Best evidence topic - Cardiac general

Is an early invasive approach superior to a conservative strategy in patients with acute coronary syndrome?

Darbhamulla V. Nagarajan, Philip S. Lewis, Michael Maguire, Joel Dunning*

Department of Cardiology, Stepping Hill Hospital, Stockport, Manchester, UK

Received 10 February 2004; accepted 13 February 2004

Summary

A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was whether an early invasive approach (involving early coronary angiography followed by revascularisation if suitable) is superior to a conservative approach (with revascularisation only in patients with failed medical therapy) in patients with acute coronary syndrome. Altogether 282 papers were found using the reported search, of which seven 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 in patients diagnosed with acute coronary syndrome, an early invasive approach is clearly superior to a conservative approach.

© 2004 Elsevier B.V. All rights reserved.

Keywords: Evidence-based medicine; Thoracic surgery; Acute coronary syndrome; Review

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 a cardiology registrar who is seeing a 63-year-old builder, admitted 5 days previously to coronary care unit with unstable angina. On admission it turned out that he has had NYHA grade-II angina for 2 years now although he had never mentioned it, and he is a current smoker. He has now been stabilised on oral medical treatment and has been pain free for the last 4 days. He is keen to get home as he had never been in hospital before and has found the whole experience very traumatic. However, you wonder whether an early angiography with revascularisation if appropriate would be safer for him while an inpatient, and if this strategy would increase his long-term prognosis.

3. Three-part question

In (patients diagnosed with acute coronary syndrome) is (early invasive approach) compared to (conservative approach) the best treatment in terms of preventing (myocardial infarction or death).

4. Search strategy

Medline 1966—Feb 2004 using the OVID interface (exp Unstable Angina/ OR unstable coronary-artery disease.mp OR non-ST elevation infarction.mp OR acute coronary syndrom$.mp OR non-Q wave myocardial infarction.mp) AND (exp Myocardial Revascularisation OR Intervention.mp OR exp Coronary angiography OR exp Angioplasty OR exp Coronary Artery Bypass) AND (exp Myocardial Infarction OR myocardial infarction.mp OR Death.mp OR exp treatment outcome) AND randomised controlled trial.pt.
### 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/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RITA-3 trial</strong> (2002), <em>Lancet</em>, UK [2]</td>
<td><em>N</em> = 1810 patients with non-ST elevation MI or unstable angina from 45 hospitals. Patients were assigned to early intervention (895 patients) or conservative strategy. Both groups received enoxaparin, aspirin, B-blocker, anti-anginals and GPIIb/IIIa if indicated.</td>
<td>PRCT with blinded outcome measure assessment level 1b</td>
<td>Treatment after randomisation</td>
<td>Early treatment: 865 patients, 311 had PCI at median 3 days, 184 had CABG at median 22 days. Conservative Rx: 915 patients; 149 patients had PCI, 109 patients had CABG and 48% of patients had an angiogram within a year.</td>
<td>Median follow-up is currently 2 years although all patients will be followed up for 5 years (results awaited). Well-conducted study.</td>
</tr>
<tr>
<td><strong>FRISC-II invasive study</strong> (1999), <em>Lancet</em>, Sweden [3]</td>
<td><em>N</em> = 2457 patients with unstable angina or non-ST elevation MI (ineligible for thrombolysis) from 58 hospitals randomised to early invasive treatment with revascularisation within 7 days or non-invasive treatment. Note the parallel randomisation to placebo or long-term low molecular mass heparin for 3 months.</td>
<td>PRCT with parallel groups Level 1b</td>
<td>Treatment after randomisation</td>
<td>(1) Combined rate of death, non-fatal myocardial infarction, or refractory angina at 4 months. Intervention vs conservative treatment. 9.6 vs 14.5% <em>P</em> = 0.001 (2) Death or myocardial infarction at 12 months. 7.6 vs 8.3% <em>P</em> = 0.58</td>
<td>Also of interest: combined endpoint (1) maintained significance at 1 year (risk ratio 0.72; CI 0.58–0.90); 15 MIs in intervention group related to PCI or angiography. The symptoms of angina and use of anti-anginal medication significantly reduced with interventional strategy (<em>P</em> &lt; 0.0001). During the first 6 months, minor elevations in cardiac markers following angioplasty were recorded as myocardial infarction even without any other signs or symptoms.</td>
</tr>
<tr>
<td><strong>FRISC-II trial</strong> (2000), <em>Lancet</em>, Sweden [4]</td>
<td>The above-mentioned patients followed for 12 months</td>
<td>PRCT level 1b</td>
<td>Death</td>
<td>Invasive vs non-invasive. 9.4 vs 12.1% <em>P</em> = 0.031</td>
<td>Conservative strategy used very stringent criteria for ischaemia and consequently only 10% of patients underwent cardiac catheterisation during initial hospital admission. Definition of MI was different for those post-PCI or CABG and those receiving conservative treatment, in terms of CK-MB levels.</td>
</tr>
<tr>
<td><strong>FRISC trial</strong> (2002), <em>J Am Coll Cardiol</em>, Sweden [5]</td>
<td>Above patients followed up for 24 months</td>
<td>PRCT level 1b</td>
<td>Reduction in mortality</td>
<td>In contrast to the two earlier reports MIs were now classified as procedural or non-procedural MIs. During the first 6 months two-thirds of MIs were procedure related, most after angioplasty.</td>
<td>In contrast to the two earlier reports MIs were now classified as procedural or non-procedural MIs. During the first 6 months two-thirds of MIs were procedure related, most after angioplasty. (continued on next page)</td>
</tr>
</tbody>
</table>
5. Search outcome

A total of 282 papers were found of which seven were deemed to be relevant [2–8]. An additional three randomised trials were found but were not included due to small study size [9–11], one large PRCT was excluded as the patients were recently post-thrombolysed MI [12] and one large study was excluded as treatment arms were significantly out of date [13]. The included studies are summarised in Table 1.

Table 1 (continued)

<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/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TACTICS-TIMI-18 trial (2001), N Engl J Med, North America [6]</strong></td>
<td>$N = 2220$ patients from 18 hospitals with unstable angina or myocardial infarction without ST segment elevation randomised to early invasive or conservative approach. All patients treated with aspirin, heparin or tirofiban.</td>
<td>PRCT Level 1b</td>
<td>Treatment after randomisation</td>
<td>Invasive group: 1114 patients, 459 had PCI (mean 25 h) and 220 patients had CABG (mean 89 h). Non-invasive: 1106 patients, 561 had PCI (mean 79 h) and 142 patients had CABG (mean 144 h).</td>
<td>Of note: patients with Troponin T levels &gt; 0.01 ng/ml had relative risk reduction of risk of primary end point of 39% with invasive strategy ($P &lt; 0.001$). In patients with Troponin T levels &lt; 0.001 there was no difference in both groups.</td>
</tr>
<tr>
<td><strong>VANQUISH trial (1998), N Engl J Med, North America [7]</strong></td>
<td>$N = 920$ patients with Non-Q-wave myocardial infarction randomly assigned to invasive or conservative management. Average follow-up of 23 months. All patients received aspirin and long acting diltiazem.</td>
<td>PRCT level 1b</td>
<td>Treatments after randomisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TIMI-IIIB trial (1994), Circulation, North America [8]</strong></td>
<td>$N = 1473$ patients from 25 centres with unstable angina or non-Q wave myocardial infarction randomly assigned to 1 of 4 treatments: (1) TPA vs placebo as initial therapy; (2) early invasive (early coronary angiography followed by revascularisation if suitable) or early conservative therapy (coronary angiography if medical treatment failed)</td>
<td>PRCT level 1b</td>
<td>Treatments after randomisation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. Search outcome

A total of 282 papers were found of which seven were deemed to be relevant [2–8]. An additional three randomised trials were found but were not included due to small study size [9–11], one large PRCT was excluded as the patients were recently post-thrombolysed MI [12] and one large study was excluded as treatment arms were significantly out of date [13]. The included studies are summarised in Table 1.
6. Results

The RITA-3 trial [2] showed that among patients with unstable coronary syndromes, the combined end point of death, non-fatal myocardial infarction, or refractory angina is significantly reduced in patients assigned to early intervention. These results were significant at 4 months and 1 year. The biggest effect found was on refractory angina but there was a trend towards a significant reduction in death or MI and the 5-year results will give more conclusive evidence for this in 2006. Of note this was a very well-conducted 45-centre trial with good treatment separation among groups and blinded outcome assessment.

The FRISC-2 invasive study reported its results at 6, 12 and 24 months [3–5]. The study showed that in patients with unstable coronary artery disease, an early invasive approach leads to decreased mortality, morbidity, hospital readmissions and need for late revascularisation. Maximum benefit was seen during the first 6 months. This study demonstrated a Number Needed to Treat (NNT) of 28 patients to prevent 1 death or MI and an NNT of 58 to prevent a death over the next 2 years. There were also significant reductions in the use of anti-anginal medication.

The FRISC trial has had the methodology of their diagnosis of MI criticised by the RITA-3 investigators. The FRISC trial required a CK-MB rise of above the local limit for non-procedure related MI but in those undergoing PCI an enzyme rise above 1.5 times the local limit was required and for patients post-CABG new Q waves were the only method for diagnosis. The RITA trial in contrast required a clinical event in addition to biochemical markers required and for patients post-CABG new Q waves were the only method for diagnosis.

The TACTICS-TIMI-18 study [6] showed that in patients with unstable angina or myocardial infarction without ST elevation, an early invasive strategy is superior to a conservative strategy in reducing the incidence of major cardiac events. Maximum benefit was achieved in high-risk patients with troponin T levels greater than 0.01 ng/l. They demonstrated an NNT of 45 patients to prevent one death or MI in the first 6 months after early invasive treatment.

The VANQWISH trial [7] had different findings to those above. They demonstrated that in patients with non-Q wave infarction there was no significant difference in outcomes between invasive and conservative approach. However, there were several drawbacks to this study. First the study achieved poor treatment separation with 44% of patients in the invasive group receiving revascularisation and 33% receiving revascularisation in the conservative group. Secondly a significant proportion of those who died in the invasive group died prior to any intervention being performed on them. Lastly this study was in the pre-stenting and pre-gpII/IIIb drug era.

The TIMI-IIIb study [8] showed that in patients with unstable angina or non-Q wave myocardial infarction, an invasive strategy reduced the length of hospitalisation and the use of anti-anginal medication, but no significant difference in mortality at 6 weeks was found. However, this study also suffered from poor treatment separation between the groups with virtually identical revascularisation rates by the end of the study.

7. Clinical bottom line

Current trials clearly show a benefit for the early invasive approach of angiography followed by revascularisation in post-acute coronary syndrome patients with an NNT of around 50 to prevent a death or MI.

References

[8] Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIb Trial.


