CRD summary
This review concluded that survival rates and associated morbidity are not significantly different when heart transplantation is a primary or secondary heart operation; however, reoperations require longer operation times. Since these conclusions are based on the results of a small number of studies exhibiting statistical and clinical variability, they should be interpreted with caution.

Authors’ objectives
To compare the outcome of heart transplantation as a primary or secondary operation in cardiac patients.

Searching
PubMed, Ovid and the Cochrane Library were searched; the search terms were listed. The authors did not state which specific databases within these electronic sources were searched, or the time period used. The reference lists from retrieved articles were checked.

Study selection
Study designs of evaluations included in the review
The authors did not specify which types of study design were eligible for inclusion in the review; however, it is implicit that comparative studies were eligible.

Specific interventions included in the review
Studies comparing heart transplantation carried out as a primary cardiac surgical procedure with heart transplantation carried out after one or more cardiac surgeries (reoperation) were eligible for inclusion.

Participants included in the review
Studies of cardiac patients requiring heart transplantation were eligible for inclusion. Studies which were limited to paediatric populations were excluded from the review. Studies were also excluded if more than 15% of reoperation patients had undergone previous heart transplantation. The participant study groups included in the review were matched for one or more of the following characteristics: gender, pre-transplantation haemodynamic parameters, pre-transplantation biochemistry, origin of heart failure, age and urgency of transplantation. The most common causes of heart failure in decreasing order were ischaemic heart disease, cardiomyopathy and valve disease.

Outcomes assessed in the review
Eligible studies had to report at least one of the following outcomes of interest: intra-operative outcomes (e.g. total operative time, cross-clamp time, cold ischaemic time, bypass time), post-operative outcomes (e.g. re-exploration, wound infection rates, renal failure, 30-day mortality), causes of death (e.g. graft rejection, multi-organ failure, infection and malignancy), resources (e.g. length of hospital stay, length of intensive care stay) and actuarial outcomes (e.g. 1-, 2- and 5-year mortality rates). Studies where the outcome in both study groups was zero were excluded from the analysis of that outcome.

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
Study quality was assessed using the modified Newcastle-Ottawa Scale for non-randomised studies, which assesses study selection, group comparability and outcome assessment. Studies scoring 8 or more stars out of 9 were classified as high-quality studies. The authors did not state how many reviewers performed the validity assessment.
Data extraction
Three reviewers independently extracted the data from the included studies. There was 100% agreement between the three reviewers. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes, hazard ratios (HRs) with 95% CIs for time-to-event outcomes, and means with standard deviations for continuous outcomes. Where zero events occurred in one study group, 0.5 was added to the outcome in both study groups. If not reported, HRs were calculated, where possible, from the available data or estimated from Kaplan-Meier curves.

Methods of synthesis
How were the studies combined?
The studies were grouped according to outcome and pooled ORs, HRs or weighted mean differences (WMDs) were calculated, along with 95% CIs, using a random-effects model. Publication bias was assessed using funnel plots.

How were differences between studies investigated?
Statistical heterogeneity was calculated using chi-squared and I-squared statistics. Potential sources of heterogeneity were explored using sensitivity analyses comparing study quality (8 stars or more), study size (more than 145 patients) and year of publication (in last 10 years). The results of both random-effects and fixed-effect analyses were compared.

Results of the review
Seven retrospective studies (n=1,004) were included in the review; these evaluated 381 reoperation patients and 623 primary transplantation patients.

Two studies scored 9 stars for quality, three scored 8 and two scored 7.

Intra-operative outcomes.
Reoperations were associated with significantly longer total operative times (WMD 59.44, 95% CI: 28.96, 89.93, p<0.001; 5 studies), cold ischaemic times (WMD 14.62, 95% CI: -0.03, 29.27, p=0.05; 5 studies), cardiopulmonary bypass times (WMD 25.24, 95% CI: 10.39, 40.10, p<0.001; 5 studies) and aortic cross-clamp times (WMD 7.93, 95% CI: 5.26, 10.60, p<0.001; 4 studies).

Post-operative outcomes.
Significantly more re-exploration procedures (OR 3.51, 95% CI: 1.97, 6.26, p<0.001; 6 studies) and a greater volume of blood transfusions (WMD 2.21, 95% CI: 1.24, 3.17, p<0.001; 4 studies) were required for reoperation surgeries compared with primary transplantation surgeries. All other post-operative complications were greater in the reoperation group, but none of the differences reached statistical significance. No statistically significant differences between the two intervention groups were seen for the cause of mortality. Six studies assessing graft rejection showed that rejection episodes were similar in the two intervention groups; a meta-analysis was not possible due to differences in the outcome measures used.

Resources.
Patients experienced longer hospital and intensive care unit (ICU) stays in the reoperation group compared with those in the primary transplantation group, but only the difference in length of ICU stay was statistically significant (WMD 1.37, 95% CI: 0.21, 2.54, p=0.02).

Thirty-day mortality and actuarial survival.
There were no significant differences between the reoperation and primary transplantation groups with regard to 30-day mortality and 1-, 2- and 5-year mortality rates.

Sensitivity analysis.
The lack of studies meant that the volume of blood transfusions could not be assessed in the analysis of study quality and study size; length of ICU stay was also excluded from the analysis of study size. For the majority of outcomes tested the differences between reoperation and primary transplantation remained significant when the effects of study quality, study size and publication date were investigated. However, the differences between reoperation and primary transplantation became non significant for cold ischaemic time and length of ICU stay when only studies published after 1996 were included in the analysis. Study quality appeared to account for some of the heterogeneity observed in all of the outcomes analysed, while study size appeared to account for some of the heterogeneity observed in the assessment of cold ischaemia.

Publication bias.

The funnel plots suggested no evidence of publication bias.

Authors' conclusions
Survival and associated morbidity are not significantly different between primary and secondary transplantations; however, reoperations are technically more demanding, requiring longer operation times.

CRD commentary
This review answered a clear research question although the authors did not specifically define what types of study design were eligible. Although the authors appear to have used several databases, the search for studies was poorly described, both in terms of the specific sources and the publication dates searched. Since it is unclear whether any limits were placed on the language of publication, it is not possible to assess the risk of language bias. There also appears to have been no specific attempt to locate unpublished material, although the authors did use funnel plots to investigate publication bias and found no evidence for its existence. However, given the small number of included studies, such an assessment is unlikely to be reliable. The authors made attempts to reduce bias and errors during the data extraction but, again, there were few details about how studies were selected for inclusion in the review and how their quality was assessed; it is therefore difficult to assess the risk of bias and error associated with these stages of the review process. Quality was assessed using a published tool specifically designed for non-randomised studies, and a breakdown of each individual study score was provided. All of the studies used a retrospective design and most were judged to be of high quality. However, there were insufficient study details to judge how clinically different the studies were.

The studies were combined using meta-analysis, although for many comparisons only small numbers of studies were combined; statistical heterogeneity was also frequently associated with the pooled effect sizes. The authors investigated potential sources of heterogeneity but, again, the numbers of studies included in these sensitivity analyses were small and so their reliability is unclear. In summary, the authors' conclusions are drawn from the combined results of only small numbers of retrospective studies with statistical and clinical heterogeneity, suggesting that the effect sizes should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors stated that intensive care staff should anticipate a higher rate of immediate post-operative complications in reoperation patients and therefore ensure closer observation and monitoring.

Research: The authors stated that further research is required in a number of areas. Specifically: haemostatic agents and their role in reoperation patients; higher quality prospective studies; outcomes in reoperations after a specific primary operation and/or cause of heart failure; and studies focusing on simple or complicated primary heart conditions.

Bibliographic details
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.