Efficacy and safety of initial combination of DPP-IV inhibitors and metformin versus metformin monotherapy in type 2 diabetes: a systematic review of randomized controlled trials

CRD summary
The authors concluded that compared with equal-dosage metformin monotherapy, initial combination of metformin and dipeptidyl peptidase-IV inhibitors was more effective in type 2 diabetes glycaemic control without additional risk of adverse events. Although the authors' conclusions reflect the results, the varied patients and treatments plus the lack of reporting of trial quality mean the reliability of the evidence is unclear.

Authors' objectives
To compare the effectiveness and safety of initial dipeptidyl peptidase-IV inhibitors and metformin combination therapy with equal-dosage metformin monotherapy for patients with type 2 diabetes.

Searching
MEDLINE and EMBASE were searched for articles published in English. Search terms were reported. Clinicaltrials.gov was also searched.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) that compared dipeptidyl peptidase-IV inhibitors combined with metformin versus equal dosage metformin monotherapy. Eligible participants were drug/treatment-naïve adults (18 years or older) with type 2 diabetes. Trials had to last for a minimum of 12 weeks, report at least one baseline and post-treatment efficacy or safety outcome of interest, and report a dispersion measure for both treatment arms.

In included trials, dipeptidyl peptidase-IV treatments used were sitagliptin (50mg twice daily), vildagliptin (50mg twice daily), saxagliptin (5mg daily) or linagliptin (2.5mg daily) in combination with metformin (either 500mg or 1000mg twice daily or 2000mg daily). The metformin monotherapy control dose was either 1000mg or 2000mg daily. The average duration of diabetes ranged from 1.8 years to 4.5 years (where reported). The percentage of women ranged from 42% to 51%. The average age of the participants ranged from 50 to 55 years. The baseline glycated haemoglobin (HbA1c) ranged from 8.6% to 9.9%.

Two reviewers independently selected trials for inclusion. Disagreements were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed trial quality including adequacy of randomisation and concealment of allocation, blinding methods, losses to follow-up, and whether an intention-to-treat analysis was conducted.

Data extraction
Data were extracted on the change from baseline in glycated haemoglobin, fasting glucose, post-prandial glucose, beta-cell function and insulin resistance; these were used to calculate mean differences. Data were used to calculate risk ratios with corresponding 95% confidence intervals for: percentage of patients achieving glycated haemoglobin below 7%; incidence of total adverse events; gastrointestinal adverse events; drug-related adverse events; serious adverse events; discontinuation due to adverse events; and incidence of hypoglycaemia. Where multiple dosages of dipeptidyl peptidase-IV inhibitors in the combination therapy arm were reported, the authors chose the dosage recommended by the instructions.

One reviewer extracted data which was verified by a second reviewer. Disagreements were resolved by discussion or recourse to a third reviewer.

Methods of synthesis
A fixed-effect model was used to pool weighted mean differences, risk ratios and 95% confidence intervals. Statistical heterogeneity was assessed using $I^2$. Sensitivity analyses were conducted where $I^2$ was greater than 25%, and for low quality studies. Egger's test and the trim-and-fill method were used to assess publication bias.

Data on postprandial glycaemia, B-cell function, insulin sensitivity, and body weight were described narratively.

**Results of the review**

Five RCTs were included in the review with 3,796 participants (range 577 to 1,246). All the trials were randomised and double blind, but none detailed allocation concealment. Withdrawal rates were around 20% in all trials. Follow-up ranged from 18 to 24 weeks.

**Glycated haemoglobin (HbH1c):** Compared with metformin monotherapy, initial combination therapy with dipeptidyl peptidase-IV inhibitors resulted in statistically significantly lower glycated haemoglobin from baseline (WMD -0.55%, 95% CI -0.63 to -0.46; $I^2=0$%). Patients that received dipeptidyl peptidase-IV inhibitor initial combination therapy were more likely to achieve the glycated haemoglobin goal of below 7% than those who received metformin monotherapy (RR 1.55, 95% CI 1.43 to 1.67).

**Fasting plasma glucose:** Patients who received combination therapy reported a lower fasting plasma glucose than those on monotherapy (WMD -0.97 mmol/L, 95% CI -1.26 to -0.68). However, this analysis showed significant heterogeneity ($I^2=68$%). Sensitivity analyses excluding studies using sitagliptin reduced heterogeneity ($I^2=0$) and still reported a significant decline in fasting plasma glucose.

Comparing to monotherapy, combination therapy reported a greater change from baseline for postprandial glycaemia (two trials) and index of beta-cell function (three trials), but there were no statistical differences between the two treatment groups for incidence of hypoglycaemia (three trials) and body weight increase (five trials).

There were no statistically significant differences between groups for any adverse events.

The trim-and-fill analysis suggested publication bias may not significantly affect the results.

**Authors’ conclusions**

Compared with equal-dosage metformin monotherapy, the initial combination of metformin and dipeptidyl peptidase-IV inhibitors were more effective in glycaemic control without additional risk of adverse events. Therefore the initial combination of metformin and dipeptidyl peptidase-IV inhibitors could be considered as a more beneficial therapeutic regimen for drug-naive type 2 diabetes patients.

**CRD commentary**

The review question and inclusion criteria were clearly defined. Some relevant data sources were searched. Restriction to studies in English may mean some data was missed. Appropriate methods to reduce reviewer error and bias were reported. The methods of analysis appear appropriate.

Trial quality was assessed but results were only broadly reported. The authors stated that due to the small number of trials, it was not possible to conduct subgroup analysis for each dipeptidyl peptidase-IV inhibitor or investigate heterogeneity caused by the types of drugs from other factors. They also reported that not all patients enrolled in trials as drug-naive were newly diagnosed type 2 diabetes patients and that some patients received additional treatment after additional therapy, which may have affected the results.

The authors' conclusions reflect the evidence presented, but the lack of reporting of trial quality and the variation in patients and treatment mean that the reliability of the evidence is unclear.

**Implications of the review for practice and research**

**Practice:** The authors stated that different baseline glycated haemoglobin (HbA1c) levels should be considered when starting initial combination therapy.

**Research:** The authors stated that more head to head trials and long-term observational research was needed to determine which route was more appropriate for complicated type 2 diabetes patients.
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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.