Cardiac medical therapy in patients after undergoing coronary artery bypass graft surgery: a review of randomized controlled trials

Okrainec K, Platt R, Pilote L, Eisenberg M J

CRD summary
This review found evidence to support the use of aspirin and antilipaemic agents after coronary artery bypass grafting. Limited evidence suggested that angiotensin-converting enzyme inhibitors may be beneficial, but there was no evidence for the use of betablockers, nitrates or calcium-channel blockers. There were some problems with the review and the conclusions should be treated with caution.

Authors' objectives
To review the evidence from randomised controlled trials (RCTs) on the effects of cardiac medical therapy on people who have undergone coronary artery bypass grafting (CABG).

Searching
MEDLINE was searched from 1966 to 2004; the search terms were given. In addition, the reference lists of identified studies were checked. Only English language papers were sought.

Study selection
Study designs of evaluations included in the review
Randomised placebo-controlled trials with 100 or more participants, and a follow-up of at least one year, were eligible for inclusion.

Specific interventions included in the review
Studies on cardiac medical therapy given post-CABG were sought. The medications considered were aspirin, antilipid agents, beta-blockers, calcium-channel blockers (CCBs), nitrates and angiotensin-converting enzyme (ACE) inhibitors. Trials that tested the use of cardiac medication before CABG or peri-operatively were excluded unless the medication continued after hospital discharge.

Details on the medication regimens were given in the included studies. In the aspirin studies some participants also received dipyridamole or warfarin. The antilipaemic agents assessed were lovastatin, gemfibrozil, colestipol and niacin; the beta-blocker was metoprolol, the CCB was diltiazem and the ACE inhibitor was quinapril. In one study aspirin was initiated 12 months post-operatively. Antilipid agents were initiated between 3 months and 11 years post-operatively. In the study on diltiazem, all participants received the drug until one year post-operatively and then were randomised to continue or discontinue treatment. All other treatments were initiated either pre-operatively or up to 21 days post-operatively.

Participants included in the review
Studies on people who had undergone CABG were sought. Studies on cardiac patients that included a subset of people who had been treated post-myocardial infarction (MI) or post-percutaneous coronary intervention were not included. People with diabetes or low left ventricular ejection fraction, or smokers, were excluded from some studies. No other details of the included participants were given.

Outcomes assessed in the review
The outcomes of interest were cardiovascular outcomes (e.g. unstable or stable angina, MI, cardiovascular death), total mortality, native coronary artery or bypass graft occlusion (assessed by angiography only), and the need for revascularisation. The results of exercise tests were also reported. Studies assessing the effects of beta-blockers or CCBs on atrial fibrillation were excluded, as were those that looked at the effect of nitrates or CCBs on vasospasm.

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. The percentages of cardiovascular events in each group, along with P-values, were extracted.

**Methods of synthesis**
How were the studies combined?
The studies were combined in a narrative discussion and in tabular format, grouped by type of medication.

How were differences between studies investigated?
The studies were grouped according to type of study medication, and differences were discussed in the narrative.

**Results of the review**
Fourteen RCTs (5,779 participants) were included.

Aspirin (8 trials, 2,609 participants): between 8 and 50% of the participants were excluded from the studies’ final analyses as they failed to undergo follow-up angiography. Two trials found that aspirin, started within one day of CABG, had a beneficial effect on graft occlusion at 12 months. Six trials, one starting aspirin pre-operatively, four between 2 and 5 days, and one at one year post-operatively, found no significant difference in graft occlusion. Two trials looked at cardiovascular events and found no significant difference in the incidence of angina, MI or death between the placebo- and aspirin-treated groups.

Antilipid agents (3 trials, 1,934 participants): there was a significant reduction in the progress of atherosclerosis with antilipid agents. Subsequent cardiovascular events were not significantly reduced at the 4-year follow-up, but were at the 7-year follow-up (1 trial).

Beta-blockers (1 trial, 967 participants): at 2 years there was no difference in exercise test capacity between the groups. However, those taking placebo were found to have a higher (worse) chest pain score. None of the end points of repeat revascularisation, unstable angina, MI or death were found to be significantly different.

CCBs (1 trial, 120 participants): at the 4-year follow-up there were no significant differences in recurrence of angina, residual ischaemia or cardiac death.

ACE inhibitors (1 trial, 149 participants): there were no differences in exercise testing between the two groups. However, quinapril appeared to improve the incidence of ischaemic events (angina, death, MI revascularisation, stroke or transient ischaemic attacks) at one year; the event rate was 3.5% in the quinapril group and 15% in the placebo group (P=0.02).

No trials assessing the use of nitrates were found.

**Authors’ conclusions**
Very few studies were found that specifically assessed cardiac medical therapy post-CABG. The use of aspirin and antilipid agents seems warranted. There was limited evidence to suggest that ACE inhibitors may be beneficial, but more evidence is needed. There was little evidence to support the use of beta-blockers, CCBs or nitrates after CABG.

**CRD commentary**
The aims of this review were only partially described. In particular, criteria regarding the initiation of medication regimens in relation to the timing of CABG were not defined. The database search was limited to MEDLINE and only English language studies were included. It is therefore possible that studies might have been missed, which could affect the conclusions of the review. The methods of the review were not described, so it is possible for bias to have been introduced during the study selection or data extraction processes; this could have affected the results of the review. The authors do not appear to have formally assessed quality, although they did describe some problems with the included studies. As the authors pointed out, many of the studies had large losses to follow-up and this could have resulted in bias in the results. There was very little information on the participants in the included studies, what was given indicated that some studies excluded people of high risk. This could affect the generalisability of the results. In view of these comments, the authors' conclusions should be treated with caution.

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

Practice: The authors stated that aspirin should be started immediately after CABG and continued indefinitely, and that the routine use of antilipid agents appears well justified.

Research: The authors stated that there is an urgent need for more RCTs to assess the benefits of cardiac medical therapy post-CABG.

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the reliability of the review and the conclusions drawn.