Adverse events in coronary artery bypass graft (CABG) trials: a systematic review and analysis

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CRD summary
This review assessed the incidence of major adverse events within 30 days of surgery in clinical trials and cohort studies. The authors concluded that incidence varies widely across studies and patient populations. Study quality was not assessed and this could have affected the reliability of the findings. However, the authors’ conclusions appear suitably conservative.

Authors’ objectives
To quantify the incidence of major adverse events occurring within 30 days of coronary artery bypass graft (CABG) surgery.

Searching
MEDLINE and Current Contents were searched for studies published in English between 1990 and 2001; the search terms were given. Bibliographies of identified papers and reviews were also checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), non-randomised controlled trials (non-RCTs) and cohort studies were eligible for inclusion. To be included, RCTs or non-RCTs had to have enrolled at least 20 people per group and cohort studies at least 50 people.

Specific interventions included in the review
Studies of standard isolated CABG surgery were sought. Studies comparing different bypass techniques or types of anaesthesia were excluded. In the included studies, some CABG were emergencies, with warm blood cardioplegia. The mean number of grafts was 3.2 (range: 1 to 4.5).

Participants included in the review
The participants were those undergoing CABG surgery. Studies where all the participants were considered to be at a high risk were excluded. High risk was defined as people with particular co-morbidities such as diabetes, prior myocardial infarction (MI), renal dysfunction, poor ejection fraction (less than 30%), unstable angina, over 70 years of age, reoperation, or emergency CABG. However, studies that enrolled general populations where some participants were at a high risk were included. In the included studies, 82% of the participants were male and the mean age was 62.8 years. Some participants were of New York Heart Association (NYHA) class III to IV; some had a low ejection fraction, diabetes, renal dysfunction, hypertension, history of stroke, MI or cardiovascular disease, unstable angina, hypercholesterolaemia, prior CABG or other heart surgery, or prior revascularisation (percutaneous transluminal coronary angioplasty).

Outcomes assessed in the review
The outcome was a major adverse event, defined as post-operative MI, stroke, gastrointestinal bleeding, renal failure or death, occurring within hospital or within 30 days after surgery. Outcomes from only ‘placebo’, ‘standard’ or ‘control’ treatment arms of the trials were considered; these terms were not defined. The definition of MI was taken as that in the included studies; it varied across the studies. Studies that reported intra- or peri-operative outcomes, or those where it was unclear whether the outcomes were peri- or post-operative, were excluded.

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**

One reviewer extracted the data onto a form and a second reviewer checked it. The extracted data included patient and treatment characteristics and the number of participants with each adverse event outcome. In addition, follow-up times were classified as either ‘in hospital’ or ‘30 days’.

**Methods of synthesis**

How were the studies combined?

A meta-analysis was undertaken to estimate the incidence of major adverse events. A random-effects model was used. The median and mean number of events with standard errors were also reported. The odds ratio and 95% confidence intervals were calculated for 30-day mortality. A fixed-effect model was used for mortality results grouped by age.

How were differences between studies investigated?

Separate analyses were performed to investigate the influence of study location (North America, Europe or other), single versus multicentre, study design, and group variables (e.g. studies that included emergency CABG, participants with prior CABG, ejection fraction greater than 50% versus less than or equal to 50%, and mean age). A bivariate meta-regression, which related selected study characteristics to each of the individual adverse events, was also performed.

**Results of the review**

A total of 176 six studies (205,667 participants) were included: 69 RCTs (9,598 participants), 13 non-RCTs (2,019 participants) and 94 cohort studies (194,050 participants).

In-hospital events.

The most common adverse event across all studies and all stratified categories was MI (total and nonfatal; 52 studies, 69,487 participants). The average incidence of MI (total) was 3.9% (median 2.9%, range: 0 to 29). The incidence of MI differed significantly between RCTs and cohort studies (6.3% versus 2.7%, P<0.05), and between single and multicentre studies (2.8% versus 7.9%, P<0.01). Older age (older than 60 years) and lower ejection fraction (less than or equal to 50%) were not associated with a higher incidence of MI. Nonfatal strokes were reported in 21 studies (26,750 participants) and occurred in 1.3% (median 1.3%, range: 0 to 3.2). The incidence was significantly lower in RCTs than in cohort studies (1.0% versus 1.5%, P<0.01).

The incidence of gastrointestinal bleeding (8 studies, 12,897 participants) was 1.5% (median 1.2%, range: 0.7 to 2.7). There were no significant differences when different variables were investigated.

Renal failure requiring dialysis was reported in 23 studies (22,798 participants) and the incidence was low, i.e. 0.8% (median 0.7%, range: 0 to 6.2). The incidence was significantly higher in cohort studies than in RCTs (1.0% versus 0.4%, P<0.05).

The within-hospital post-operative mortality rate was 1.7% (median 1.5%, range: 0 to 6.6). The incidence was significantly lower in those studies that only included elective CABG than in those with mixed elective and emergency CABG (1.5% versus 1.8%, P<0.05). There was a significantly lower incidence in RCTs than in cohort studies (1.5% versus 1.8%, P<0.05), and in single-centre studies than in multicentre studies (1.5% versus 2.5% P<0.05).

Thirty-day events.

Death was the only adverse event commonly reported at 30 days (70 studies, 81,136 participants). The average death rate was 2.1% (median 2.0%, range: 0 to 7.7%). When comparing subgroups, death was higher in the mixed CABG group compared with elective CABG, multicentre compared with single-centre studies, and in those aged older than 60 years compared with those aged 60 and younger. Other outcomes were too infrequently reported at 30 days.

Older age, female gender, presence of diabetes or hypertension, and history of prior heart surgery or MI were associated with an increased risk of death after CABG surgery.
Authors’ conclusions
The incidence of major adverse events varied widely across studies and patient populations. These differences must be considered when interpreting adverse events in CABG trials and when planning such studies.

CRD commentary
This was a clearly written review with well-stated aims. The search was limited to publications in English and there was no mention of attempts to find unpublished studies. It is therefore possible that studies were missed. Some methods of the review were not described (e.g. study selection, quality assessment). Subjective decisions during selection can introduce bias. The authors did not include full details of the included studies, but they did present a summary table and narrative description. No attempt was made to assess the quality of the studies included. Since study design made a difference to the incidence of adverse events, it is likely that study quality might also affect the reported result. A large number of subgroup analyses were carried out and it is possible that some differences between the groups may have been the result of chance. The authors' conclusions are suitably conservative.

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

Research: The authors stated that future trialists should use uniform definitions and terminology (e.g. for MI) and always provide minimum baseline risk factors, for instance, those identified by the Society for Thoracic Surgeons (see Other Publications of Related Interest).

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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.