Cost-effectiveness of invasive strategy in unstable coronary disease — what are we waiting for?

Despite years of enquiry and thousands of publications, best practice in the management of unstable coronary disease remains uncertain. In particular, is it best to adopt a practice of routine early catheterization with revascularization as appropriate (a so-called, ‘invasive strategy’), or restrict catheterization and revascularization to those with evidence of spontaneous or inducible ischaemia (a so-called, ‘conservative strategy’)? It is well known that patterns vary widely, especially from country to country, but it remains unclear what effect this has on outcome, if any[1]. Over the last few years four large trials have specifically addressed this question and have given apparently conflicting results[2–5]. In this issue, Janzon et al. present an economic analysis of the well-known FRISC II invasive trial which represents the first economic analysis of any such trial to be published[6].

The results of the FRISC II invasive trial are well known[4]. In short, 2457 patients with non-Q wave acute coronary syndromes were treated with dalteparin for 5–7 days and then randomized to an invasive or a conservative strategy (as well as to ongoing dalteparin or placebo). At 1 year, the rate of death or MI was significantly lower in the invasive group than in the conservative group (10.4% vs 14.1%, \( P=0.005 \)). Janzon et al. present a detailed analysis of the costs incurred by the actual patients in the trial over 1 year using data collected prospectively. They obtain a cost of SEK201622 (22427 Euros according to the exchange rate on 20.02.01) for the invasive strategy and SEK177746 (19771 Euros) for the conservative strategy, a difference of SEK23876 (2655 Euros) or 13%, all over 1 year. These data in turn generate an incremental cost-effectiveness ratio of SEK1404000 (156174 Euros) per life saved and SEK645000 (71746 Euros) per life saved or MI averted for the invasive strategy compared with the conservative strategy.

The FRISC II invasive trial is a good study. It was conducted relatively recently during what has been a period of rapid change in acute cardiac care and interventional cardiology. It was conducted in Europe rather than America, which may make it more relevant to the current readership. The results are clearly positive and robustly so, indeed they are more positive at 1 year than they were at 6 months[4,5]. The economic analysis has been rigorously conducted using prospectively collected data from the actual trial patients. The economic analysis has been kept simple which is important, for those who have most need of imbibing this sort of information have little want of getting to grips with complicated economic modelling or sophisticated statistical wizardry. It is perhaps unfortunate that the authors have not seen fit to express their results in terms of life years gained, which would make comparison with other analyses easier, or quality-adjusted life years, particularly as the FRISC II data clearly demonstrate significant improvements in quality of life in terms of improvements in symptoms of angina for the invasive group[7]. Notwithstanding, it is possible that the authors have played down the significance of their results. Almost all clinicians will be much less interested in the incremental cost-effectiveness ratio than in the actual cost of an invasive compared with a conservative strategy. This study provides valuable ‘real world’ information about the cost of an invasive compared with a conservative strategy. Knowing the cost of an invasive compared with a conservative strategy is what is required for the individual clinician to weigh up the costs and benefits for the individual patient. This is very easy for a drug, where the costs at least are readily apparent, but much more difficult for a treatment strategy, where the costs as much as the benefits are much less tangible.

To date this is the only published economic analysis of a comparison between an invasive and a conservative strategy. This is not surprising, since the FRISC II invasive trial was the first comparison between an invasive and a conservative strategy to give a positive result. Why TIMI IIIB and

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VANQWISH gave a negative result and FRISC II and TACTICS-TIMI 18 gave a positive result has been and will be debated at length, but in the current context it is worth reiterating a few points. First, FRISC II and TACTICS-TIMI 18 are more recent than TIMI IIIB and VANQWISH, and therefore closer to contemporary practice in terms of use of, for example, stents and glycoprotein inhibitors. Second, FRISC II and TACTICS-TIMI 18 are significantly larger (2457 patients and 2220 patients respectively) than TIMI IIIB and VANQWISH (1473 patients and 920 patients respectively), and therefore arguably more reliable. Third, FRISC II is the only one out of the four conducted exclusively in Europe rather than North America (although TACTICS-TIMI 18 included a small proportion of patients from Germany). Fourth, (perhaps partly as a consequence of the foregoing), FRISC II and TACTICS-TIMI 18 achieved a much greater difference in revascularization rates than TIMI IIIB and VANQWISH (78% vs 43% and 64% vs 45%, compared with 64% vs 58% and 44% vs 33%) and especially in rates of CABG (38% vs 23% and 22% vs 16%, compared with 30% vs 30% and 23% vs 21%). Under the circumstances, it is hardly surprising that FRISC II and TACTICS-TIMI 18 gave positive results in contradistinction to what had come before.

Although there are no economic analyses of negative studies such as TIMI IIIB and VANQWISH, there is information about length-of-stay and rehospitalizations, which are potent cost-drivers in economic analysis and make for a number of interesting comparisons. In TIMI IIIB the length of stay was 0.7 days shorter in the invasive group, in VANQWISH the length of stay was 1.3 days longer in the invasive group, and in FRISC II the length of stay was 3.9 days longer in the invasive group. This may reflect the European experience of delays in the availability of revascularization, or it may reflect the higher rate of CABG obtained, or it may reflect the fact that only 16 out of the 58 centres in FRISC II were interventional centres, and therefore there must have been some delay in waiting for interhospital transfers (it is a little unfortunate that the cost of such interhospital transfers was not included in the costings). It is therefore possible, if European centres could offer revascularization services without delay, that the cost-effectiveness of an invasive strategy might be much greater. TIMI IIIB, but not VANQWISH, also provided information about rehospitalization. The relative risk reduction of 21% in the number of rehospitalizations in TIMI IIIB compares favourably with a relative risk reduction of 35% in the number of rehospitalizations in FRISC II and confirms that there is a potential for further cost savings.

The results of TACTICS-TIMI 18 have recently been published[3] and they demand comparison with FRISC II and the results of Janzon et al. in a number of ways. As we have already seen, TACTICS-TIMI 18 is an even more recent study, of similar size, conducted largely in North America, and with a similar positive result. TACTICS-TIMI 18 showed a reduction in length of stay (5 vs 6 days) and a reduction in rehospitalizations (11% vs 13.7% over 6 months). Indeed, it is partly because rehospitalizations were included in the primary end-point (unlike TIMI IIIB, VANQWISH and FRISC II) that TACTICS-TIMI 18 was so positive. If rehospitalizations had been included in the primary end-point of FRISC II it would surely have been even more positive. More importantly, TACTICS-TIMI 18 included cost data and quality of life data gathered prospectively, just like FRISC II, although this data is not published yet. The results over 6 months ($20723 vs $19870, a difference of $853) really are remarkably similar to the results of Janzon et al. over 1 year (22427 Euros vs 19771 Euros, a difference of 2656 Euros), given the approximate parity of the dollar and the Euro and perhaps greater costs in America than in Europe.

Economic analysis should be a help not a hindrance to clinical decision making. Despite the results of FRISC II and TACTICS-TIMI 18 the question of whether to pursue an invasive or a conservative strategy in unstable coronary artery disease appears to remain a controversial one. Current guidelines from Britain, Europe and America are remarkably conservative in their recommendations[8–10]. The results of Janzon et al. confirm that the incremental cost of pursuing an invasive strategy is relatively modest (13%), whatever the incremental cost-effectiveness ratio may be. We already know that the gains are significant and, especially in terms of quality of life, substantial. Greater service provision will almost certainly be required to deliver these gains, especially in Europe. There remain some reservations over the role of an invasive strategy in the management of low risk patients and, for example, women[11]. Notwithstanding, the real question is, what are we waiting for?

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ST depression in ECG at entry indicates severe coronary lesions and large benefits of an early invasive treatment strategy in unstable coronary artery disease — the FRISC II ECG substudy

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More than a million patients per year are admitted worldwide with non-ST segment elevation acute coronary syndromes, and recent studies have shown that rates of death or myocardial infarction at 30 days range from 5-9% to 15-7%[1]. Hence there is a need for accurate predictors to risk stratify patients who need an aggressive management strategy.

ST segment depression on the admission ECG is a well known tool for risk stratification[1-6] in such patients. It has also been shown that survival during a 4 year follow-up[7] is related to the degree of initial ST depression. While troponins have been shown to be excellent markers[8,9] for risk stratification the ECG remains a cheap and universally available tool for such purpose.

Prior to the Fragmin and Fast Revascularisation during Instability in Coronary artery disease (FRISC II) study there were no data indicating that an early invasive strategy in patients with unstable coronary disease and ST depression on the admission ECG influenced outcome. The Thrombolysis in Myocardial Infarction (TIMI) IIIB and Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) studies found no mortality benefit at 1 and 3 years, respectively, of an early invasive and/or revascularization strategy compared with an early conservative approach in patients with unstable angina and non-Q wave myocardial infarction[7].

The early invasive strategy of the FRISC II trial showed that in patients with unstable coronary artery disease after initial medical stabilization there was a significant reduction in death and myocardial infarction at 6 months and 1 year[10,11].

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