The safety of metformin in heart failure
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CRD summary
This review assessed the safety of metformin for people with diabetes and heart failure. The authors concluded that although metformin may be safe, further studies are needed to provide conclusive evidence. There were methodological limitations to the review, but these conclusions are suitably conservative given the limited evidence presented.

Authors' objectives
To assess the safety of metformin in people with diabetes and heart failure.

Searching
MEDLINE and International Pharmaceutical Abstracts were searched from 1966 to February 2007; the search terms were reported.

Study selection
Study designs of evaluations included in the review
No inclusion criteria were given for the study design, with the exception that case reports were eligible if CHF was the only contraindication to metformin use. Retrospective cohort studies and prospective randomised studies were included. The duration of follow-up ranged from 1 to 4 years.

Specific interventions included in the review
Studies assessing metformin were eligible for inclusion. The comparators in the included studies included thiazolidinedione (TZD), insulin and sulfonylurea. One study included a group taking metformin and sulfonylurea combined therapy. One study compared continuation of metformin therapy with discontinuation of metformin therapy. The participants were also taking other drugs for heart failure.

Participants included in the review
Studies of people with type 2 diabetes and congestive heart failure (CHF) were sought. The participants in the included studies were people with CHF and diabetes, patients recently discharged from hospital with CHF and diabetes, and users of metformin with an elevated serum creatinine between 1.5 and 2.5 mg/dL and coronary artery disease, CHF or chronic obstructive pulmonary disease. One study excluded people who had been hospitalised for CHF in the previous 3 years. One study excluded participants younger than 65 years; in the other studies the mean ages ranged from 64 to 72 years.

Outcomes assessed in the review
Studies that reported clinical outcomes were eligible for inclusion. The outcomes reported were incidence of lactic acidosis, mortality, rate of myocardial infarction or cardiovascular events, and hospital readmission rates.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
The studies were described separately.
How were differences between studies investigated?
Differences between the studies were discussed.

Results of the review
Three studies (18,643 participants) were included: one prospective randomised controlled trial (393 participants; 94 with CHF) and two retrospective cohort studies (18,250 participants).

In the randomised controlled trial (393 participants; 94 with CHF) there were no cases of lactic acidosis. There were no differences between the group continuing metformin therapy and the group discontinuing metformin therapy in mortality or cardiovascular outcomes.

In one study (16,417 participants) metformin use, compared with sulfonylurea or insulin, was associated with a lower risk of death from all causes (adjusted hazard ratio 0.86, 95% confidence interval: 0.78, 0.97). Metformin use was also associated with lower unadjusted rates of hospital readmissions for CHF and all causes, compared with sulfonylurea or insulin. However, multivariate analysis showed no statistically significant difference in hospital admission rates for all causes in those taking metformin or TZD compared with those taking insulin or sulfonylurea.

In one study (1,833 participants) fewer deaths occurred in the metformin group (monotherapy 33%, combined with sulfonylurea 31%) than in the sulfonylurea monotherapy group (52%). There was no difference in hospitalisation rates. Metformin was not associated with an increased risk of lactic acidosis, and none of the deaths or hospitalisations were attributable to acidosis.

Authors’ conclusions
Current data suggest that metformin may be safe for people with CHF. However, large prospective trials are needed to provide conclusive evidence.

CRD commentary
The inclusion criteria for this review were only partially stated: criteria for study design and outcomes of interest were vague. Searching was limited to two databases and there were no attempts to identify unpublished studies. It is possible that studies were missed and this could have affected the results of the review. The methods of the review were not described, thus it is not possible to comment on any likelihood of reviewer bias, or the possible introduction of errors into the process of the review. The quality of the included studies does not appear to have been systematically assessed, although the authors commented on several limitations of the included studies, particularly the retrospective studies, in which metformin use might have been avoided in patients with more severe CHF. The authors acknowledged that the information from the review is limited by the types of studies available for inclusion. Cohort studies are open to selection bias, and other factors, that make it difficult to establish a cause and effect relationship. The authors’ conclusions are suitably conservative given the limited evidence presented.

Implications of the review for practice and research
Practice: The authors stated that metformin should probably not be routinely used for people with CHF. If it is used, patients should be monitored closely for lactic acidosis.

Research: The authors stated that a large randomised placebo-controlled trial would be required to confirm the safety of metformin therapy in patients with CHF, although they acknowledged that this may not be practicable. A retrospective study that controls for disease and participant characteristics and drug dosages could provide additional information.

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Record Status
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.