Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review
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CRD summary
This generally well-conducted review examined antidiabetic agents and morbidity and mortality outcomes in people with heart failure and diabetes. The authors concluded that the only agent not associated with harm was metformin, which reduced mortality. These conclusions are likely to be reliable but were based on small numbers of mainly observational and variable studies.

Authors' objectives
To examine the association between antidiabetic agents and morbidity and mortality in people with heart failure and diabetes.

Searching
MEDLINE, HealthSTAR, EMBASE, CINAHL, International Pharmaceutical Abstracts, AMED, the Cochrane CENTRAL Register and Web of Science were searched from inception to July 2007. The reference lists of retrieved studies and reviews were screened, and experts and authors of included studies were contacted in order to locate further primary studies. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Studies with a contemporaneous control group were eligible for inclusion. The included studies were randomised controlled trials (RCTs) and prospective and retrospective cohort studies.

Specific interventions included in the review
Studies of antidiabetic agents were eligible for inclusion. The included studies evaluated insulin, metformin, thiazolidinediones and sulfonylureas. The comparators included insulin, metformin, thiazolidinediones, sulfonylurea, non-sulfonylurea secretagogues, alpha-glucosidase inhibitors, diet and placebo.

Participants included in the review
Studies of people with both diabetes and heart failure were eligible for inclusion.

Outcomes assessed in the review
Studies reporting all-cause hospital admission, hospital admission for heart failure or mortality outcomes were eligible for inclusion. Although some of the included studies assessed other outcomes, the review focused on these predefined outcomes.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the primary studies. Any disagreements were resolved by consensus after consulting a third reviewer.

Assessment of study quality
Methodological quality was assessed using the validated Downs 1998 checklist for randomised and non-randomised studies. A score of 12 (38%) or more out of 32 on the checklist was considered to indicate acceptable quality. Two reviewers independently performed the quality assessment.

Data extraction
Two reviewers independently extracted the data. Crude and adjusted odds ratios (ORs) for all-cause mortality and hospital admission, together with 95% confidence intervals (CIs), were extracted from each study. Where insufficient information was provided, authors were contacted for further details.
Methods of synthesis
How were the studies combined?
ORs were pooled using a random-effects model providing there was no significant statistical heterogeneity (defined as p<0.10 or I-squared>50%) to generate pooled ORs with 95% CIs. It appears that crude rather than adjusted ORs were used for the meta-analysis.

How were differences between studies investigated?
The studies were grouped according to antidiabetic agent assessed. Statistical heterogeneity was assessed using the Q test and the I-squared statistic.

Results of the review
Eight studies (31,284 participants) were included in the review: 1 RCT, 2 post hoc subgroup analyses from RCTs, 1 prospective cohort study and 4 retrospective cohort studies.

All studies were considered to be of acceptable quality, with scores ranging from 13 (41%) to 22 (69%); the median score was 16 (50%).

Insulin (4 studies, 19,205 participants).

Studies only reported on the outcome of all-cause mortality and were too heterogeneous to pool. Three studies found increased risks of all-cause mortality, cardiovascular morbidity and mortality, and/or hospital admission with insulin compared with diet, sulfonylurea, metformin and thiazolidinediones. One study reported no difference in all-cause mortality for insulin-treated patients compared with those using sulfonylurea metformin, thiazolidinediones, non-sulfonylurea secretagogues and alpha-glucosidase inhibitors.

Metformin (3 studies, 17,501 participants).

One study found no difference in mortality between patients using metformin and those taking sulfonylurea, non-sulfonylurea secretagogues, alpha-glucosidase inhibitors and insulin. Two studies reported reduced mortality with metformin, alone or in combination with sulfonylurea, compared with sulfonylurea, non-sulfonylurea secretagogues, alpha-glucosidase inhibitors and insulin. Studies were too heterogeneous to pool for this outcome. All-cause hospital admission at 1 year was also reduced (OR 0.85, 95% CI: 0.76, 0.95; 2 studies; I-squared 20.9%; p=0.26).

Thiazolidinediones (4 studies, 22,476 participants).

In a pooled analysis, thiazolidinediones were associated with reduced mortality compared with sulfonylurea, non-sulfonylurea secretagogues, alpha-glucosidase inhibitors and insulin (OR 0.83, 95% CI: 0.71, 0.97; 4 studies), although there was moderate statistical heterogeneity (I-squared 52%; p=0.10). Hospital admission for heart failure was, however, increased with thiazolidinediones (OR 1.13, 95% CI: 1.04, 1.22; 4 studies; I-squared 0%). One study reported no effect on all-cause hospital admission.

Sulfonylurea (2 studies, 18,042 participants).

One study found no difference in risk of mortality for sulfonylurea compared with non-sulfonylurea secretagogues, alpha-glucosidase inhibitors, metformin, thiazolidinediones and insulin. The other study found that sulfonylurea monotherapy was associated with a higher risk of mortality than metformin or a metformin-sulfonylurea combination.

Authors' conclusions
Metformin was the only antidiabetic agent not associated with harm in patients with heart failure and diabetes; it was associated with reduced mortality.
CRD commentary
The review question and inclusion criteria were clear. The search for primary studies employed a wide range of databases, as well as other strategies and sources of unpublished material, and was conducted without language restrictions; the likelihood of relevant studies being missed is therefore low. Two independent reviewers performed the study selection, quality assessment and data extraction, thus minimising the risk of reviewer error and bias during these processes. Study quality was assessed and methodological limitations of the included studies were discussed. The study results were pooled only where studies were sufficiently similar, and appropriate statistical methods were used. The review was generally well-conducted and is likely to be reliable. However, the strength of the authors' conclusions is limited by the small numbers of mainly observational and heterogeneous studies available. The recommendation for further research appears justified.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that research is needed to determine the optimal approach for glycaemic control in patients with heart failure. They advised that an RCT be performed using metformin or thiazolidinedione, to evaluate effects on glycaemic control, long-term outcomes, morbidity and mortality.

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