Editorial

Revascularisation for everyone?

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This editorial refers to “Association of revascularisation with low mortality in non-ST elevation acute coronary syndrome, a report from GUSTO IV-ACS” by J.P. Ottervanger et al. on page 1494

The approach to the treatment of patients with acute coronary syndrome (ACS) has become much more aggressive over the past several years. With regard to the optimal use of coronary angiography and revascularisation for patients with ACS, it was only a decade ago that the first randomised trial of an invasive vs. a conservative strategy for patients with unstable angina (UA) and non-ST elevation myocardial infarction (NSTEMI) was published.1 The Thrombolysis and Myocardial Ischaemia (TIMI) IIIB trial hypothesised that early angiography and revascularisation would be beneficial in preventing subsequent cardiac events. Overall the study found only a weak trend for prevention of death or myocardial infarction (MI), however there were significant reductions in recurrent angina requiring re-hospitalisation as well as reductions in hospital length stay.1 Questions about the benefit of revascularisation for ACS were raised with the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial which suggested that a conservative strategy was associated with lower mortality.2 However beginning with the FRagmin and Fast Revascularisation during InStability in Coronary (FRISC) II trial,3 then TACTICS-TIMI 18 trial,4 and finally the Randomised Intervention Trial of unstable Angina (RITA) 3 trial,5 it has been very clearly shown that an early invasive approach to patients with UA/NSTEMI is beneficial. The overall endpoint assessed in the randomised trial has been death, MI or recurrent ischaemia and the endpoint of death or MI has been significantly reduced in all three of the most recent trials.

Interestingly, mortality was significantly improved solely in the FRISC II trial and there was no significant difference mortality in TACTICS TIMI 18 and actually an adverse effect on mortality seen in VANQWISH.2 As shown in Fig. 1, there appears to be a direct relationship between higher use of revascularisation and lower mortality: The greater the difference in the rate of revascularisation between the invasive and conservative strategy in the trial, the greater the benefit on mortality.

The randomised trials of two strategies all look at a clinical approach to the patient. Thus, they study an early invasive strategy where everyone undergo cardiac catheterisation and only a proportion undergo revascularisation as appropriate based on the anatomy. This is compared with a strategy of medical management followed by exercise stress testing to identify significant ischaemia as well as monitoring for rest ischaemia, with revascularisation as needed for recurrent ischaemia. Thus cardiac catheterisation is a significant (and planned) part of an “early conservative” strategy, and is utilised in approximately 20–40% of the patients in the large randomised trials.

If however one wanted to ask the pure question of what benefit revascularisation provides over (pure) medical therapy, one would have to be extremely strict in the conservative arm (well beyond current clinical guidelines) by doing a randomised trial where you would not allow any revascularisation. Alternatively, one can look at clinical databases and compare (in an observational fashion) patients who underwent revascularisation compared with those who did not. Because many differences in patients would exist between those who do vs. those who do not undergo revascularisation, one has to use multivariate adjustment for these differences in baseline characteristics. Propensity analysis (which determines factors that are associated with a higher use of the treatment [revascularisation in this case] and adjusts for those factors as well) can be used to try to eliminate other biases. One such analysis was made in the Swedish registry and found that there was about a 25% lower adjusted mortality among patients who under went revascularisation following acute coronary syndromes (including STEMI in that
study), as compared to patients that didn’t undergo revascularisation. The Global Use of Strategies to Open Occluded Arteries (GUSTO) IV-ACS Investigators did a similar analysis in a population with UA/NSTEMI. In order to evaluate the benefits of revascularisation, they compared patients who underwent revascularisation within the first 30 days following their ACS event, which comprised 30% of the 7800 patients enrolled, and compared these with the remaining 70% of patients. To avoid bias of including patients too sick to undergo revascularisation (and thus who would die soon after their ACS event), the investigators only compared patients who survived 30 days (with vs. without revascularisation) and looked at their subsequent one year mortality. They observed that the mortality rate was approximately 50% lower among those who had undergone revascularisation. These data suggest that the addition of revascularisation on top of medical therapy provides a substantial benefit to patients. This analysis is again consistent with the randomised trials, and if one plots the difference in the rate of revascularisation (100%) against the difference in mortality of one year on the Figure, it does appear to be consistent with the trial data. As such, the added use of revascularisation appears to provide benefit in improving mortality. Thus, the old belief that revascularisation does not improve mortality in coronary disease but just improves symptoms, is no longer true for patients with ACS. With the results from this analysis and the multiple randomised trials, there is a very clear reduction in mortality (and recurrent MI) among patients with ACS treated with an early invasive strategy.

One of the biggest remaining problems is that this strategy is vastly under utilised. This is especially true at community hospitals based on the recent analysis from the CRUSADE Registry. When looking at recent registry data, about 60% of high risk ACS patients undergo angiography of whom approximately two-thirds undergo revascularisation (based on the anatomy). However, only about 40–45% patients undergo the angiography within the first 48 hours after admission (i.e., an early invasive strategy). Since the CRUSADE registry was made in the United States, where we have a reputation of being very aggressive with interventions, it highlights that in some cases, we are not aggressive enough. Thus, we have to work in the cardiology and medical community to try and implement better the recommendations supported by the evidence, and to refer appropriate patients for angiography early after presentation for ACS.

A final issue is whether the benefits of revascularisation as seen for ACS patients would also be true for patients with stable angina, i.e., those who only have only evidence of ischaemia on an exercise stress test. Here, we really do not have evidence to support an early invasive strategy. In fact, there is evidence to the contrary with the RITA 2 and AVERT trials demonstrating higher rates of death or MI and cardiac events among patients undergoing intervention for stable angina. This may relate to peri-procedural events and the complications of interventions in those studies. Fortunately many advances have occurred since those trials including the use of high-dose clopidogrel, glycoprotein IIb/IIIa inhibitors and drug-eluting stents, which reduce early complications and the long-term occurrence of angina and cardiac events following intervention. Thus we are all looking forward to the results of randomised trials of an invasive vs. conservative strategy in stable patients such as the COURAGE trial. Given the advances in medical therapy with dual antiplatelet therapy, high dose statin treatment, ACE-inhibition or angiotensin receptor blockade, the medical management of stable atherothrombotic disease has improved substantially and there may not need to be coronary interventions (in the absence of any unstable symptoms). The evidence supporting the role of revascularisation really holds with the ACS population and the use of interventions for stable population should be driven by the need to control symptoms.

References