Best evidence topic - Cardiac general

Is clopidogrel beneficial following coronary bypass surgery?

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Summary

A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was whether clopidogrel is superior to aspirin in preventing adverse events post coronary arterial bypass grafting. Altogether 220 papers were found using the reported search, of which four presented the best evidence to answer the clinical question. The author, journal, date and country of publication, patient group studied, study type, relevant outcomes, results, and study weaknesses of these papers are tabulated. We conclude that if aspirin is not tolerated, clopidogrel is an acceptable alternative, but there is no strong evidence that clopidogrel is superior to aspirin postcoronary surgery.

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1. Introduction

A best evidence topic was constructed according to a structured protocol. This protocol is fully described in the ICVTS [1].

2. Clinical scenario

You are on a ward round, seeing a 70 year old man who is 7 days post coronary artery bypass grafting, having been admitted with unstable angina 3 weeks ago. He is now well and pain free, but he asks you why you are sending him home only on aspirin instead of clopidogrel. He tells you that when he came into hospital 3 weeks ago the consultant cardiologist told him that clopidogrel was like aspirin but was a much better drug to be on as it was ‘stronger’ and more modern. You are unable to answer him to your satisfaction and thus you resolve to see if there is any evidence for the benefit of clopidogrel over aspirin postoperatively.

3. Three-part question

In (patients following CABG) is use of (clopidogrel) of any benefit in terms of (prolonging event free survival).

4. Search strategy

Medline 1966–August 2003 using the OVID interface ((exp coronary artery bypass OR CABG.mp OR exp thoracic surgery OR cardiopulmonary bypass.mp OR cardiovascular surgical procedures OR Cardiac Surgery.mp) AND (clopidogrel.mp OR plavix.mp)). This search was repeated in Cochrane Central Register of Controlled Trials.

5. Search outcome

A total of 220 papers were found of which one was directly relevant and two provided further interesting evidence. In addition the American Heart Association guidelines for CABG surgery were reviewed. These papers are presented in Table 1 [2–5].
Table 1
Summary of best evidence papers

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhatt et al. (2001), <em>Circulation</em>, USA [2]</td>
<td>Patients who had recent MI/stroke/PVD with previous history of cardiac surgery</td>
<td>Subgroup analysis of a randomised, double-blinded, PRCT (level 2b)</td>
<td>Combined end point of vascular mortality, MI, and ischaemic stroke</td>
<td>Aspirin vs clopidogrel 9.1% vs 5.8% event rate per year $P = 0.004$; 36.3% overall relative risk reduction (95% CI 13.4–53.1)</td>
<td>Exact date of previous cardiac surgery unknown. Proportion of patients receiving venous or arterial grafts unknown</td>
</tr>
<tr>
<td>CAPRIE Study group (1996), <em>Lancet</em>, USA [3]</td>
<td>19,185 patients with recent ischaemic stroke, recent myocardial infarction, or symptomatic peripheral arterial disease</td>
<td>Double-blind PRCT (level 1b)</td>
<td>Annual risk of ischaemic stroke, myocardial infarction, or vascular death</td>
<td>Clopidogrel 5.32% vs aspirin 5.83% annual risk ($P = 0.043$); relative-risk reduction of 8.7% in favour of clopidogrel (95% CI 0.3–16.5)</td>
<td>Significant heterogeneity of effect between the three subgroups of recent stroke, recent MI and peripheral arterial disease, indicating that the benefit may not be equal for each subgroup. One-third of all patients had had an MI within 30 days</td>
</tr>
<tr>
<td>Gerschutz et al. for the CURE study group (2002), <em>N Engl J Med</em>, USA [4]</td>
<td>12,562 patients with acute coronary syndrome without ST elevation</td>
<td>Double-blind PRCT (level 1b)</td>
<td>Death from cardiovascular causes, nonfatal MI or stroke</td>
<td>Clopidogrel 9.3% vs aspirin 11.4% in aspirin group $P &lt; 0.001$</td>
<td>21% of the clopidogrel group stopped the medication permanently during the study (and 18% of the placebo)</td>
</tr>
<tr>
<td>American College of Cardiology Task Force on Practise Guidelines (1999), <em>J Am Coll Cardiol</em>, USA [5]</td>
<td>Systematic review of a wide range of issues in coronary arterial bypass grafting</td>
<td>Systematic review (level 2a)</td>
<td>Antiplatelet therapy postCABG</td>
<td>Aspirin should be considered the first-line drug but ticlopidine and clopidogrel are alternatives if aspirin is contraindicated. This is a grade 1 recommendation</td>
<td>Search strategies not given</td>
</tr>
</tbody>
</table>
6. Results

Bhatt et al. [2] in their subgroup analysis of the CAPRIE trial [3] showed that clopidogrel was superior to aspirin for reducing recurrent ischaemic events in patients with a history of cardiac surgery and a recent myocardial infarction (MI) or recent stroke or symptomatic peripheral vascular disease (PVD). In these patients they found that one adverse event could be avoided for every 33 patients treated.

However, it must be realised that this is a substudy of a larger trial. The inclusion criteria for the CAPRIE study was recent MI, stroke or PVD and the finding that these patients had received cardiac surgery in the past was elicited retrospectively from their database. Thus Bhatt et al. could not state the details of the operation received, i.e. whether it was total arterial revascularisation or how long ago the operation was performed prior to entry into the study. This is a very different group to those patients immediately post-CABG. Thus caution should be taken when interpreting these results other than calling for further studies in this area.

Bhatt et al. is the only study that directly looks at clopidogrel vs aspirin post-cardiac surgery. In the full study of which the Bhatt paper was a subset, the CAPRIE trial, which enrolled over 19,000 patients found that clopidogrel had a significant but modest relative risk benefit over aspirin of only 8.7% of events per year avoided.

In the other major study into clopidogrel, the CURE trial [4] found that clopidogrel in addition to aspirin did provide a benefit in terms of risk reduction of major adverse events, but there was also a significant increase in the rate of bleeding side effects. Their paper did provide a subanalysis of patients with a history of revascularisation finding that the adverse event rate was 8.4% in the clopidogrel and aspirin group but 14.4% in the aspirin-only group. They did, however, caution against putting too much weight on the importance of this subanalysis as they performed multiple subanalyses in finding these results.

Thus in summary it is clear that clopidogrel as a substitute for aspirin is at least as efficacious, and can be safely started without an increased rate of bleeding. This is the recommendation from the American Heart Association for the use of clopidogrel post-CABG [5]. The paper by Bhatt et al. is the first study to suggest that there may be an increased benefit and although there may be some support for this in the CURE trial, these studies were not PRCTs on patients immediately post-CABG.

In order to provide convincing evidence of the superiority of clopidogrel over aspirin, a double-blinded, randomised controlled trial is required. Using the figures for event rates from the Bhatt study, a total of 2100 patients would need to be recruited in total to have an 80% chance of finding a significant result.

7. Clinical bottom line

Clopidogrel is a safe alternative to aspirin if aspirin is not tolerated but there is no strong evidence that clopidogrel is superior to aspirin post-CABG. However, two papers that suggest that this might be the case should stimulate further research in this area.

References