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RESEARCH

Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis

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Abstract

Objective To assess the efficacy and safety of dipeptidyl peptidase-4 (DPP-4) inhibitors compared with metformin as monotherapy, or with other commonly used hypoglycaemic drugs combined with metformin, in adults with type 2 diabetes mellitus.

Design Systematic review and meta-analysis of randomised controlled trials.

Data sources Medline, Embase, the Cochrane Library, conference proceedings, trial registers, and drug manufacturers' websites.

Eligibility criteria Randomised controlled trials of adults with type 2 diabetes mellitus that compared a DPP-4 with metformin as monotherapy or with a sulfonylurea, pioglitazone, a glucagon-like peptide-1 (GLP-1) agonist, or basal insulin combined with metformin on the change from baseline in glycated haemoglobin (HbA_{1c}).

Data extraction The primary outcome was the change in HbA_{1c}. Secondary outcomes included the proportion of patients achieving the goal of HbA_{1c} <7%, the change in body weight, discontinuation rate because of any adverse event, occurrence of any serious adverse event, all cause mortality, and incidence of hypoglycaemia, nasopharyngitis, urinary tract infection, upper respiratory infection, nausea, vomiting, and diarrhoea.

Results 27 reports of 19 studies including 7136 patients randomised to a DPP-4 inhibitor and 6745 patients randomised to another hypoglycaemic drug were eligible for the systematic review and meta-analysis. Overall risk of bias for the primary outcome was low in three reports, unclear in nine, and high in 14. Compared with metformin as monotherapy, DPP-4 inhibitors were associated with a smaller decline in HbA_{1c} (weighted mean difference 0.20, 95% confidence interval 0.08 to 0.32) and in body weight (1.5, 0.9 to 2.11). As a second line treatment, DPP-4 inhibitors were inferior to GLP-1 agonists (0.49, 0.31 to 0.67) and similar to pioglitazone (0.09, −0.07 to 0.24) in reducing HbA_{1c} and had no advantage over sulfonylureas in the attainment of the HbA_{1c} goal (risk ratio in favour of sulfonylureas 1.06, 0.98 to 1.14). DPP-4 inhibitors had a favourable weight profile compared with sulfonylureas (weighted mean difference −1.92, −2.34 to −1.49) or pioglitazone (−2.96, −4.13 to −1.78), but not compared with GLP-1 agonists (1.56, 0.94 to 2.18). Only a minimal number of hypoglycaemias were observed in any treatment arm in trials comparing a DPP-4 inhibitor with metformin as monotherapy or with pioglitazone or a GLP-1 agonist as second line treatment. In most trials comparing a DPP-4 inhibitor with sulfonylureas combined with metformin, the risk for hypoglycaemia was higher in the group treated with a sulfonylurea. Incidence of any serious adverse event was lower with DPP-4 inhibitors than with pioglitazone. Incidence of nausea, diarrhoea, and vomiting was higher in patients receiving metformin or a GLP-1 agonist than in those receiving a DPP-4 inhibitor. Risk for nasopharyngitis, upper respiratory tract infection, or urinary tract infection did not differ between DPP-4 inhibitors and any of the active comparators.

Conclusion In patients with type 2 diabetes who do not achieve the glycaemic targets with metformin alone, DPP-4 inhibitors can lower HbA_{1c}, in a similar way to sulfonylureas or pioglitazone, with neutral effects on body weight. Increased unit cost, which largely exceeds that

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Appendix 1: Search strategy
Appendix 2: Summary of risk of bias assessment
Appendix 3: Funnel plot based on mean difference for change in HbA_{1c} and study precision
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of the older drugs, and uncertainty about their long term safety, however, should also be considered.

Introduction

The American Diabetes Association and the European Association for the Study of Diabetes consensus algorithm for the treatment of type 2 diabetes mellitus endorses starting treatment with metformin at diagnosis along with lifestyle interventions.[1] When treatment with metformin alone proves inadequate to sustain the glycaemic goal, addition of basal insulin or a sulfonylurea is advocated as a well validated therapeutic strategy, whereas pioglitazone or glucagon-like peptide-1 (GLP-1) agonists are proposed as less well validated combined treatments.[1] In 2007, metformin was the most commonly used hypoglycaemic drug, prescribed in 54% of all visits for diabetes treatment in the United States, either as monotherapy or combined with insulin, sulfonylureas, thiazolidinediones (mainly pioglitazone), or dipeptidyl peptidase 4 (DPP-4) inhibitors.[2]

DPP-4 inhibitors are relatively new oral hypoglycaemic drugs. Sitagliptin, vildagliptin, saxagliptin, and linagliptin are currently approved by the US Food and Drug Administration or the European Medicines Agency, while others are awaiting approval or are in development. Their place in the 2009 consensus algorithm was not established because of limited clinical data, high costs, and lower or equivalent effectiveness compared with other agents.[1] The National Institute for Health and Clinical Excellence (NICE) clinical guideline for type 2 diabetes suggests adding a DPP-4 inhibitor instead of a sulfonylurea as second line treatment to first line metformin if there is a considerable risk for hypoglycaemia or if a sulfonylurea is contraindicated or not tolerated. This recommendation, however, is based on a small number of trials and a Cochrane systematic review, all published before 2009.[3 4] Thus, the potential role of DPP-4 inhibitors among the existing hypoglycaemic drugs needs to be updated and clarified. Previous systematic reviews of randomised controlled trials have assessed their efficacy and safety.[4-8] These included mainly[4 5 8] or exclusively[6] placebo controlled trials. Placebo controlled trials are usually less useful in the clinical setting than trials comparing new interventions against current best practice.[9] Moreover, most trials included in previous meta-analyses were of short duration (less than 30 weeks), thus limiting the assessment of the long term clinical profile of DPP-4 inhibitors.[8]

We carried out a systematic review and meta-analysis to offer an updated picture of the efficacy and safety of DPP-4 inhibitors compared with metformin as monotherapy, or compared with other commonly used hypoglycaemic drugs combined with metformin, based on published and unpublished randomised controlled trials of adult patients with type 2 diabetes.

Methods

We followed a protocol that was developed by the coauthors in which the eligibility criteria, all outcomes, main analyses, and most sensitivity analyses were prespecified. We present the methods and results of our systematic review and meta-analysis according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) recommendations and checklist.[10]

Eligibility criteria

A study was considered eligible if it was a randomised controlled trial (either of parallel or cross over design) that treated non-pregnant adults (aged over 18) with type 2 diabetes; the duration of the intervention was at least 12 weeks; it reported glycated haemoglobin (HbA_{1c}) as an outcome; and it compared a DPP-4 inhibitor with metformin as monotherapy or with a sulfonylurea, basal insulin, pioglitazone, or a GLP-1 agonist combined with metformin. We did not include rosiglitazone as one of the active comparators because it has been removed from the consensus algorithm[1] and its use has declined substantially because of its association with an increased risk of myocardial infarction and cardiovascular death.[11] We also excluded hypoglycaemic drugs that have not been widely adopted in clinical practice (a-glucosidase inhibitors, glinides, amylin agonists).[1 2]

Data sources and searches

We conducted an electronic search of Medline (via PubMed) without date limitations, Embase (via OVID) from 1980 to 2011, and the Cochrane Library. We did not use any language restrictions. We used the keywords "DPP-4", "dpp-iv", "dipeptidyl peptidase 4", and "dipeptidyl peptidase iv", combined with relevant MeSH terms and the substance names of both marketed and pre-marketed DPP-4 inhibitors. For our Medline search we added a highly sensitive filter for identifying randomised trials developed by the Cochrane Collaboration.[12] For Embase we used the filter for randomised trials proposed by the Scottish Intercollegiate Guidelines Network.[13] The complete search strategy is described in appendix 1 on bmj.com. The last search was run on 15 March 2011.We retrieved additional studies by hand searching the abstracts of the 2009 and 2010 annual meetings of the American Diabetes Association, the European Association for the Study of Diabetes, and the American Association of Clinical Endocrinologists. Completed but unpublished trials were identified by searching the websites of relevant pharmaceutical companies and public registers of clinical trials (www.clinicaltrials.gov/ and www.clinicalstudyresults.org/).

Study selection

Publications retrieved from Medline, Embase, and the Cochrane Library were imported in a reference management software. After removing the duplicate results, two reviewers (TK and PP) independently screened all titles and abstracts and investigated full texts for eligible studies. Differences in opinion between the two reviewers were resolved by consensus with a third reviewer (AT). One reviewer (TK) conducted the search of conference abstracts, trial registries, and websites of pharmaceutical companies. Eligible trials retrieved from these sources were juxtaposed against the search results from the three electronic databases to identify any unpublished studies.

Data extraction

We designed a data extraction form and piloted it on three randomly selected eligible studies. Two reviewers (TK and PP) independently abstracted data, and any discrepancies were resolved by consensus. From each study we extracted study characteristics (author identification, year of publication, National Clinical Trial (NCT) number, sample size for each group, duration of intervention); participants' baseline characteristics (age, sex, race, duration of type 2 diabetes, previous antidiabetic treatment, HbA_{1c}, body weight, body mass index (BMI)); and prespecified outcomes of efficacy and safety. Our primary outcome was glycaemic efficacy as measured by the change in HbA_{1c} from baseline to end point of the intervention. Secondary efficacy outcomes included the change from baseline to end point in body weight and the percentage

of patients achieving the glycaemic goal of HbA_{1c} <7%. Safety outcomes extracted included the percentage of patients experiencing at least one hypoglycaemic event, discontinuation rate from any adverse event, occurrence of any serious adverse event, all cause mortality, and incidence of nasopharyngitis, urinary tract infection, upper respiratory infection, nausea, vomiting, and diarrhoea, based on their clinical relevance or relatively high frequency in previous syntheses.[4 5] If data for our primary outcome were missing or incomplete, such as sample size and measures of variance, we emailed the corresponding authors or the sponsors (pharmaceutical companies). In case of multiple reports or companion papers of the same study (either published results of an extension period or unpublished results disclosed in trial registries and websites of drug manufacturers) we extracted outcome data separately for each report and subsequently collated all relevant data to maximise yield of information.[14]

Risk of bias assessment

We used the Cochrane Collaboration's risk of bias tool[15] to assess risk of bias in random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, and selective reporting. As risk of bias might differ between the primary phase and the extension phase of a study, we assessed this separately for each report. Blinding of participants and personnel, incomplete outcome data (because of high rate of discontinuation, type of analysis, or imputation of missing data), and selective reporting were assessed separately for each outcome within each report. We summarised the risk of bias of all six domains to produce an overall risk of bias for every outcome within every different report. This was deemed high in the presence of high bias in any domain, low if all key domains (all domains except random sequence generation and allocation concealment) were of low bias, and unclear in all other cases. A priori we planned to perform a sensitivity analysis for every outcome based on its overall risk of bias (excluding reports at high overall risk of bias). This could be different among outcomes, hence the subset of studies included in every sensitivity analysis might be different. Two reviewers (TK and PP) independently assessed the risk of bias, which was subsequently determined through consensus with a third reviewer (AT).

Data synthesis and analysis

Weighted mean differences between the intervention group (DPP-4 inhibitors) and the active comparator group and 95% confidence intervals were calculated for continuous outcomes with an inverse variance random effects model. If a study did not report a standard deviation, this was calculated from the sample size and the standard error or the 95% confidence interval. Additionally, for our primary outcome (change in HbA_{1c}) analyses, we calculated 95% prediction intervals to estimate a predicted range for the true treatment effect in any one individual study.[16] For dichotomous outcomes we calculated risk ratios and 95% confidence intervals, again using an inverse variance random effects model. We used data for intention to treat (all participants randomised) or modified intention to treat (all randomised participants who received intervention and had at least one measurement after baseline) populations when these were available either in a published paper or on websites of pharmaceutical companies and trial registries. Additionally, we requested intention to treat or modified intention to treat data for our primary outcome through email contact with the corresponding authors or sponsors if a study reported such an analysis in its methods but not in the results. In our meta-analyses we used data from the group randomised to the approved DPP-4 inhibitor dose (100 mg daily for sitagliptin and vildagliptin and 5 mg daily for saxagliptin and linagliptin). In the absence of a group receiving the approved doses we analysed the group receiving the highest dose.

In our main analysis for each outcome we used the report with the longest duration of follow-up (extension) for each study. We assessed statistical heterogeneity with the I^2 statistic. I^2 values of 30-60% and over 75% represent moderate and considerable heterogeneity, respectively.[17] We decided a priori to explore potential causes of heterogeneity by performing a sensitivity analysis for every outcome, excluding reports at high overall risk of bias. In this analysis, in case of multiple reports of the same study we used the report with the lowest overall risk of bias and the longest duration of follow-up. We performed additional sensitivity analyses for the primary outcome, excluding unpublished reports or using only the reports from the main (not extension) phase of studies. The robustness of the results was also tested by repeating the main analysis with an inverse variance fixed effect model. We assessed publication bias for the primary outcome with a funnel plot, both visually and formally with Egger's test.[18] All analyses were done with RevMan 5.1 (Nordic Cochrane Centre) and Stata version 10 (StataCorp, College Station, TX).

Results

Search results

Figure 1 shows the study selection process⇓. From the search of the three major electronic databases we identified 23 eligible reports, 15 of which were primary studies[19-33] and eight[34-41] were extensions of seven primary studies.[20 22 24 26 28 31 32] Six additional eligible completed trials were retrieved through the search of other sources. These included two trials with undisclosed results in www.clinicaltrials.gov/ (NCT00622284, NCT00676338), one abstract from the 2010 American Diabetes Association (70th) Scientific Sessions,[42] and three extensions[43-45] of placebo controlled studies[46-48] in which the group randomised to placebo during the base study switched to an active comparator during the follow-up period. A total of 27 reports (15 published primary studies, eight published extensions, three unpublished extensions, and one conference abstract) with 7136 patients randomised to a DPP-4 inhibitor and 6745 patients randomised to another hypoglycaemic drug were included in the systematic review and meta-analyses. Of these, 12 reports[19-24 34-36 41 43 44] compared a DPP-4 inhibitor with metformin as monotherapy. A DPP-4 inhibitor combined with metformin was compared with metformin combined with a sulfonylurea, pioglitazone, and a GLP-1 agonist in nine,[25-29 33 37 38 45] four,[30 31 39 42] and three reports,[30 32 40] respectively. We did not identify any eligible trial comparing a DPP-4 inhibitor with insulin combined with metformin.

Study characteristics

Table 1 summarises the characteristics of the included studies⇓. Almost all studies were multicentre and sponsored by pharmaceutical companies. All studies were parallel and included an active control group in a double blind design, except for the study by Pratley et al[32 40] (open label design), the study by Forst et al[29] (in which patients were randomised to receive double blind linagliptin (1, 5, and 10 mg) or placebo or open label glimepiride), and the study by Handayani et al[42] (no blinding mentioned). Nine reports (six primary studies and three extensions) were published in 2010, while three (one primary study and two extensions) were published in 2011. The duration

of intervention was equal to or longer than one year (52 weeks) in 12 studies (including their extension periods). The primary end point in all studies was the change in HbA_{1c} from baseline. Participants' baseline characteristics were equally balanced between the study arms in each study (table 1⇓).

Data collection and assessment of risk of bias

We requested missing or additional data for the primary outcome of the change in HbA_{1c} for one unpublished[43] and three published[27 29 33] studies through email contact with the corresponding authors or drug manufacturers. As requested data could not be retrieved for two of these studies,[29 43] we did not include them in the primary outcome analysis.

Appendix 2 on bmj.com summarises the assessment of risk of bias performed at the study level and at the primary outcome level**.** Random sequence generation and allocation concealment were described adequately in 16[19 20 24-26 29-35 37 39-41] and 10[24 25 29-33 39-41] of the 27 eligible reports, respectively. Overall risk of bias for the primary outcome was low in three,[25 30 38] unclear in nine,[19-23 27 31 33 39] and high in 14 reports[24 26 28 29 32 34-37 40 41 43-45] (mainly because of inadequate handling of outcome data (per protocol analysis) or attrition bias resulting from high discontinuation rate). We did not assess risk of bias for the study of Handayani et al[42] because it was available only as an abstract. There was no evidence of publication bias from the visual interpretation of the funnel plot or Egger's test (P=0.363) (see appendix 3 on bmj.com).

Glycaemic efficacy

Figure 2 shows the effect estimates of our main analysis for the primary outcome (change in HbA_{1c} from baseline)⇓. Seven trials (n=3237) comparing a DPP-4 inhibitor with metformin monotherapy and 10 trials (n=8912) that compared DPP-4 inhibitors with other hypoglycaemic drugs combined with metformin contributed to this analysis. Figure 3 shows the risk ratio for achieving an HbA_{1c} of less than 7%⇓.

Compared with metformin monotherapy, DPP-4 inhibitors were associated with a smaller decline in HbA_{1c} (weighted mean difference 0.20, 95% confidence interval 0.08 to 0.32, 95% prediction interval −0.14 to 0.54; I^2=60%) (fig 2⇓) and a lower chance of attainment of the HbA_{1c} goal of less than 7% (risk ratio in favour of metformin 1.18, 95% confidence interval 1.07 to 1.29, I^2=34%) (fig 3⇓). Exclusion of the reports at high risk of bias did not alter the effect estimate or heterogeneity (see appendix 4 on bmj.com).

As a second line treatment, DPP-4 inhibitors achieved a smaller decline in HbA_{1c} than the other hypoglycaemic drugs (overall weighted mean difference 0.12, 0.04 to 0.2, 95% prediction interval −0.13 to 0.37; I^2=70%). Exclusion of reports at high risk of bias did not alter the effect estimate or heterogeneity (see appendix 4 on bmj.com).

When we analysed data separately for each type of active comparator, DPP-4 inhibitors were less effective than sulfonylureas in reducing HbA_{1c} (weighted mean difference 0.07, 0.03 to 0.11, 95% prediction interval 0.02 to 0.13; I^2=0%) (fig 2⇓). There was no significant difference, however, in the attainment of the HbA_{1c} goal of less than 7% (risk ratio in favour of sulfonylureas 1.06, 0.98 to 1.14; I^2=26%) (fig 3⇓).

There was no difference in the change in HbA_{1c} achieved between DPP-4 inhibitors and pioglitazone (weighted mean difference 0.09, −0.07 to 0.24, 95% prediction interval −1.4 to 1.57, I^2=40%) (fig 2⇓). Pioglitazone, however, was associated with a higher chance of reaching the goal of less than 7% (risk ratio in favour of pioglitazone 1.33, 1.09 to 1.63, I^2=0%) (fig 3⇓).

Finally, DPP-4 inhibitors were inferior to GLP-1 agonists both in reducing HbA_{1c} (weighted mean difference 0.49, 0.31 to 0.67; I^2=27%) (fig 2⇓) and in achieving the glycaemic goal of less than 7% (risk ratio in favour of GLP-1 agonists 1.33, 1.09 to 1.63; I^2=26%) (fig 3⇓).

Body weight

Twelve trials (n=9156) contributed data in the main analysis for the change in body weight (fig 4⇓). As monotherapy, DPP-4 inhibitors were less effective in decreasing body weight than metformin (weighted mean difference 1.50, 0.90 to 2.11; I^2-74%). When added to metformin, DPP-4 inhibitors had a favourable weight profile compared with sulfonylureas (−1.92, −2.34 to −1.49; I^2=69%) or pioglitazone (−2.96, −4.13 to −1.78; I^2=79%) but not compared with GLP-1 agonists (1.56, 0.94 to 2.18; I^2=0%).

Hypoglycaemia

As the definition of hypoglycaemia varied across trials, we did not calculate a pooled estimate for risk. Table 2⇓ shows the number of participants experiencing at least one episode of hypoglycaemia in each treatment group, using the report with the longest duration of follow-up for each study. Only a few hypoglycaemias were observed in any treatment arm in trials that compared a DPP-4 inhibitor with metformin as monotherapy or with pioglitazone or a GLP-1 agonist as second line treatment. On the contrary, in most trials comparing a DPP-4 inhibitor with sulfonylureas combined with metformin the risk for hypoglycaemia was higher in the group receiving a sulfonylurea.[25 33 37 38 45] Across all studies analysed, severe hypoglycaemia (defined as an episode that required the help of another person) occurred in six patients receiving a DPP-4 inhibitor (n=6615). In the control groups, one patient receiving metformin as monotherapy (n=1647), 51 receiving a sulfonylurea (n=3873), one patient receiving a GLP-1 agonist (n=381), and none of the 445 patients receiving pioglitazone experienced at least one episode of severe hypoglycaemia.

All cause mortality and serious adverse events

Information on mortality and incidence of serious adverse events was available in almost all trials. None of the trials, however, was designed to analyse these outcomes. All cause mortality did not differ between DPP-4 inhibitors and any of the comparators (table 3⇓). There were 23 deaths in patients receiving a DPP-4 inhibitor (n=6789) and 28 deaths in patients receiving an active comparator (n=6505). Incidence of any serious adverse event was lower with DPP-4 inhibitors than with pioglitazone (risk ratio 0.47, 0.27 to 0.82; I^2=0%) and similar compared with the other active treatments (table 3⇓).

Other adverse events

Treatment with a DPP-4 inhibitor resulted in lower discontinuation rate because of any adverse event compared with metformin monotherapy (risk ratio 0.69, 0.51 to 0.94; I^2=0%) or with a GLP-1 agonist combined with metformin (0.40, 0.21 to 0.76; I^2=0%) (table 3⇓). Diarrhoea, vomiting, and nausea were also more common in patients receiving metformin or a GLP-1 agonist than DPP-4 inhibitors. No difference in the incidence of gastrointestinal events was evident between DPP-4 inhibitors and sulfonylureas or pioglitazone. Overall, DPP-4 inhibitors were not associated with an increased risk of

nasopharyngitis (1.06, 0.95 to 1.19; I^2=0%), upper respiratory tract infection (1.0, 0.83 to 1.22; I^2=20%), or urinary tract infection (0.86, 0.51 to 1.45; I^2=64%) compared with any of the hypoglycaemic drugs in the control groups. Table 3 summarises the findings of the main analyses for safety outcomes⇓.

Discussion

In our meta-analysis DPP-4 inhibitors seemed to be inferior to metformin in terms of glycaemic efficacy and reduction in body weight, thus our findings support the current guidelines which propose the use of metformin as first line treatment.[1 3] DPP-4 inhibitors have not been included in the 2009 American Diabetes Association and the European Association for the Study of Diabetes consensus algorithm, partly because of limited clinical data. Their incorporation in the National Institute for Health and Clinical Excellence clinical guideline has been based on the results of a systematic review[4] and a limited number of trials,[3] all published before 2009. In this meta-analysis we investigated the therapeutic role of DPP-4 inhibitors for type 2 diabetes, and the quality of data supporting their use in everyday clinical practice. We explored their efficacy and safety as first or second line treatment using data from eight randomised controlled trials comparing a DPP-4 inhibitor with metformin as monotherapy, and 11 trials that directly compared a DPP-4 inhibitor with other commonly used hypoglycaemic drugs combined with metformin.

In terms of clinical efficacy, our analysis supports the inferiority of DPP-4 inhibitors to metformin as monotherapy and GLP-1 agonists as second line treatment in reducing HbA_{1c} and body weight. Both metformin and GLP-1 agonists, however, were associated with a higher discontinuation rate because of any adverse event, which is possibly related to the higher incidence of diarrhoea, nausea, and vomiting with these drugs. Compared with sulfonylureas or pioglitazone, DPP-4 inhibitors seemed to be similar in glycaemic efficacy. Additionally, they had a favourable weight profile over both active comparators, and, in most studies they were associated with a lower incidence of hypoglycaemia than sulfonylureas and a lower incidence of any serious adverse event than pioglitazone. Finally, treatment with DPP-4 inhibitors did not seem to increase the risk for nasopharyngitis, urinary tract, and upper respiratory tract infections.

Strengths and limitations

The strengths of our meta-analysis are related to the incorporation of direct evidence from both unpublished and recently published head to head trials, the inclusion of follow-up extension studies, the variety of outcomes assessed, and the investigation of plausible clauses of heterogeneity by sensitivity analyses and calculation of prediction intervals for the primary outcome of the change in HbA_{1c}. Nevertheless, some limitations should also be recognised. We did not conduct separate analyses for each DPP-4 inhibitor because of scarcity of data to determine relative differences between DPP-4 inhibitors, while our conclusions regarding their comparative efficacy and safety versus GLP-1 agonists and pioglitazone as second line treatment are not robust enough because of the small number of relevant trials. Furthermore, we did not conduct sensitivity analyses or meta-regression to examine the contribution of participants' baseline characteristics (such as baseline HbA_{1c} and duration of type 2 diabetes) to the effect estimate of our primary outcome, based on findings from recent meta-analyses suggesting minimal[49] or no effect[50 51] of these parameters on the change of HbA_{1c}. Moreover, there was considerable variation in the risk of bias across studies and across the outcomes of the same study. Exclusion of trials at high risk of bias in a sensitivity analysis however, did not alter the results of the main analysis. Additionally, although we did not formally rate the overall strength of evidence of our analyses using the GRADE system,[52] we used only trials that directly answer our clinical question, we conducted separate analyses excluding trials at high risk of bias, and we did not detect any publication bias from the visual interpretation of the funnel plot or Egger's test. Finally, none of the included studies was designed to assess the comparative effect of DPP-4 inhibitors on cardiovascular end points, hence any conclusions regarding hard outcomes, such as cardiovascular morbidity or mortality, should be considered with caution. Ongoing trials (NCT00790205, NCT01243424, NCT01107886) are expected to deal with this question in near future.

Implications and conclusions

DPP-4 inhibitors could be an alternative therapeutic option only in patients who cannot tolerate metformin because of gastrointestinal adverse events. In our analysis comparing DPP-4 inhibitors with metformin on the change in HbA_{1c}, however, we noted a considerable amount of heterogeneity and the prediction interval was not significant, even after exclusion of studies at high risk of bias, which might be because of variability of metformin dose across the studies or other uncharacterised or unexplained underlying factors.[16]

In patients who do not achieve their glycaemic targets with metformin monotherapy, two recent meta-analyses[50 53] assessing the efficacy and safety of hypoglycaemic drugs combined with metformin concluded that DPP-4 inhibitors achieved relative reductions in HbA_{1c} similar to other active drugs when compared with placebo. Our findings corroborate this conclusion regarding a direct comparison of DPP-4 inhibitors against sulfonylureas or pioglitazone. For reductions in both HbA_{1c} and body weight, however, our analysis suggests that GLP-1 agonists seem to have an advantage over DPP-4 inhibitors. Hence, they might be preferred in patients in whom glycaemic control or weight reduction are key in therapeutic decision making. In patients who opt not to use a GLP-1 agonist, DPP-4 inhibitors are a good alternative to combine with metformin, given their glycaemic efficacy, which is similar to that of sulfonylureas or pioglitazone, their neutral effect on body weight, and their low risk for hypoglycaemia.

In contrast with previous meta-analyses that suggest a possible association of DPP-4 inhibitors with nasopharyngitis,[4 5 7] urinary tract infections,[4 5 7] and upper respiratory tract infections,[4] we did not find any significant difference between DPP-4 inhibitors and the active comparators. Additionally, DPP-4 inhibitors were not associated with an increase in mortality or serious adverse events compared with the other agents. Our analysis cannot provide firm conclusions about these outcomes, however, because none of the included trials was designed to analyse such end points.

Of note, the number of trials directly comparing DPP-4 inhibitors with pioglitazone[30 31 39 42] and GLP-1 agonists[30 32 40] combined with metformin was small, thus the results of our comparisons regarding these drugs should be interpreted with caution. Moreover, we did not retrieve any eligible trial comparing a DPP-4 inhibitor with insulin. Future research should therefore focus on head to head studies that compare DPP-4 inhibitors with pioglitazone, GLP-1 agonists, or basal insulin as a second line treatment. Finally, from our search we identified only one study directly comparing two different DPP-4 inhibitors (saxagliptin versus sitagliptin both in combination

with metformin).[54] Hence, further head to head trials are required to investigate any potential differences between individual DPP-4 inhibitors in terms of efficacy and safety.

Given the increasing prevalence of type 2 diabetes and its complications throughout the world,[55] cost should also be considered in the therapeutic decision making to support proper allocation of healthcare resources. Existing data regarding the cost effectiveness of DPP-4 inhibitors are rather conflicting. A 2010 Health Technology Assessment did not reach a definite conclusion regarding the cost effectiveness of DPP-4 inhibitors compared with thiazolidinediones.[56] Two studies with data from European countries suggested that sitagliptin[57] and saxagliptin[58] could be cost effective alternatives compared with sulfonylureas combined with metformin. Conversely, analyses conducted in the US[59] and Canada[60] concluded that the addition of a sulfonylurea is more cost effective compared with DPP-4 inhibitors and that increased use of DPP-4 inhibitors over older drugs could confer a considerable financial burden to healthcare systems.

In summary, in patients with type 2 diabetes who do not achieve their glycaemic targets with metformin alone, DPP-4 inhibitors can lower HbA_{1c}, in a similar way to sulfonylureas or pioglitazone, with neutral effect on body weight. Increased unit cost, which largely exceeds that of older drugs and uncertainty about their long term safety, should also be considered.

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Contributors: TK, PP, and AT were responsible for study concept and design. TK and PP participated in the study search and data collection and extraction. TK and AT did the statistical analysis. All authors interpreted the data. TK wrote the first draft of the report, which was critically revised by DRM, KP, and AT. TK, PP, and AT had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AT supervised the study and is guarantor.

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Ethical approval: Not required.

Data sharing: Additional data regarding forest plots are available on request from the corresponding author.

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What is already known on this topic

DPP-4 inhibitors are a relatively new class of oral hypoglycaemic drugs for type 2 diabetes and are associated with a considerable reduction in HbA_{1c}, no weight gain, and no risk of hypoglycaemia compared with placebo

Indirect meta-analyses assessing the efficacy of various hypoglycaemic drugs suggest that DPP-4 inhibitors achieve similar reductions in HbA_{1c} compared with other second line treatments

Evidence has been insufficient to enable existing guidelines to advise on the therapeutic role of DPP-4 inhibitors for type 2 diabetes mellitus

What this study adds

As monotherapy, metformin is superior to DPP-4 inhibitors in reducing HbA1c and body weight but is associated with a higher incidence of diarrhoea, nausea, and vomiting

Combined with metformin, DPP-4 inhibitors seem to have similar glycaemic efficacy to sulfonylureas but have a neutral effect on body weight and low risk for hypoglycaemia

DPP-4 inhibitors can be used as second line treatment in patients with type 2 diabetes who do not achieve their glycaemic targets with metformin alone, but questions about their long term safety still remain to be answered from ongoing trials

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Tables

Table 1| Characteristics of studies and participants included in systematic review of dipeptidyl peptidase-4 (DPP-4) inhibitors for treatment of type 2 diabetes

Primary study	Extension period(s)	Study duration (primary study + extension), weeks	Source of information	Study arms included in meta-analyses	No of patients randomised	Mean HbA_{1c} at baseline (%)	Mean duration of type 2 diabetes (years)
Monotherapy: DPP-4 inhibitors *v* metformin							
Aschner 2010[19]	NA	24	Journal article, trial register	Sitagliptin 100 mg once/day	528	7.2	2.6
				Metformin 1000 mg twice/day	522	7.3	2.1
Goldstein 2007[20]	Williams-Herman 2009[34] + Williams-Herman 2010[35]	104 (24+30+50)	Journal article, trial register	Sitagliptin 100 mg once/day	179	8.9	4.4
				Metformin 1000 mg twice/day	182	8.7	4.4
Hanefeld 2007[46*]	Study 014-10[43*]†	52 (12+40)	Journal article (primary study), trial register (extension)	Sitagliptin 100 mg once/day	110	7.8	3.6
				Metformin 850 mg twice/day	111	7.6	3.3
Bosi 2009[21]	NA	24	Journal article	Vildagliptin 50 mg twice/day	300	8.7	2.1
				Metformin 1000 mg twice/day	294	8.6	2.2
Schweizer 2009[23]	NA	24	Journal article	Vildagliptin 100 mg once/day	169	7.8	2.9
				Metformin 1500 mg/d	166	7.7	3
Schweizer 2007[22]	Goke 2008[36]	104 (52+52)	Journal article, company website	Vildagliptin 100 mg once/day	526	8.7	1.1
				Metformin 1000 mg twice/day	254	8.7	1
Jadzinsky 2009[24]	Pfutzner 2011[41]	76 (24+52)	Journal article, company website	Saxagliptin 10 mg once/day	335	9.6	1.7
				Metformin 1000-2000 mg/day	328	9.4	1.7
Rosenstock 2009[47*]	CV181-011LT[44*]	206 (24+182)	Journal article (primary study), company website (extension)	Saxagliptin 5 mg once/day	106	8	2.5
				Metformin 500 once/day	95	7.9	2.3
Combination treatment with metformin: DPP-4 inhibitors *v* other hypoglycaemic agents							
Nauck2007[26]	Seck 2010[37]	104 (52+52)	Journal article, trial register	Sitagliptin 100 mg once/day	588	7.7	6.5
				Glipizide 5-20 mg/day	584	7.7	6.2
Arechavaleta 2011[25]	NA	30	Journal article, trial register	Sitagliptin 100 mg once/day	516	7.5	6.8
				Glimepiride 1-6 mg/day	519	7.5	6.7
Charbonnel 2006[48*]	Study 020 Phase B[45*]	104 (24+80)	Journal article (primary study), trial register (extension)	Sitagliptin 100 mg once/day	464	8	6
				Glipizide 5-15 mg/day	237	8	6.6
Ferrannini 2009[28]	Matthews 2010[38]	104 (52+52)	Journal article, company website	Vildagliptin 50 mg twice/day	1562	7.3	5.7
				Glimepiride 2-6 mg/day	1556	7.3	5.7
Filozof 2010[27]	NA	52	Journal article, email contact‡	Vildagliptin 50 mg twice/day	513	8.5	6.4
				Gliclazide 80-120 mg/day	494	8.5	6.8
Goke 2010[33]	NA	52	Journal article, company website, email contact‡	Saxagliptin 5 mg once/day	428	7.7	5.5
				Glipizide 5-20 mg/day	430	7.7	5.4
Forst 2010[29]†	NA	12	Journal article	Linagliptin 5 mg once/day	66	8.5	7.3
				Glimepiride 1-3 mg/day	65	8.2	6.7
Handayani 2010[42]	NA	16	Abstract (() Scientific Sessions)	Sitagliptin 100 mg once/day	60	NR	NR
				Pioglitazone 30 mg once/day	60	NR	NR
Bolli 2008[31]	Bolli 2009[39]	52 (24+28)	Journal article, company website	Vildagliptin 50 mg twice/day	295	8.4	6.4
				Pioglitazone 30 mg once/day	281	8.4	6.4
Bergenstal 2010[30]	NA	26	Journal article	Sitagliptin 100 mg once/day	172	8.5	5
				Pioglitazone 45 mg once/day	172	8.5	6
				Exenatide 2 mg once/week	170	8.6	6

Table 1 (continued)

Primary study	Extension period(s)	Study duration (primary study + extension), weeks	Source of information	Study arms included in meta-analyses	No of patients randomised	Mean HbA_{1c} at baseline (%)	Mean duration of type 2 diabetes (years)
Pratley 2010[32]	Pratley 2011[40]	52 (26+26)	Journal article, company website	Sitagliptin 100 mg once/day	219	8.5	6.3
				Liraglutide 1.2 mg once/day	225	8.4	6

HbA_{1c}= glycated haemoglobin; NA=not applicable; NR=not reported.

*In these three trials DPP-4 inhibitor was compared with placebo in primary study (main phase), while in extension period placebo arm switched to active comparator. Hence, only extensions and not primary studies were included in meta-analyses.

†Trials not included in meta-analysis for primary outcome (change in HbA_{1c}) because of missing data, which could not be retrieved through email contact with corresponding authors or drug manufacturers.

‡Data from intention to treat population regarding primary outcome retrieved through email contact with corresponding authors.

Table 2| Number of patients experiencing at least one hypoglycaemic episode, risk ratio (95% confidence interval) for hypoglycaemia with DPP-4 v active comparator, and definition of hypoglycaemia in each treatment arm across all studies in systematic review of dipeptidyl peptidase-4 (DPP-4) inhibitors for treatment of type 2 diabetes

	No with outcome/No of participants analysed			
Study ID*	**DPP-4 inhibitor**	**Active comparator**	**RR (95% CI)**	**Definition of hypoglycaemia**
Monotherapy: DPP-4 inhibitors *v* metformin				
Aschner 2010[19]	9/528	17/522	0.52 (0.24 to 1.16)	Symptomatic hypoglycaemia, threshold value of fingerstick glucose is not reported
Williams-Herman 2010[35]	2/179	4/182	0.51 (0.09 to 2.74)	Symptomatic hypoglycaemia, documentation of fingerstick glucose was not required
Goke 2008[36]	1/304	0/158	1.56 (0.06 to 38.17)	Symptomatic hypoglycaemia, confirmed by fingerstick glucose <3.1 mmol/L
Bosi 2009[21]	2/297	2/292	0.98 (0.14 to 6.93)	Symptomatic hypoglycaemia, confirmed by fingerstick glucose <3.1 mmol/L
Schweizer 2009[23]	0/167	2/165	0.2 (0.01 to 4.09)	Symptomatic hypoglycaemia, confirmed by fingerstick glucose <3.1 mmol/L
Pfutzner 2011[41]	0/335	2/328	0.2 (0.01 to 4.06)	Symptomatic hypoglycaemia, confirmed by fingerstick glucose ≤2.8 mmol/L
Combined with metformin:DPP-4 inhibitors *v* sulfonylurea				
Seck 2010[37]	31/588	199/584	0.15 (0.11 to 0.22)	Symptomatic hypoglycaemia, documentation of fingerstick glucose was not required
Arechavaleta 2011[25]	36/516	114/518	0.32 (0.22 to 0.45)	Symptomatic hypoglycaemia, documentation of fingerstick glucose was not required
Study 020 phase B[45]†	17/464	41/237	0.21 (0.12 to 0.36)	Symptomatic hypoglycaemia, documentation of fingerstick glucose was not required
Filozof 2010[27]	6/510	11/493	0.53 (0.2 to 1.41)	Symptomatic hypoglycaemia, confirmed by fingerstick glucose <3.1 mmol/L
Matthews 2010[38]	35/1553	281/1546	0.12 (0.09 to 0.17)	Symptomatic hypoglycaemia, confirmed by fingerstick glucose <3.1 mmol/L
Goke 2010[33]	0/428	38/430	0.01 (0 to 0.21)	Symptomatic hypoglycaemia, confirmed by fingerstick glucose ≤2.8 mmol/L
Forst 2011[29]	0/66	3/65	0.14 (0.01 to 2.67)	NR
Combined with metformin: DPP-4 inhibitors *v* pioglitazone				
Bergenstal 2010[30]	5/166	1/165	4.97 (0.59 to 42.08)	Symptomatic hypoglycaemia, confirmed by fingerstick glucose <3 mmol/L
Bolli 2009[39]	1/295	1/280	0.95 (0.06 to 15.1)	Symptomatic hypoglycaemia, confirmed by fingerstick glucose <3.1 mmol/L
Combined with metformin: DPP-4 inhibitors *v* GLP-1 agonists				
Bergenstal 2010[30]	5/166	2/160	2.41 (0.47 to 12.24)	Symptomatic hypoglycaemia, confirmed by fingerstick glucose <3 mmol/L
Pratley 2010[32]‡	10/219	13/221	0.78 (0.35 to 1.73)	Symptomatic hypoglycaemia, confirmed by fingerstick glucose <3.1 mmol/L

GLP-1= glucagon like peptide-1; NA= not available

*For each trial, data presented on incidence of hypoglycaemia was extracted from report with longer duration of intervention. Studies 014-10,[43] CV181-011LT,[44] and Handayani 2010[42] not included because data on number of patients experiencing at least one episode of hypoglycaemia were not available in respective reports.

†Data presented are from both 12 week placebo controlled phase (Hanefeld 2007[46]) and 40 week active controlled extension phase (Study 020 phase B[45]).

‡Pratley 2011 report[40] (extension of Pratley 2010 study[32]) not included because it describes hypoglycaemia rates rather than number of patients experiencing at least one episode of hypoglycaemia.

Table 3| **Findings of random effects meta-analyses comparing dipeptidyl peptidase-4 (DPP-4) inhibitors with active comparators on safety outcomes**

Outcome and type of active comparator	No of studies contributing data	No of participants, DPP-4 inhibitors/active comparator		Inverse variance random effects RR (95% CI), DPP-4 inhibitors *v* active comparator	I^2 (%)
		Analysed	With outcome		
All cause mortality					
Metformin	8	1981/1805	5/7	0.65 (0.21 to 1.99)	0
Sulfonylureas	7	4128/3874	15/20	0.79 (0.38 to 1.62)	0
Pioglitazone	2	461/445	1/0	2.98 (0.12 to 72.67)	NA
GLP-1 agonists	2	385/381	3/1	2.30 (0.34 to 15.59)	0
Any serious adverse event					
Metformin	8	1981/1805	79/62	1.09 (0.77 to 1.52)	0
Sulfonylureas	7	4125/3873	444/434	0.96 (0.85 to 1.09)	0
Pioglitazone	2	461/445	17/35	0.47 (0.27 to 0.82)	0
GLP-1 agonists	2	385/381	17/14	1.21 (0.61 to 2.42)	0
Discontinuation because of any adverse event					
Metformin	8	2203/1901	77/92	0.69 (0.51 to 0.94)	0
Sulfonylureas	7	4128/3874	235/251	0.98 (0.73 to 1.31)	40
Pioglitazone	2	461/445	17/22	0.74 (0.40 to 1.38)	0
GLP-1 agonists	2	385/381	12/30	0.40 (0.21 to 0.76)	0
Diarrhoea					
Metformin	6	1810/1647	70/209	0.28 (0.22 to 0.37)	0
Sulfonylureas	6	3609/3355	235/210	1.05 (0.87 to 1.26)	0
Pioglitazone	2	461/445	30/26	1.12 (0.68 to 1.87)	0
GLP-1 agonists	2	385/381	30/49	0.60 (0.39 to 0.92)	0
Nausea					
Metformin	4	1171/1161	20/61	0.35 (0.20 to 0.61)	11
Sulfonylureas	2	1619/1611	76/93	0.81 (0.60 to 1.08)	0
GLP-1 agonists	2	385/381	28/86	0.33 (0.21 to 0.52)	24
Vomiting					
Metformin	4	1515/1245	15/33	0.34 (0.18 to 0.66)	0
GLP-1 agonists	2	385/381	15/36	0.39 (0.27 to 0.64)	61
All active comparators					
Nasopharyngitis	15	6452/6021	603/528	1.06 (0.95 to 1.19)	0
Urinary tract infection	6	2260/2178	110/105	0.86 (0.51 to 1.45)	64
Upper respiratory tract	10	4480/4239	326/277	1.00 (0.83. 1.22)	20

GLP-1= glucagon-like peptide-1; NA=not applicable.

Figures

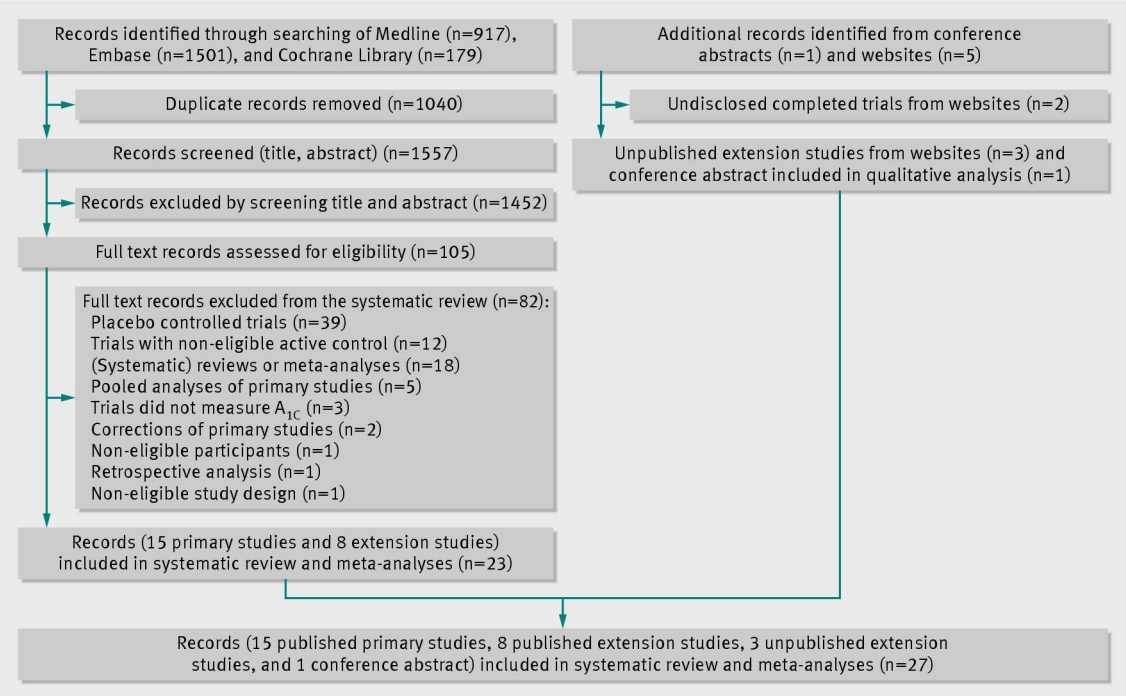

Fig 1 Flow diagram of study selection process

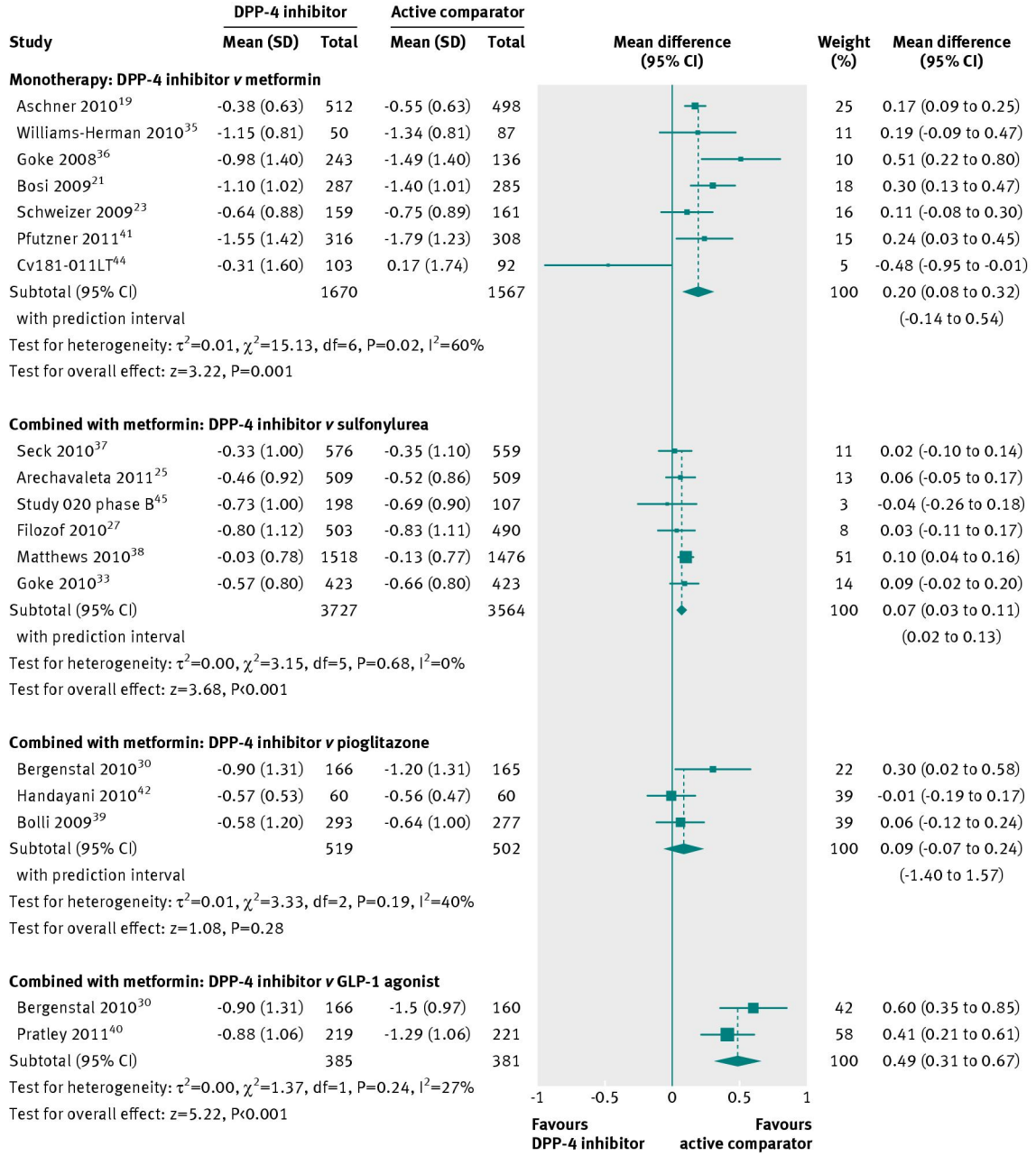

Fig 2 Weighted mean difference in change in HbA_{1c} (%) from baseline. Inverse variance random effects meta-analysis comparing DPP-4 inhibitors and other hypoglycaemic drugs

Study	Events/total: DPP-4 inhibitor	Events/total: Active comparator	Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
Monotherapy: DPP-4 inhibitor *v* metformin					
Aschner 2010[19]	334/439	314/455		34	1.10 (1.02 to 1.20)
Williams-Herman 2010[35]	39/87	16/50		4	1.40 (0.88 to 2.23)
Schweizer 2007[22]	113/249	179/511		17	1.30 (1.08 to 1.55)
Bosi 2009[21]	123/283	114/285		16	1.09 (0.89 to 1.32)
Schweizer 2009[23]	98/161	78/159		15	1.24 (1.01 to 1.52)
Pfutzner 2011[41]	109/314	80/320		11	1.39 (1.09 to 1.77)
Cv181-011LT[44]	19/92	28/103		3	0.76 (0.46 to 1.27)
Subtotal (95% CI)	835/1625	809/1883		100	1.18 (1.07 to 1.29)
with prediction interval					(0.94 to 1.47)
Test for heterogeneity: τ^2=0.01, χ^2=9.14, df=6, P=0.17, I^2=34%					
Test for overall effect: z=3.40, P<0.001					
Combined with metformin: DPP-4 inhibitor *v* sulfonylurea					
Arechavaleta 2011[25]	260/436	232/443		26	1.14 (1.01 to 1.28)
Seck 2010[37]	218/559	242/576		20	0.93 (0.81 to 1.07)
Filozof 2010[27]	125/393	114/386		11	1.08 (0.87 to 1.33)
Matthews 2010[38]	386/1009	388/1051		28	1.04 (0.93 to 1.16)
Goke 2010[33]	155/325	140/329		15	1.12 (0.95 to 1.33)
Subtotal (95% CI)	1144/2722	1116/2785		100	1.06 (0.98 to 1.14)
with prediction interval					(0.88 to 1.27)
Test for heterogeneity: τ^2=0.00, χ^2=5.40, df=4, P=0.25, I^2=26%					
Test for overall effect: z=1.43, P=0.15					
Combined with metformin: DPP-4 inhibitor *v* pioglitazone					
Bolli 2009[39]	89/273	73/285		60	1.27 (0.98 to 1.65)
Bergenstal 2010[30]	56/128	42/137		40	1.43 (1.04 to 1.96)
Subtotal (95% CI)	145/401	115/422		100	1.33 (1.09 to 1.63)
Test for heterogeneity: τ^2=0.00, χ^2=0.30, df=1, P=0.59, I^2=0%					
Test for overall effect: z=2.78, P=0.005					
Combined with metformin: DPP-4 inhibitor *v* GLP-1 agonist					
Bergenstal 2010[30]	66/122	42/137		42	1.76 (1.31 to 2.38)
Pratley 2011[40]	111/221	59/219		58	1.86 (1.45 to 2.40)
Subtotal (95% CI)	177/343	101/356		100	1.82 (1.50 to 2.21)
Test for heterogeneity: τ^2=0.00, χ^2=0.07, df=1, P=0.78, I^2=0%					
Test for overall effect: z=6.06, P<0.001					

Fig 3 Risk ratio for achieving HbA_{1c} <7%. Inverse variance random effects meta-analysis comparing hypoglycaemic drugs and DPP-4 inhibitors

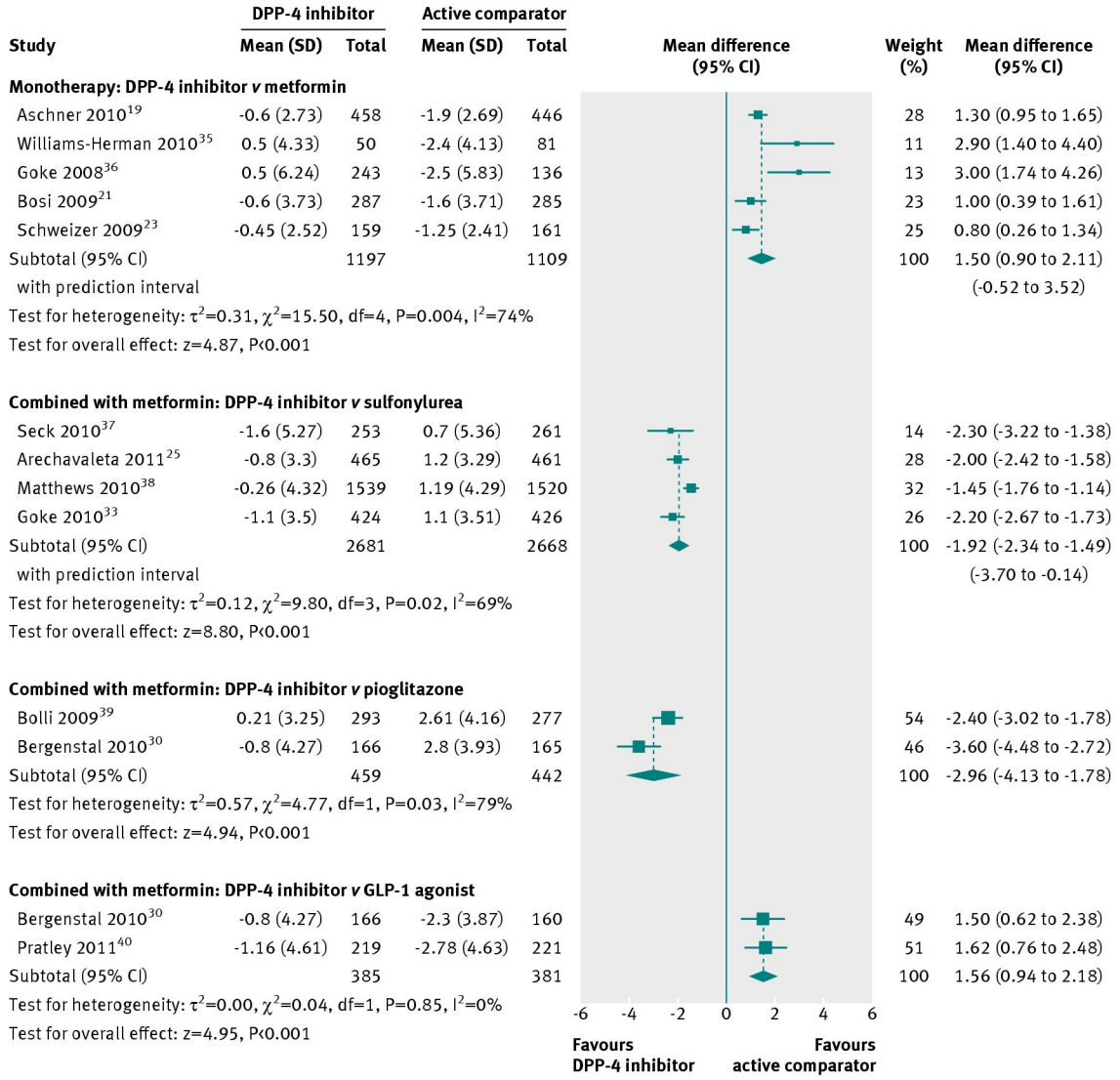

Fig 4 Weighted mean difference in change in body weight (kg) from baseline. Inverse variance random effects meta-analysis comparing DPP-4 inhibitors and other hypoglycaemic drugs