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Risk of hypoglycaemia related to DPP-4 inhibitors plus 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. Cochrane Collaboration's 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 pooled. The number of patients needed to be treated to observe a harmful outcome (Number Needed to Harm, NNH) 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 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 of 26.9 (19.5 to 43.3). The RR related to full dose DPP4-i was 1.66 (1.34 to 2.06), with a corresponding NNH of 19.4 (13.9 to 32.2). The RR related to low dose DPP4-i did not reach significance (RR 1.33; 0.92 to 1.94).

Conclusions: Associating DPP4-i with SU in patients with type II diabetes would lead to a 50% increase in risk of hypoglycaemia and to a supplementary case of this for every 27 treated patients. This highlights the need to strictly respect recommendations for a decrease in SU dose when initiating DPP4-i, and to urgently assess the effectiveness of this risk minimization strategy.

What this paper adds

What is already known on this subject

Hypoglycaemia could be related to an increased morbidity and mortality in Type II diabetic patients. It is known the risk of hypoglycaemia is increased when DPP4-i are used concomitantly with SU. However, its magnitude has not been measured.

What this study adds

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

INTRODUCTION

Hypoglycaemia is a potentially life-threatening event associated with an increased risk of hospital admission,[1] cardiovascular disease, and mortality.[2, 3] In the ACCORD trial evaluating intensive glucose lowering in Type II diabetic patients, a 2.5-fold increase in hypoglycaemic events was noted. This trial was prematurely stopped for 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]

Dipeptidyl peptidase 4-inhibitors (DPP4-i) are a recently marketed class of oral antidiabetic 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. Notably, the mechanisms of action of these hypoglycaemic drugs are different. For instance, target tissue sensitivity to insulin is increased by thiazolidinediones,[7] hepatic gluconeogenesis is suppressed by metformin,[8] and insulin secretion is increased indirectly by DPP4-i (via the inhibition of incretin catabolism[9]) and directly by SU.[10, 11]

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 SU.[12] These RCTs indicate an acceptable safety profile when DPP4-i are used in patients treated with metformin or thiazolidinediones.[12, 13] Conversely, when DPP4-i are used in association with SU an increased frequency of hypoglycaemia was noted.[14, 15] The summaries of product characteristics (SmPCs) of DPP4-i acknowledge the increased risk of hypoglycaemia due to this association;[16-20] however, this risk remains insufficiently assessed and it was never 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

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 eligible for this meta-analysis were those: i) that were performed in adults with Type-2 diabetes mellitus; ii) that studied the effect of DPP4-i used at daily doses approved in clinical practice, in addition to SU, with or without other oral antidiabetic drug(s); iii) that included at least 50 patients treated with DPP4-i. Reports concerning RCT extension phases were not eligible.

Search strategy

Medline, ISI Web of Science, SCOPUS, and Cochrane Central Register of Controlled Trials databases were searched in 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. 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 published 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) reviewed and screened independently title and abstract of the potentially relevant RCTs, and performed their final eligibility through examination of full-texts. Disagreements were solved 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 to the principal authors.

Data extraction

Two authors (FS and AP) extracted independently the following information: i) methods: study design, study duration, and allowed use of metformin and doses; 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; v) allowed insulin treatment. Disagreements were solved through discussion and/or revision of the full-text.

Quality assessment and evidence quality

Study quality assessment was performed using the Cochrane Collaboration's 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] 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. 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] 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’’ suggests that it is very unlikely for conclusions about effect estimates to change, whereas ‘‘very low quality’’ very likely for conclusions about effect estimates to change.[23] This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (see research checklist supplement).[24]

Statistical analysis

The risk of hypoglycaemia in patients treated with DPP4-i + SU was estimated in comparison with that in patients treated with placebo + SU. All studies meeting the inclusion criteria were included in the quantitative analysis irrespectively of their quality.[21]

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] or, in case of significant heterogeneity between estimates, using random-effect models.[26] 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 I^2 index.[27] 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 mostly recommended in patients with renal impairment; see eTable 1 in supplement), according to the presence of a clear definition of hypoglycaemia.

Moreover, sensitivity analyses were conducted excluding studies with a high risk of bias (i.e. at least one item), or studies allowing the use of insulin.

Publication bias was evaluated using a funnel plot and Egger's regression test.[28] The Number Needed to Harm (NNH) was calculated for each study and pooled in a forest plot.[29] The analyses were conducted using 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 the meta-analysis objective and context, and the principles and modalities of the literature search and the data analysis was 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 irrelevant and excluded. The remaining 57 records underwent full-text examination (results detailed in the supplement); ten were finally included in this meta-analysis (Figure 1).[14, 30-38]

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.[14] 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;[14, 32, 35 , 38] use of insulin was allowed in two RCTs.[14, 38] Baseline mean (standard deviation) glycated haemoglobin A_{1C} (HbA_{1c}) of patients included in these RCTs ranged from 7.8% (0.8) to 8.6% (0.8).

Three RCTs studied in linagliptin 5 mg/day, for a total of 1,038 patients.[14, 34, 35] Vildagliptin 100 mg/day was studied in two RCTs,[31, 33] and vildagliptin 50 mg/day in one,[31] 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] 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] Saxagliptin (248 patients with 2.5 mg/day, and 253 with 5 mg/day)[30] and sitagliptin 100 mg/day (222 patients)[32] 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] There was a high risk of reporting bias in three of the included studies,[31-33] one RCT also presented a high risk of detection bias (Figure 2).[32] 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 was 26.9 (19.5 to 43.3; Figure 4). The pooled RR did not markedly change when RCTs with 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 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 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 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).

DISCUSSION

This meta-analysis found 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 treated patients. This risk was confirmed for full doses of DPP4-i, while it cannot 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] Such drugs should therefore act on glycaemia only in response to such intakes, 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 tremendous number of induced hypoglycaemias, some of which could be severe.[39] The present meta-analysis did not allow the investigation as to 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 risk is, however, acknowledged in the SmPCs for DPP4-i; most recommend using full dose DPP4-i but reduced SU dose in patients taking such combinations, although the magnitude of reduction is not stated.[16-20] Currently, to what extent this recommendation would lower the number of excess cases of induced hypoglycaemia is unknown. 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 existence of this risk cannot however be fully ruled-out by the present results; 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.

The present analysis has important strengths. Firstly, it is based on large sample of patients; over 4,000 treated with a combination of DPP4-i and SU, and over 2,500 treated with PBO SU. Secondly, the quality of the included studies appeared high overall according to the Cochrane Collaboration's 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, 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 meta-analysis does, however, have certain limitations. Firstly, certain studies presented with high risk for detection and reporting bias risk of bias were included in the main analysis,[31-33] but exclusion of these from 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 SU.[40-42] However, in view of the GRADE framework, including results from these studies would be unlikely to significantly change the results 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] The absence of heterogeneity in estimates found from the ten included studies further supports this hypothesis. Thirdly, the definition of hypoglycaemia varied among included RCTs, and not reported in five. Other authors have not performed a meta-analysis on hypoglycaemia risk on the basis of this lack of homogeneity in its definition across the RCTs;[12] 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.

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, 43] In addition, it should not be neglected that these frequent events and their 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 not be minimized by considering that only severe episodes would be of clinical concern.

In conclusion, this meta-analysis found 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 event of hypoglycaemia for every 27 treated patients. This has the potential to represent a tremendous 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 hypoglycaemia risk.

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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

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.

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 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.

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 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.

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 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.

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 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.

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 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. AP is the guarantor.

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 the following interests: in the previous 3 years, FS, MA, ER, FdP, and BB, and have no relationships with companies that might have an interest in the submitted work; NM and PR has 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 their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and that have no non-financial interests that may be relevant to the submitted work.

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Data sharing

No additional data available.

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Figures

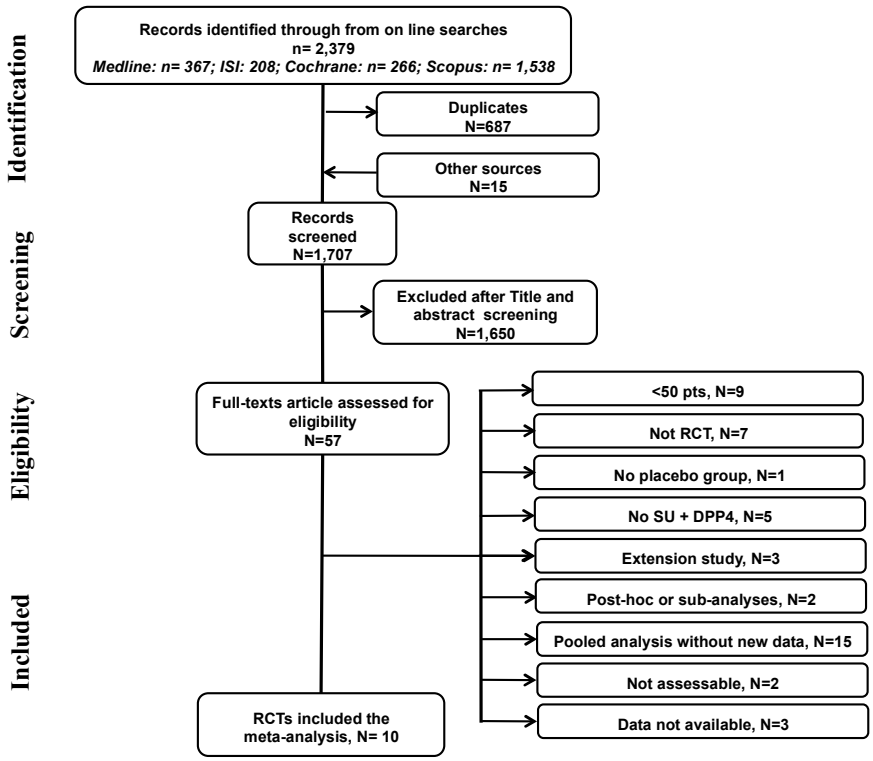

Figure 1. Flow diagram of study identification, selection, and inclusion. The search strategy identified 2,379 records, of which 687 were duplicates and removed. Fifteen references were retrieved by other sources, thus a total of 1,707 individual titles and abstracts were assessed, leading to the exclusion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

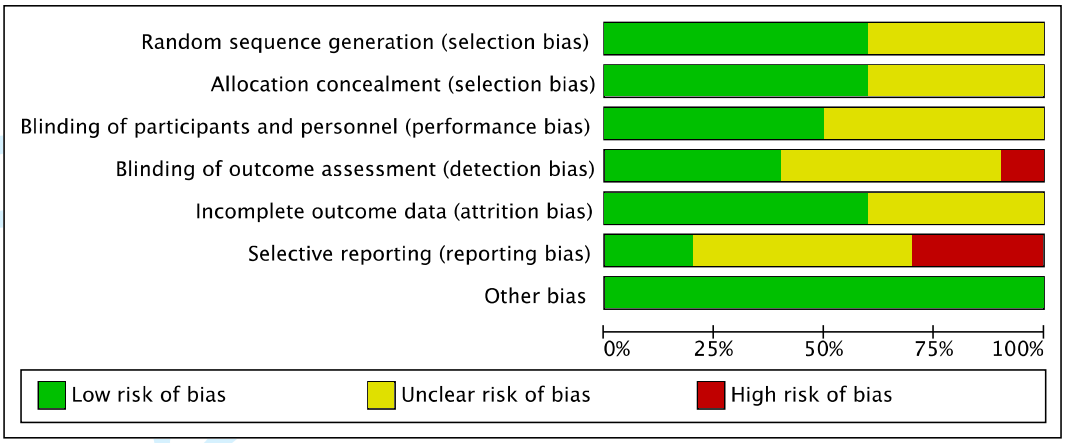

Figure 2. Risk of bias graph. Review authors' judgments for each 'Risk of bias' item presented as percentages across all included studies. The risk of bias of the included studies is presented in different colors: green represents a low risk of bias, red represents a high risk of bias, yellow represent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

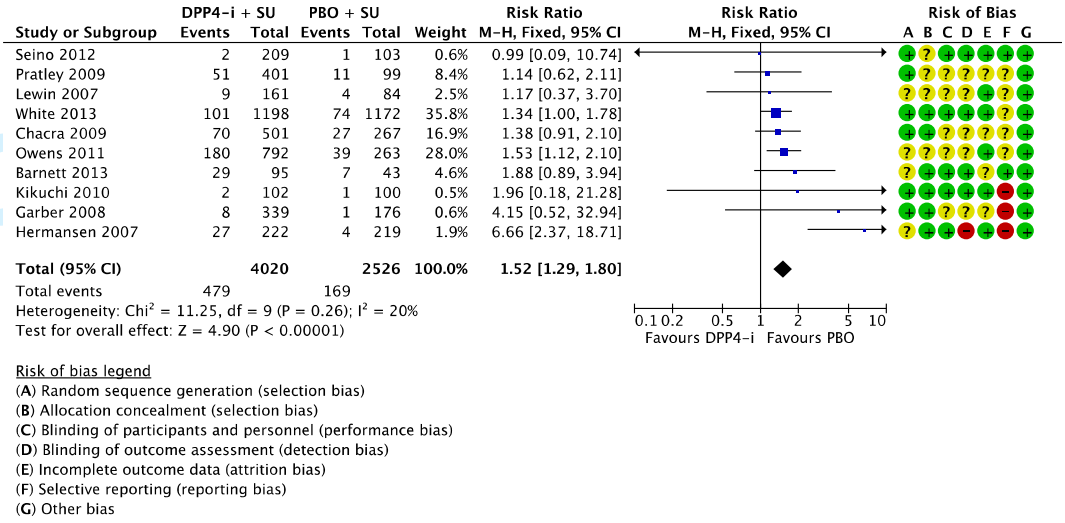

Figure 3. Forest plot of the risk of hypoglycaemia in patients treated with DPP4-i + SU in comparison with those treated with PBO + SU. Risk ratios (RR) calculated for individual randomized controlled trials (RCTs) with 95% confidence intervals (CI) are presented; arrows indicate the CI exceeding the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

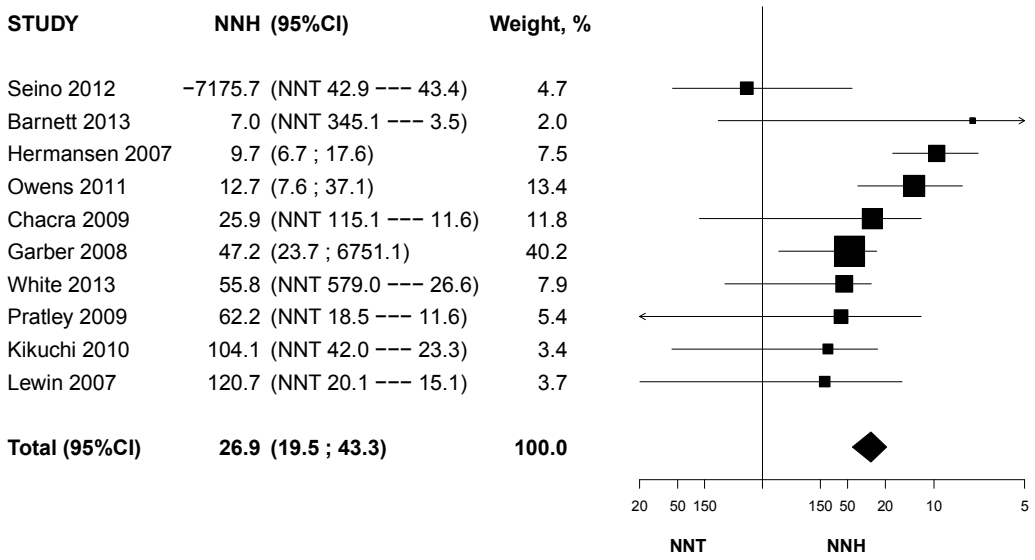

Figure 4. Forest plot of the Number Needed to Harm (NNH) of hypoglycaemia in patients treated with DPP4-i + SU in comparison with those treated with PBO + SU. NNH calculated for individual randomized controlled trials (RCTs) with 95% confidence intervals (CI) are presented; arrows indicate the CI exceeding 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).

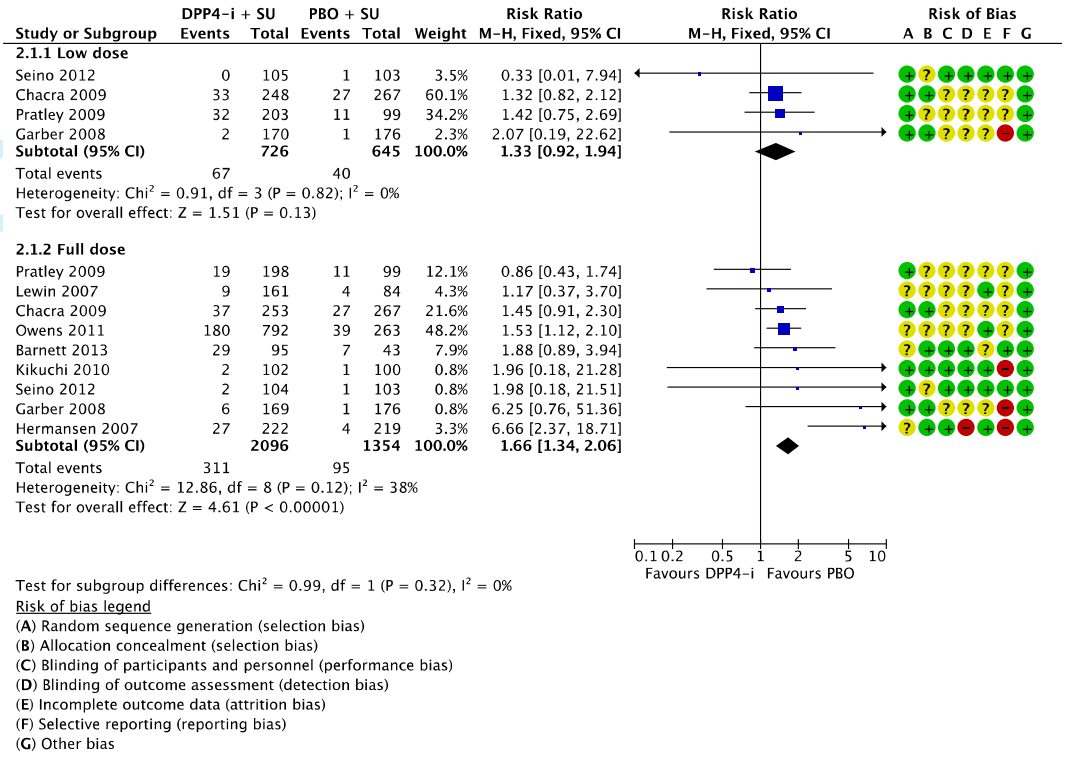

Figure 5. Forest plot of the risk of hypoglycaemia in patients treated with full or low DPP4-i doses + SU in comparison with those treated with PBO + SU. Risk Ratio (RR) calculated for individual randomized controlled trials (RCTs) with 95% confidence interval (CI) is presented; arrows indicate the CI 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 using Q statistic ($p<0.10$ considered significant), and the proportion of total variation contributed by between-study variance was estimated using 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 an unclear risk of bias.

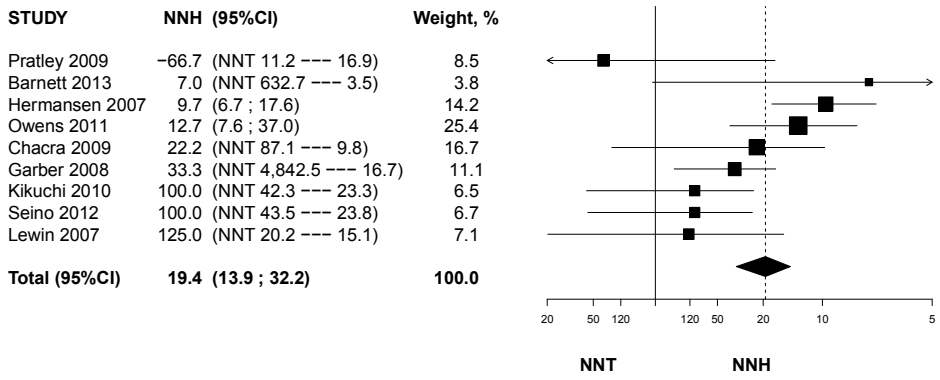

Figure 6. Forest plot of the Number Needed to Harm (NNH) of hypoglycaemia in patients treated with full DPP4-i dose + SU in comparison with those treated with PBO + SU. NNH calculated for individual randomized controlled trials (RCTs) with 95% confidence intervals (CI) are presented; arrows indicate 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).

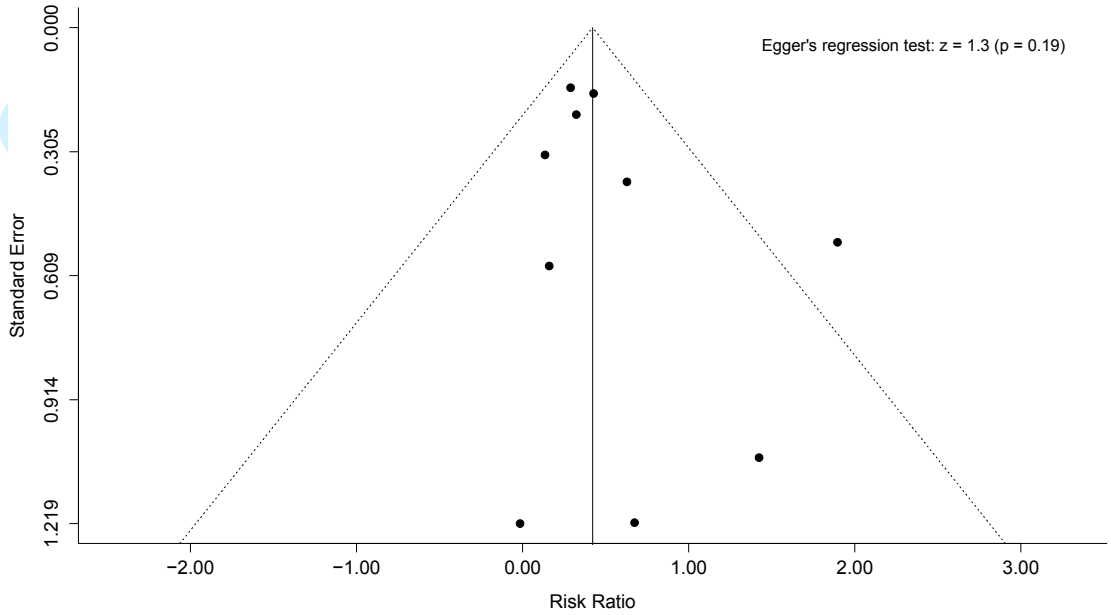

Figure 7. Funnel plot for publication bias. Scatter plot reporting risk ratio of the studies testing DPP4-i +SU in comparison in comparison with those treated with PBO + SU (horizontal axes), against their standard error (vertical axes).

TABLES

Table 1. Study characteristics

	Study duration, weeks	Intervention, daily dose (n)	Associated SU	Mean HbA_{1c} at baseline	Mean age of participants (years)
Barnett *et al.*[14]	24	Linagliptin 5 mg (95 pts) or PBO (43 pts)	SU, not specified	7.8%	75
Chacra *et al.*[30]	24	Saxagliptin 2.5 mg (248 pts), saxagliptin 5 mg (253 pts), or PBO (267 pts)	Glyburide	8.4%*	55
Garber *et al.*[31]	24	Vildagliptin 50 mg (170 pts) or 100 mg (169 pts), or PBO (176 pts)	Glimepiride	8.5%	58
Hermansen *et al.*[32]	24	Sitagliptin 100 mg (222 pts) or PBO (219 pts)	Glimepiride	8.3%	NR
Kikuchi *et al.*[33]	12	Vildagliptin 100 mg (102 pts) or PBO (100 pts)	Glimepiride	7.9%	60
Lewin *et al.*[34]	18	Linagliptin 5 mg (161 pts) or PBO (84 pts)	SU, not specified	8.6%	57
Owens *et al.*[35]	24	Linagliptin 5 mg (792 pts) or PBO (263 pts)	SU, not specified	8.1%	58
Pratley *et al.* [36]	26	Alogliptin 12.5 mg (203 pts), alogliptin 25 mg (198 pts), or PBO (99 pts)	Glyburide	NR	57
Seino *et al.*[37]	12	Alogliptin 12.5 mg (105 pts), alogliptin 25 mg (104 pts), or PBO (103 pts)	Glimepiride	8.5%**	60
White *et al.*[38]	76***	Alogliptin any doses (1,198), or PBO (1,172 pts)	SU, not specified	8.0%	61

HbA_{1c} Glycated hemoglobin A_{1C}; NR: not reported; PBO: placebo; Pts: patients; SU: sulphonylureas; y=years old.

*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%.

*** Median exposure weeks for alogliptin treated patients.

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

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 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 mortality and of cardiovascular events. Symptoms related to hypoglycaemia (e.g. nervousness, sweating, trembling, weakness, palpitations) reduce the quality of life of affected patients.

Supplement

Salvo F, et al. Risk of hypoglycaemia related to DPP-4 inhibitors plus sulfonylureas: 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]

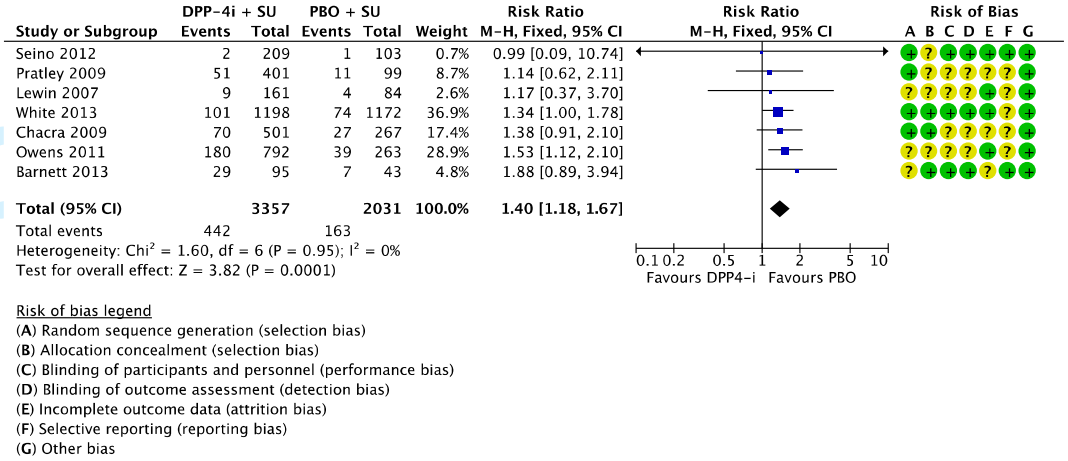
Studies excluded after full-text review: reasons for exclusion.

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 not a 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 were not assessable,[43, 44] and three because they did not report data on hypoglycaemia on patients treated with DPP4-i + SU, and authors/investigators did not agree to share data.[45-47]

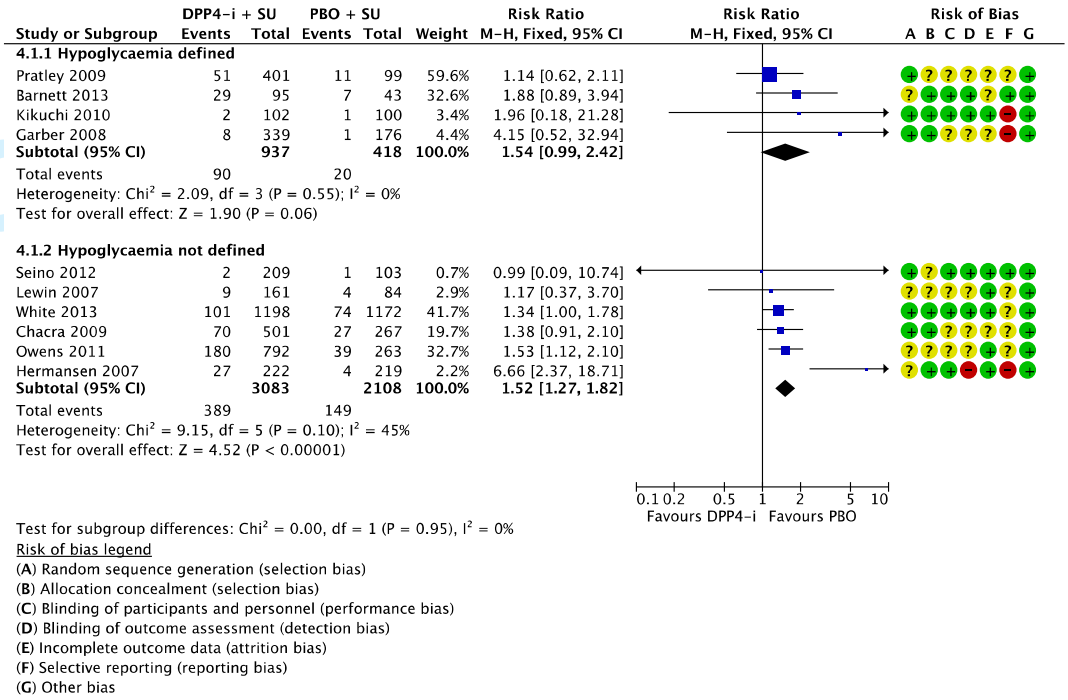
eTable 1. Low and full daily dose of DPP4 inhibitors.

	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



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. Overall RR is also presented (black diamond). An estimate of the weight of each RCT on overall risk ratio is reported as a percentage and graphically (blue square size). Statistical heterogeneity among studies was evaluated using Q statistic ($p<0.10$ considered significant), and the proportion of total variation contributed by between-study variance was estimated using 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 represent an unclear risk of 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 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. Overall RR is also presented (black diamond). An estimate of the weight of each RCT on overall risk ratio is reported as a percentage and graphically (blue square size). Statistical heterogeneity among studies was evaluated using Q statistic ($p<0.10$ considered significant), and the proportion of total variation contributed by between-study variance was estimated using 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 represent an unclear risk of bias.

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