Unstable angina: the case for selective aggression

Even for 'aggressive' interventionists, the optimal management of unstable angina (UA) and acute myocardial infarction without ST-segment elevation remains unclear. There is no doubt that these acute coronary syndromes (ACS) carry a prognosis that is far from benign. In PRAIS-UK, for example, the rate of death or non-fatal myocardial infarction (MI) was 12.2% at six months, with a composite of death, new MI, refractory angina or re-admission with UA of 30%. The OASIS registry of nearly 8,000 patients in six countries produced similar statistics with six-month rates of 10.1% and 22%, respectively.[1,2] These data certainly justify a desire to be aggressive about therapy but the direction of such aggression remains contentious.

Specifically, it remains a matter for debate as to whether an early invasive approach is superior to a conservative strategy for all ACS patients with markers of 'high risk'. In the UK, there is particular concern that resources are not adequate to commit to the early invasive strategy for all such patients, who frequently wait for more than a week until angiography and revascularisation. Transfer is often delayed by bed space rather than catheter lab time or availability of trained staff. Whilst resources undoubtedly remain an important factor, however, there is a danger of compromising patient safety in the desire to unearth evidence that will allow us to be less aggressive. Our current strategy, and that of many others, is to revascularise all patients with ACS who have significantly elevated troponin T (> 0.1 µg/L) or ST-segment depression on admission, regardless of ongoing symptoms. We believe that this is the safest strategy based on currently available data.

In this editorial, we speculate that there may be the potential, with the help of other tests for 'high risk', to refine our strategy so that we only target in-hospital revascularisation to those who would otherwise have an early event. The remaining patients, many of whom will also require revascularisation, could then be dealt with on an out-patient basis. This would allow our aggression to be selective.

Common ground

Medical management of ACS must be aggressive. The role of aspirin, the low molecular weight heparins, beta blockers and, more recently, clopidogrel, is now universally accepted.[3-6] Stabilisation of the atherosclerotic plaque is now also a therapeutic target, a possible action of statins given at high dose early in ACS.[7] With appropriate therapy, around 90% of patients will settle symptomatically during the hospital stay. For the other 10%, who have ongoing pain or ECG changes despite optimal medical therapy, the move to invasive management is both intuitive and unavoidable.

The crux of our current clinical dilemma is that a proportion of those patients whose symptoms settle on medical treatment will remain at high risk of further events. Our goal remains the identification of these high-risk patients as candidates for a tailored, invasive strategy. The problem is that even with new screening tools we cannot predict which patients in the 'high-risk' group are actually going to have events.

Identification of high-risk ACS patients

There are now unequivocal data to confirm cardiac-specific troponins as major determinants of risk in ACS. The FRISC study investigators stratified 976 patients into low-, medium- and high-risk groups according to the maximum troponin T (cTnT) within the first 24 hours.[8] The rate of cardiac death or MI after five months rose gradually with increasing cTnT from 4.3% in patients with cTnT < 0.06 µg/L to 10.5% in patients with cTnT between 0.06 to 0.18 µg/L, and 16.1% with cTnT $\geq$ 0.18 µg/L. The risk increased further in troponin positive patients according to the type of ST-segment change (ST depression with T-wave inversion carrying the worst prognosis, followed by ST depression alone, and then isolated T-wave inversion).

Similar data are provided from several other sources.[9,10] The benefit of the availability of troponins as a screening tool is obvious. Importantly, however, it is only the minority of patients even with very high levels of troponin that succumb to a subsequent cardiac event. It is certainly not intuitive, therefore, that all such patients should derive equal (or even any) benefit from an early invasive treatment strategy. There is now evidence that supports an invasive, early revascularisation approach in patients selectively identified as being at higher risk by virtue of elevated troponins and/or ST-segment. Current 'aggressive' strategies aim to revascularise all such high-risk patients in order to benefit those who would have gone on to develop a further event. The future may allow us to be more selectively aggressive.

Selective aggression

TIMI-IIIb and VANQWISH were the first randomised trials of

an early invasive versus conservative approach in this patient group and, for all their weaknesses, demonstrated that a global invasive strategy is not beneficial and may even be harmful for some patients.[11,12] Both have been much criticised in the interventional community for their high rates of crossover, low-risk study populations and, in the case of VANQWISH, an excessive operative mortality with coronary artery bypass grafting (CABG) in the invasive arm (11.6%!). In addition, these trials now have less relevance to a contemporary practice that includes coronary stenting and the use of platelet glycoprotein IIb/IIIa receptor antagonists (GPIIb/IIIa). By contrast, the more recent FRISC II and TACTICS TIMI-18 studies have paved the way for a more selective approach to early revascularisation.[13,14]

FRISC II randomised 2,457 patients with either ECG changes or raised biochemical markers (CK-MB or cTnT) within 72 hours to early invasive or conservative treatments. In each group, 58% were troponin positive (cTnT > 0.1 µg/L). Invasive patients were investigated with coronary angiography and revascularised within 10 days. Non-invasive patients with refractory angina despite maximal medical therapy (10%), or with a strongly positive pre-discharge exercise test, also underwent angiography. Of the invasive group, 71% were revascularised within 10 days versus 9% of the non-invasive group. Thus, the crossover rate was low and predictable. At one year, the revascularisation rate in the early invasive group was 78% and 43% in the non-invasive group, illustrating that a large proportion of high-risk ACS patients will require revascularisation in the 12 months following admission. Despite this high one-year revascularisation rate in the non-invasive group, there was still a significant reduction in the rate of death, MI, and the composite of death and MI (2.2%, 8.6% and 10.4%, respectively in the early invasive group versus 3.9%, 11.6% and 14.1% in the non-invasively treated group; p=0.016, p=0.015 and p=0.005, respectively). The rate of re-admission was also significantly reduced.

In TACTICS-TIMI, 18 patients were treated with medical therapy including the GPIIb/IIIa inhibitor tirofiban for 48 to 108 hours. They were then randomised to invasive investigation and revascularisation at four to 48 hours. The primary combined end point of death, MI, or rehospitalisation for acute coronary syndromes at six months was reached in 19.4% of the conservative group versus 15.9% of the invasive group (p=0.025). Specifically, there was an absolute reduction of 10% (24% down to 14%) in those with a positive troponin (> 0.1µg/L).

These two trials therefore suggest that early revascularisation can reduce events in those identified as being at high risk, and certainly in a far broader population than simply those with refractory angina. In both trials, it was those patients with elevated troponins that gained the most benefit, as did those with ST-segment depression on the presenting ECG.

Optimal targeting

The benefits of early revascularisation in high-risk groups in FRISC II and TACTICS are the basis for the invasive strategy in many areas. This is based upon the belief that this is the safest management of the high-risk group. The strain this puts on demand for medical and cardiology beds around the country is enormous. For this, and other reasons, the imperfection of this strategy should be recognised as a stimulus for further attempts to identify which of the 'high-risk' patients are the ones who will have an event without revascularisation. The benefits we have described in high-risk patients are significant but by no means massive. In FRISC II, the absolute reduction in mortality at one year was only 1.7%, and 4% for MI. Clearly, by employing this approach we will inevitably revascularise a significant number of patients who would not have had recurrent events. For example, even the non-invasive troponin positive (> 0.1 µg/L) group in FRISC II had a six-month event rate of only 13.1%, compared with 10.1% if treated invasively. We may, therefore, be committing over 80% of such patients to a strategy that may not confer prognostic benefit but which makes a very large contribution to the logistical overload.

While this new biochemical screening tool represents a major advance in patient selection, it remains relatively blunt. Despite advocating the current strategy, it is clear that additional strategies to identify those at highest risk of events are still needed, with further randomised trials to confirm the benefit of early revascularisation in this subgroup.

Potential candidates already exist. The inflammatory response to endothelial injury is an established component of an unstable plaque event and there is clear evidence that serum CRP is an independent risk factor in ACS.[15-18] It may be that, in future, we use both markers to target those patients who have most to gain from early revascularisation. Alternatively, genotyping may allow treatment targeting in troponin positive patients. Previous studies, for example, have identified platelet polymorphisms that may predispose to restenosis or stent thrombosis after percutaneous coronary intervention (PCI).[19-21] It is exciting to speculate upon a time when a simple blood test on or shortly after admission may pinpoint the specific early treatment strategy for a given ACS patient.

Today, we employ a strategy of selective invasive aggression in 100% of those patients in a higher risk group in order to obtain optimal revascularisation therapy in less than 20% of them. Our aim must be to identify only the patients due to have events. Achieving such a goal would be beneficial in financial, logistic and scientific terms.

Summary

- The prognosis for patients with non-ST elevation acute coronary syndromes (ACS) is not benign
- Ongoing ischaemia is only one determinant of risk
- The presence of ST-segment depression or elevated level of troponins is known to identify a group of patients at high risk of further events (death, MI, re-admission with ACS). The key management issue, however, is regarding which of these patients require early (i.e. in-hospital) revascularisation
- Based upon current evidence from studies including FRISC II, TIMI-18, and the recent re-analysis of TIMI-III, our current strategy is to offer invasive investigation and revascularisation to all patients identified as 'high risk'. **This is the only way to ensure safe care for the patients within this group who would otherwise experience a further event.** The limitation of this strategy is that we are targeting in-hospital care at a majority of patients who do not in fact have events within the first 30-day period
- We therefore speculate that, in the future, it may be possible to channel this early aggressive revascularisation strategy towards a group whose risk assessment has been refined beyond simply elevation of troponin. We would then be able to target in-hospital revascularisation at the highest of the high-risk patients, and allow the remainder home to be assessed and revascularised (where necessary) on an out-patient basis

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