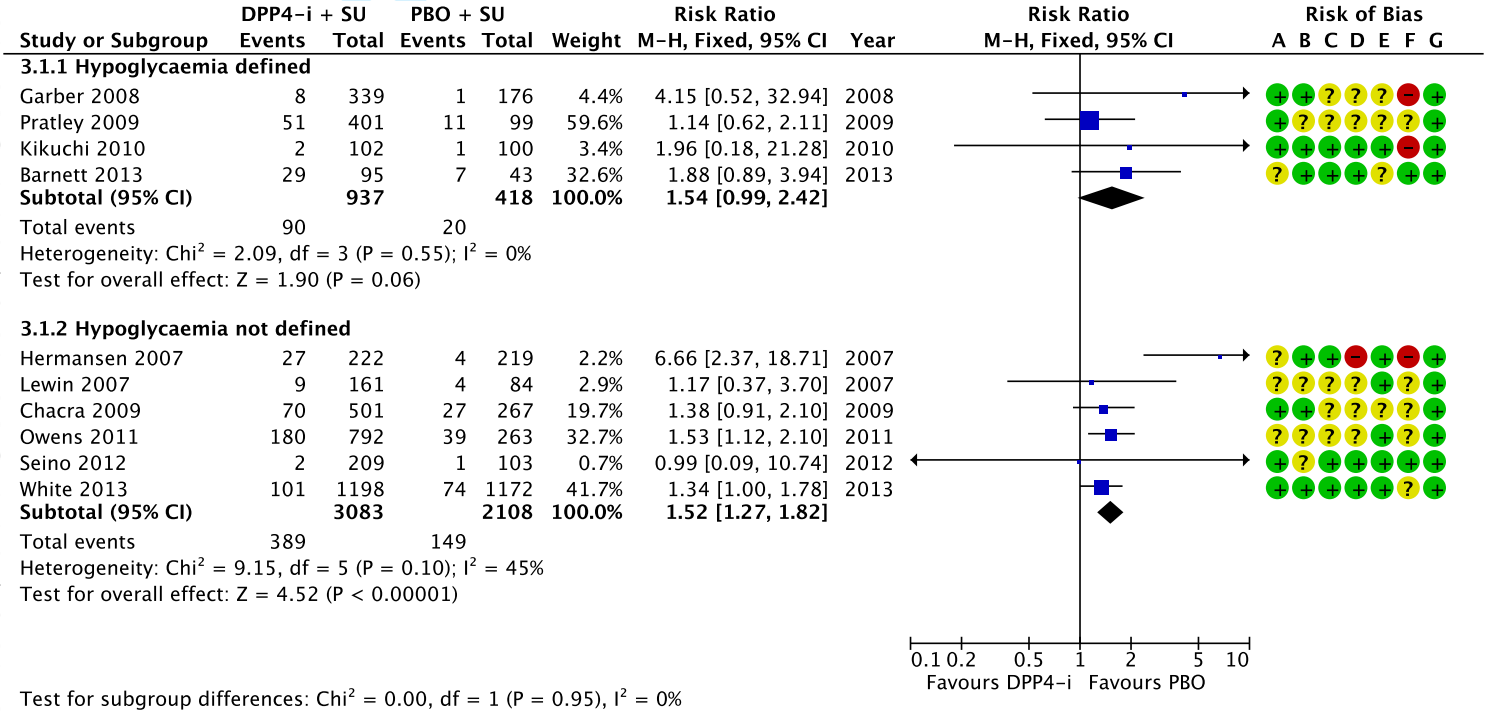

Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%

Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

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