**Supplement**

**Salvo F, et al. Risk of hypoglycaemia related the addition of DPP-4 inhibitors to 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 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]

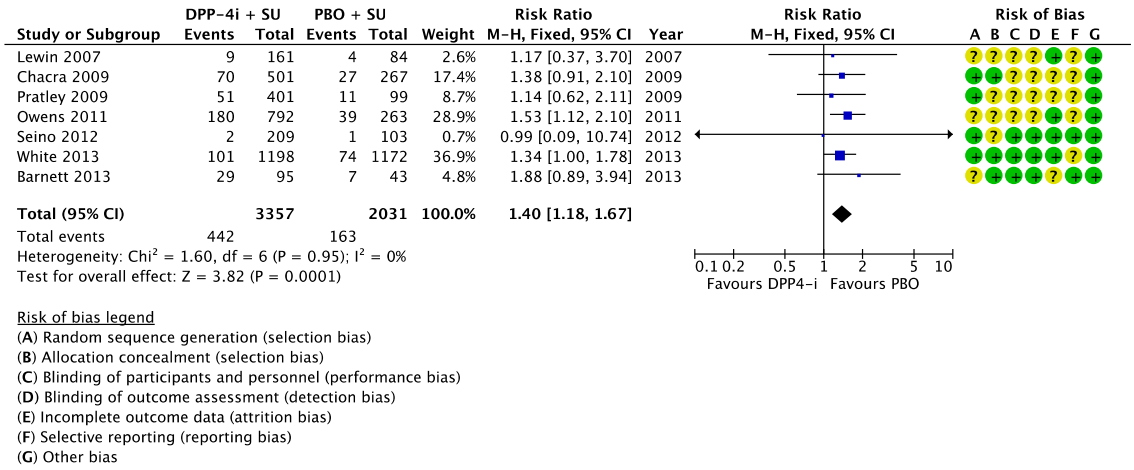
**eTable 1. Low and full daily dose of DPP4 inhibitors.**

| | 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 |

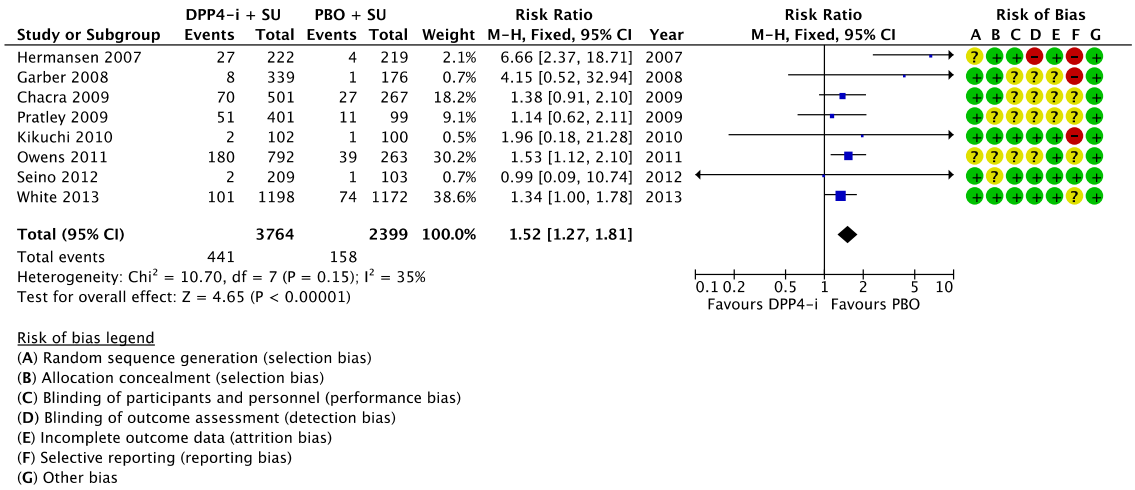
N/A: not applicable

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

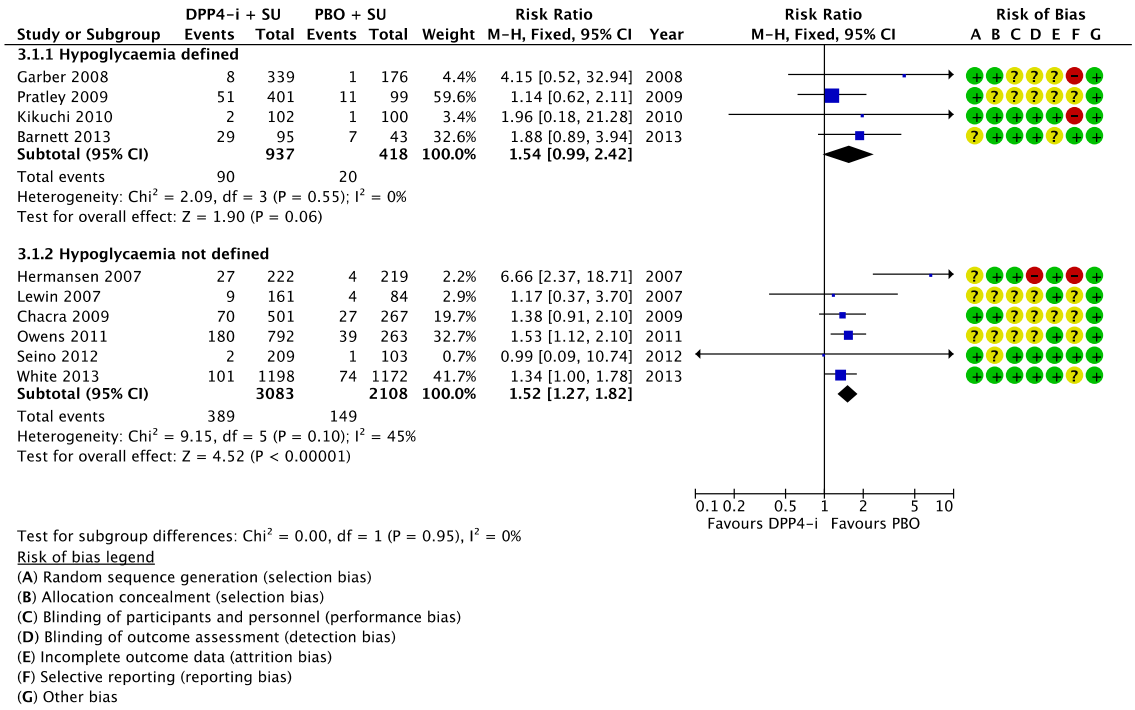
| First author | Year | Patients with hypoglycaemia, n | Total patients, n | Treatment duration, months |
|---|---|---|---|---|
| Feinbock *et al.*[49] | 2003 | 20 | 111 | 6 |
| Hermann *et al.*[50] | 1991 | 12 | 34 | 6 |
| Rosenthal & Mauersberger [51] | 2002 | 0 | 37 | 6 |
| Segal *et al.*[52] | 1997 | 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 |




**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.




**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.




**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.

**Risk of bias assessment (Cochrane Collaboration tool) of included studies.**

Barnett *et al.*[76]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Gender ratio differed among groups and SU treated patients were more represented in placebo group. It is unclear how this could affect the results |
| Allocation concealment (selection bias) | Low risk | Allocation concealed using a central interactive voice–web response system |
| Blinding of participants and personnel (performance bias) | Low risk | Linagliptin and placebo tablets were identical in appearance, and investigators and patients were masked to treatment assignment throughout the study |
| Blinding of outcome assessment (detection bias) | Low risk | Adverse events were reviewed by an independent clinical endpoint committee (CEC), consisting of three academic cardiologists and three academic neurologists who were masked to assignment |
| Incomplete outcome data (attrition bias) | Unclear risk | Patients in linagliptin group discontinued more frequently the medication because of adverse events in comparison with placebo (8 patients *vs.* 1 patient). It is unclear how this could affect the results |
| Selective reporting (reporting bias) | Low risk | Hypoglycaemia was defined as plasma glucose of 3·9 mmol/L or less, with or without symptoms |
| Other bias | Low risk | None detected |

Chachra *et al.*[77]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Patients were randomised equally in the groups with a block size of three |
| Allocation concealment (selection bias) | Low risk | Interactive Voice Response System |
| Blinding of participants and personnel (performance bias) | Unclear risk | "Throughout the study, double-blind study medication were taken twice daily, before the morning and evening meals to allow the glyburide dose to be split between morning and evening." It is unclear how this could affect the results |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not detailed |
| Incomplete outcome data (attrition bias) | Unclear risk | In the placebo arm, more patients withdrew from the study, mostly because of lack of efficacy. It is unclear how this could affect the results |
| Selective reporting (reporting bias) | Unclear risk | Hypoglycaemia was not clearly defined |
| Other bias | Low risk | None detected |

Garber *et al.*[78]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | A randomization list was produced using a health authority–inspected and validated system that automates the random assignment of treatment groups to randomization numbers in the specified ratio. |
| Allocation concealment (selection bias) | Low risk | A randomization list was produced using a health authority–inspected and validated system that automates the random assignment of treatment groups to randomization numbers in the specified ratio. |
| Blinding of participants and personnel (performance bias) | Unclear risk | No indication of how the double blinding was ensured reported in the full-text |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not detailed |
| Incomplete outcome data (attrition bias) | Unclear risk | More patients in placebo group discontinued the study than did so in the other groups, mostly for unsatisfactory therapeutic effect or consent withdrawal. It is unclear how this could affect the results |
| Selective reporting (reporting bias) | High risk | Only symptomatic hypoglycaemia was reported, and cut-off values were not used. |
| Other bias | Low risk | None detected |

Hermansen *et al.*[79]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomized study |
| Allocation concealment (selection bias) | Low risk | Patients were randomized through an interactive voice response system Interactive Voice Response System |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind study and "All assays were performed by technicians blinded to treatment sequence" |
| Blinding of outcome assessment (detection bias) | High risk | The severity and relationship to study drug for any AE were determined by the investigator |
| Incomplete outcome data (attrition bias) | Low risk | Equally distributed, no major differences. "Missing data were handled using the last observation-carried forward method" |
| Selective reporting (reporting bias) | High risk | The investigator judged the severity and relation with study drugs of the adverse event, without any mention of masking |
| Other bias | Low risk | None detected |

Kikuchi *et al.*[80]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Dynamic randomization was used to adjust for demographic differences between the treatment groups. A maximum difference of two subjects was permitted between the treatment groups at each study center (29 centers), and the six dose levels of glimepiride were used as an adjustment factor. |
| Allocation concealment (selection bias) | Low risk | Dynamic randomization was used to adjust for demographic differences between the treatment groups. |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind placebo-controlled study; dose adjustments to the treatment were not allowed at anytime after randomization. |
| Blinding of outcome assessment (detection bias) | Low risk | Patients were required to record the event and associated information such as glucose value and time of occurrence in the study diary. Haematology, biochemistry and urinalysis were performed at each scheduled visit. All laboratory assessments were processed at a central testing laboratory to ensure consistency. |
| Incomplete outcome data (attrition bias) | Low risk | The drop out rate was well balanced among groups |
| Selective reporting (reporting bias) | High risk | Only symptomatic hypoglycaemia was included |
| Other bias | Low risk | None detected |

Lewin *et al.*[81]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not detailed |
| Allocation concealment (selection bias) | Unclear risk | Not detailed |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not detailed |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not detailed |
| Incomplete outcome data (attrition bias) | Low risk | The drop out rate was well balanced among groups |
| Selective reporting (reporting bias) | Unclear risk | Not detailed |
| Other bias | Low risk | None detected |

Owens *et al.*[82]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not detailed |
| Allocation concealment (selection bias) | Unclear risk | Not detailed |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not detailed |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not detailed |
| Incomplete outcome data (attrition bias) | Low risk | The drop out rate was well balanced among groups |
| Selective reporting (reporting bias) | Unclear risk | Not detailed |
| Other bias | Low risk | None detected |

Pratley *et al.*[83]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Patients were randomised with a permuted block schedule, which was stratified for HbA1c at week |
| Allocation concealment (selection bias) | Unclear risk | Not detailed |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not detailed |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not detailed |
| Incomplete outcome data (attrition bias) | High risk | More patients in placebo group discontinued the treatment because of an hyperglycaemia |
| Selective reporting (reporting bias) | Unclear risk | The cut off of hypoglycaemia varied in symptomatic or asymptomatic patients. It is unclear how this could affect the results |
| Other bias | Low risk | None detected |

Seino *et al.*[84]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Patients were randomized 1:1:1 to each group with the daily dose of glimepiride being used as a randomization factor. |
| Allocation concealment (selection bias) | Unclear risk | Not detailed |
| Blinding of participants and personnel (performance bias) | Low risk | Double blind (Subject, Caregiver, Investigator, Outcomes Assessor) |
| Blinding of outcome assessment (detection bias) | Low risk | Assessor was blinded (from clinicaltrials.gov) |
| Incomplete outcome data (attrition bias) | Low risk | The drop out rate was well balanced among groups |
| Selective reporting (reporting bias) | Low risk | All clinical laboratory tests were carried out at a central independent laboratory |
| Other bias | Low risk | None detected |

White *et al.*[85]

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Interactive Voice Response System, randomization was stratified based on country and screening renal function |
| Allocation concealment (selection bias) | Low risk | Interactive Voice Response System |
| Blinding of participants and personnel (performance bias) | Low risk | Blinding will be maintained throughout the study by use of active drugs and matching placebo tablets of similar appearance |
| Blinding of outcome assessment (detection bias) | Low risk | Independent statistician, blinded data |
| Incomplete outcome data (attrition bias) | Low risk | The drop out rate was well balanced among groups |
| Selective reporting (reporting bias) | Unclear risk | No definition of hypoglycaemia is reported |
| Other bias | Low risk | None detected |

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