Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis

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CRD summary
This review of two new drug classes (glucagon-like peptide 1 analogues and dipeptidyl peptidase 4 inhibitors) concluded that incretin-based therapies offer an alternative to current anti-diabetic drugs, but that further research is required to evaluate their long-term efficacy and safety. Despite some limitations in the review methods and reporting, the authors' cautious conclusions appear reasonable.

Authors' objectives
To assess the efficacy and safety of incretin-based therapy for adults with type 2 diabetes.

Searching
MEDLINE and the Cochrane CENTRAL Register were searched from inception to mid-2007 for studies published in the English language; the search terms were reported. The authors also searched the prescribing information of approved medications, relevant websites, personal reference lists and the reference lists of articles retrieved from the databases. Abstracts presented at the 2005 and 2006 conferences of the American Diabetes Association and European Association for the Study of Diabetes conferences were also searched.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for the review.

Specific interventions included in the review
Studies of incretin-based therapy using glucagon-like peptide-1 (GLP-1) analogues and dipeptidyl peptidase 4 (DPP4) inhibitors were eligible for inclusion. The interventions used in the included studies were the GLP-1 analogues exenatide and liraglutide and the DPP4 inhibitors sitagliptin and vidagliptin. GLP-1 analogues were given in combination with other treatments (sulfonylurea, metformin or a thiazolidinedione) in most studies, while the DPP4 inhibitors were mostly given alone. The control interventions included placebo, insulin and other drug therapies, alone and in combination. Studies of less than 12 weeks' duration were excluded; the duration of the included studies ranged from 12 to 52 weeks.

Participants included in the review
Studies of non-pregnant adults with type 2 diabetes were eligible for the review. The mean participant age was between 50 and 60 years in all the included studies. Where reported, the proportion of women ranged from 32 to 60%, the proportion of participants who were white ranged from 42 to 100% and the duration of diabetes ranged from 1 to 15 years.

Outcomes assessed in the review
The studies were required to report outcomes related to levels of haemoglobin A1C (HbA1C). Other outcomes assessed included fasting plasma glucose level, weight and adverse events.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened studies for inclusion. Any disagreements were resolved by consensus.

Assessment of study quality
Validity was assessed based on baseline differences between groups, description of allocation concealment, intention-to-
Data extraction
Two independent reviewers extracted the data and any disagreements were resolved by consensus. Data on the numbers of outcomes in each group were extracted and used to calculate a relative risk (RR) for dichotomous outcomes or a weighted mean difference (WMD) for continuous outcomes, with corresponding 95% confidence intervals (95% CIs).

Methods of synthesis
How were the studies combined?
The studies were combined by meta-analysis within each drug class using a random-effects model. The studies were weighted by the inverse of the within-study and between-studies variance.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the I-squared statistic. Heterogeneity between trials within a drug class (GLP-1 analogues or DPP4 inhibitors) was explored using pre-specified subgroup analyses by type of comparator, duration of treatment and formulation used.

Results of the review
Nine RCTs of GLP-1 analogues (n=3,184) and 20 RCTs of DPP4 inhibitors (n=9,812) were included.

Allocation concealment was clearly described in three studies, and small baseline differences between groups were noted in three studies. Most studies did not use a true intention-to-treat analysis. Participant withdrawal was approximately 19% in GLP-1 analogue studies and 18% in DPP4 inhibitor studies.

Both GLP-1 analogues and DPP4 inhibitors reduced HbA1C compared with placebo: the WMD was -0.97% (95% CI: -1.13, -0.81) for GLP-1 analogues and -0.74% (95% CI: -0.85, -0.62) for DPP4 inhibitors. GLP-1 analogues and insulin did not differ significantly for this outcome (based on two studies), while the comparison between DPP4 inhibitors and hypoglycaemic agents showed a small but statistically significant difference favouring the latter (WMD 0.21%, 95% CI: 0.02, 0.39; based on four studies). DPP4 inhibitors were associated with weight loss compared with control interventions (WMD -2.37 kg, 95% CI: -3.95, -0.78), although heterogeneity was high for this outcome (I-squared 98%). DPP4 inhibitors were associated with a small but statistically significant increase in weight relative to placebo (WMD 0.48 kg, 95% CI: 0.30, 0.66). GLP-1 analogues were associated with increased risk of gastrointestinal adverse events relative to comparators (RR 2.92, 95% CI: 2.02, 4.24 for nausea; RR 3.32, 95% CI: 2.51, 4.41 for vomiting; RR 2.23, 95% CI: 1.72, 2.89 for diarrhoea), while DPP4 inhibitors were associated with increased risk of urinary tract infections (RR 1.52, 95% CI: 1.04, 2.21) and headache (RR 1.38, 95% CI: 1.10, 1.72). Other outcomes were reported.

Authors' conclusions
Incretin-based therapy has modest efficacy and a favourable weight change profile and offers a possible alternative to current hypoglycaemic agents for adults with type 2 diabetes.

CRD commentary
This review addressed a clear question and the inclusion criteria were clear. The authors searched a range of sources for published and unpublished studies. Only two bibliographic databases were searched and the search was restricted to English language studies. This puts the review at some risk of language bias and of missing relevant studies. Validity was assessed using appropriate criteria, although the results of the assessment were not taken into account in the analysis. Measures were taken to reduce the risk of bias and errors in the study selection and data extraction processes, but it is not clear whether similar methods were used for the validity assessment.

Adequate details of the included studies were presented. High levels of statistical heterogeneity were present for some
outcomes, suggesting that meta-analysis might not have been appropriate. As the authors noted, the review was unable to evaluate the long-term efficacy and safety of incretin-based therapy. The authors' conclusions compared incretin-based therapies with alternative hypoglycaemic agents despite the fact that most of the comparisons, especially for DPP4 inhibitors, were with placebo. Despite this caveat, the authors' cautious conclusions and recommendations for further research appear reasonable.

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

**Practice:** The authors stated that patients with mild diabetes who are at risk of hypoglycaemic events and in need of weight loss may benefit from treatment with incretin-based therapies.

**Research:** The authors stated that long-term evaluation of the safety and efficacy of these agents in both controlled trials and clinical practice is required.

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**Other publications of related interest**

This additional published commentary may also be of interest. Vella A. Review: incretin therapy improves glycemic control more than placebo in patients with type 2 diabetes. ACP J Club 2008;148:3.

**Indexing Status**

Subject indexing assigned by NLM

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