The role of revascularisation in the management of non-ST elevation acute coronary syndromes: who should you refer?

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Non-ST segment elevation (NSTE) acute coronary syndromes (ACS) account for the majority of coronary care unit admissions. Registry data from the UK reveal that six months after such an admission there is a 12.2% rate of death or non-fatal myocardial infarction (MI), and a 30% rate of death, MI, refractory angina or readmission to hospital for unstable angina.[1] The pathophysiology of these syndromes is increasingly understood and is associated with improved targeting of medical therapy.[2,3] Risk stratification is the foundation of the current strategy for early coronary angiography and revascularisation (either percutaneous or surgical) in patients with ACS, with the aim of detecting those known to be at higher risk of further events, including death, MI or readmission with further unstable symptoms. Markers of high risk have been discussed in an earlier article in this section.

In brief, the invasive cardiologist expects to be offered three categories of patients with NSTE ACS who should be referred for inpatient angiography and revascularisation because of their risk of further early events:

1 Patients with ongoing pain or ECG changes.
2 Patients with elevated troponin (Tn) levels (for example, (TnT) ⩾0.05 ng/ml).
3 Patients with ST depression on admission ECG.

What is the evidence that offering angiography and then revascularisation to patients in one of these high risk clinical categories provides them with a better outcome?

Several trials can be used to address this question. From the viewpoint of modern interventional cardiology, they may be divided into two groups: historical and contemporary. The relevance of the historical trials is dubious because they are so far away from modern clinical practice in terms of intervention (stents and drug-coated stents) and adjunctive pharmacological therapy (clopidogrel, glycoprotein (GP) IIb/IIIa inhibitors, statins, angiotensin-converting enzyme inhibitors). Even the contemporary studies provide only some indication of the potential benefit of the newer therapies available.

TRIAL ACRONYMS

CAPTURE	Chimeric 7E3 Antiplatelet Therapy in Unstable Refractory Angina
FRISC II	Fragmin and Fast Revascularisation during InStability in Coronary artery disease
GUSTO IV	Global Use of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries
ISAR-COOL	Intracoronary Stenting and Antithrombotic Regimen
RITA 3	Randomized Intervention Trial of unstable Angina 3
TACTICS-TIMI 18	Thrombolysis and Counterpulsation to Improve Cardiogenic Shock Survival-Thrombolysis in Myocardial Infarction 18
VANQWISH	Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital

The trial evidence

There have been five major randomised controlled trials: TIMI IIIB, VANQWISH, FRISC II, TACTICS-TIMI 18 and RITA 3 (see box for explanation of acronyms).[4–10] They all randomised patients with NSTE ACS to either early coronary angiography with revascularisation or an early conservative approach.

Historical studies

TIMI IIIB

Between 1989 and 1992, 1,473 patients were randomised in a 2 × 2 factorial design to tissue plasminogen activator or placebo as well as to an early invasive or conservative strategy.[4] The primary end-point of death, MI or symptom-limited exercise stress test at six weeks was reached in 16.2% patients in the invasive group and 18.1% in the conservative group ($p = 0.33$).[4] The percentage of patients rehospitalised within six weeks was significantly lower in the invasive group (7.8% vs 14.1%, $p < 0.001$). At one year, the incidence of death or MI was similar in the two groups (10.8% vs 12.2%, $p = 0.4$), although repeat hospital admissions remained significantly lower in patients in the invasive treatment group (26% vs 33%, $p < 0.005$).[5]

VANQWISH

This trial included 920 patients with non-Q wave MI. The primary end-point of death or non-fatal MI was reached in 29.9% patients randomised to the early invasive strategy and 26.9% patients in the conservative group ($p = 0.35$) at a mean of 23 months follow-up.[6] Of note is the 12% 30-day mortality associated with coronary artery bypass grafting.

Contemporary studies

FRISC II

In FRISC II, between 1996 and 1998 a total of 2,457 patients with NSTE ACS were randomly assigned to an early invasive or conservative strategy and to three months of either dalteparin or placebo using a factorial design.[7] The

patients treated invasively were revascularised within 10 days of randomisation, which itself occurred within 72 hours. The six-month primary outcome of death or MI was reached in 9.4% of patients in the early invasive group and 12.1% in the early conservative group ($p = 0.031$). Furthermore, at two-year follow-up, there was a significant absolute reduction of 4.2% (12.1% vs 16.3%) in the combined primary end-point of death or MI in the early invasive group ($p = 0.003$).[8] Both these outcomes were significantly reduced when considered as individual end-points (3.7% vs 5.4%, $p = 0.038$ for death; 9.2% vs 12.7%, $p = 0.0005$ for MI). Hospital readmissions were also significantly reduced over two years in the invasive group (44.8% vs 64.5%, $p < 0.001$). An important observation is that 43% of the conservative group had undergone some form of revascularisation within one year.

TACTICS-TIMI 18

In TACTICS-TIMI 18, 2,220 patients with NSTE ACS recruited between 1997 and 1999 were treated with intravenous tirofiban for 48 hours and then randomised to medical or invasive treatment.[9] Of the revascularised patients, 68% underwent angioplasty and stenting (percutaneous coronary intervention (PCI)). The primary end-point of death, non-fatal MI, or rehospitalisation for ACS at six months occurred significantly less frequently in the early invasive group (15.9% vs 19.4%, $p = 0.025$). Specifically, there was an absolute reduction of 10% in those patients with elevated TnT (>0.1 ng/ml).

RITA 3

The RITA 3 trial recruited 1,810 patients with ACS between 1997 and 2001. The primary end-point, death, non-fatal MI or refractory angina at four months,[10] occurred in significantly fewer patients in the early invasive group than in the early conservative group (9.6% vs 14.5%, relative risk (RR) 0.66, 95% confidence interval (CI) 0.51-0.85, $p = 0.001$). This reduction was maintained at one year ($p = 0.003$). The difference was due to a reduction in refractory angina (RR 0.56 at one year, $p = 0.0002$) with no significant decrease in death or MI at four, 12 or 24 months. In particular, angina ($p < 0.001$) and use of anti-anginal medication ($p < 0.0001$) were significantly lower in the invasive group.

Key Points

Non-ST segment elevation (NSTE) acute coronary syndromes (ACS) account for the majority of coronary care unit admissions. Registry data reveal a 12% rate of death or myocardial infarction six months after such admission, and a 30% rate of death, MI, refractory angina or readmission to hospital for unstable angina

The invasive cardiologist expects to be offered three categories of patient with ACS for angiography and revascularisation: patients with (1) ongoing pain or ECG changes, (2) elevated troponin levels (TnT ⩽0.05 ng/ml), (3) ST depression on admission ECG

Contemporary literature unequivocally demonstrates prognostic benefit for early revascularisation in patients with NSTE ACS deemed at high risk by virtue of the factors listed above

It is important to note that invasive investigation and treatment prognostic benefit is apparently achieved in the last two of the categories of patient who should undergo early (ie inpatient) even if their angina settles with medical treatment

Summary of the trial evidence

The historical trials, TIMI IIIB and VANQWISH, failed to demonstrate a difference in outcome between patients managed with early invasive and conservative strategies.

By contrast, the contemporary trials, FRISC II, TACTICS-TIMI 18 and RITA 3, all reported that early invasive assessment and subsequent revascularisation of ACS patients identified to be at higher risk led to improvements in symptomatic and prognostic outcome compared with medically treated patients. This represents the foundation for the current strategy of transfer of such patients to the care of invasive cardiologists and does *not* depend upon ongoing symptoms.

The increasing rates of stent deployment (61% of PCI cases in the invasive arm of FRISC II, 88% in RITA 3) and periprocedural GPIIb/IIIa inhibitor use (10% in FRISC II, 25% in RITA 3, 94% in TACTICS-TIMI 18) in clinical practice were paralleled by the trials and have contributed to the reduction in PCI-related MI in both settings.[7,9,10] It is likely that the benefit of PCI in these studies is therefore underestimated. In contemporary practice, both stents and GPIIb/IIIa inhibitors are used in over 90% of these ACS patients.

Practical difficulties and ongoing controversy

Analysis of the contemporary literature therefore unequivocally demonstrates prognostic benefit for early revascularisation in patients with NSTE ACS deemed at high risk by virtue of ongoing ischaemia, elevated Tn or ST depression. Importantly, patients in the last two categories apparently derive prognostic benefit even if their angina settles with medical treatment. This is the basis for the recommendation that they should be treated as inpatients, but raises the practical issue of how to treat all such patients within a reasonable amount of time and, just as important, how to do so in an equitable manner. It is ironic that most such patients treated by PCI go home the next day.

Patients with ACS who fulfil the criteria for angiography are kept waiting significantly longer if they are admitted to a feeder district general hospital (DGH) rather than to a hospital with revascularisation facilities (13 days vs five days, $p < 0.0005$)[11] (a good example of postcode medicine). The data suggest that the ideal time to achieve angio-

graphy and revascularisation is within 72 hours of presentation.

The optimal timing of PCI in NSTEACS patients is in itself controversial. It has been suggested that the benefit of the early invasive strategy in TACTICS-TIMI 18 was due to the effect of a median of 25 hours' treatment with a GPIIb/IIIa inhibitor *prior* to PCI.[9] The question of whether a 'cooling off' period prior to PCI might reduce procedure-related events was addressed in the ISAR-COOL study (American Heart Association, Chicago, 2002). In this study, 410 patients with NSTE ACS scheduled to undergo PCI were randomised to either PCI immediately (mean time 2.4 hours) or to a 'cooling off' period in which they were treated with aspirin, clopidogrel, tirofiban and heparin for 72–120 hours before the procedure was conducted. The primary end-point of death or non-fatal MI at 30 days was significantly reduced in the early PCI group (5.9% vs 11.6%, $p = 0.04$). The excess events in the 'cooling off' arm were MIs occurring before catheterisation – suggesting that delaying PCI is counterproductive.

The evidence indicating that all high risk patients with ACS should be treated by early angiography and revascularisation presents general physicians and cardiologists with a logistical nightmare – although not all patients with ACS need to be treated in this way. In the early conservative cohort of FRISC II, for example, death or MI occurred in 16.6% patients with plasma TnT concentration of 0.03 ng/ml or above compared with 8.5% patients with TnT below 0.03 ng/ml ($p < 0.001$).[12] TnT concentration of 0.03 ng/ml or above ($p = 0.008$) alone and in combination with ST depression 0.05 mV or higher on the ECG ($p < 0.001$) were independent prognostic factors for death or MI at 12 months. The early invasive strategy reduced death or MI at 12 months in patients with TnT 0.03 ng/ml or above from 16.6% to 11.6% ($p = 0.005$). In patients with both elevated TnT and ST depression whose risk was high the invasive strategy reduced the rate of death or MI at 12 months from 22.1% to 13.2% ($p = 0.001$).

By contrast, in patients with TnT below 0.03 ng/ml whose risk was lower, the benefit of an early invasive strategy was not statistically significant (7.4% vs 8.5%, $p = 0.59$). There were similar results in TACTICS-TIMI 18.

It is useful to establish that only certain subgroups of patient benefit from the early invasive approach, but risk stratification could possibly be further refined in the future.[13] Even patients with ST depression and Tn elevation have event rates of under 30%. If patients who will have further events could be identified, the intolerable pressure that this (appropriate) management puts upon DGH beds and revascularisation services could be relieved.

Other risk markers

A number of other markers have been shown to be related to the risk of further adverse cardiac events after NSTE ACS and may indicate ways of improving risk stratification.

C-reactive protein. In the FRISC II trial, for example, the probability of death at five months increased with increasing tertile of fibrinogen (1.6% vs 4.6% vs 6.9%, $p = 0.005$) and C-reactive protein (CRP) (2.2% vs 3.6% vs 7.5%, $p = 0.003$).[14] Further, CRP remained an independent predictor of death after 37 months follow-up.[15] This is consistent with data from GUSTO IV, in which CRP independently predicted death, and 30-day mortality increased with quartiles of CRP (2.0%, 3.3%, 3.9% and 6.3%, $p < 0.001$).[16]

CD40 ligand. Recently, the CAPTURE study found that soluble CD40 ligand, a marker of platelet activation, predicted risk of death or MI among 1,088 ACS patients and in a more diverse group of patients presenting with acute chest pain.[17]

In the future there may be models for risk stratification involving a combination of markers that represent different levels of the pathophysiological cascade of NSTE ACS. These markers may facilitate increasingly effective targeting of medical and invasive interventions.

Currently, optimal management of the three categories of patients referred to above who are under the care of general

Table 1. American College of Cardiology/American Heart Association class 1 recommendations for an early invasive or early conservative strategy in the management of nonST segment elevation acute coronary syndromes.

1 **An early invasive strategy in patients with UA/NSTEMI without serious comorbidity who have any of the following high-risk indicators** (*Level of Evidence: A*):
   - (a) Recurrent angina/ischaemia at rest or with low-level activities despite intensive anti-ischaemic therapy
   - (b) Elevated TnT or TnI
   - (c) New or presumably new ST segment depression
   - (d) Recurrent angina/ischaemia with CHF symptoms, an S3 gallop, pulmonary oedema, worsening rales, or new or worsening MR
   - (e) High risk findings on non-invasive stress testing
   - (f) Depressed LV systolic function (eg EF <40% on non-invasive study)
   - (g) Haemodynamic instability
   - (h) Sustained ventricular tachycardia
   - (i) PCI within 6 months
   - (j) Prior CABG

2 **In the absence of any of these findings, either an early conservative or an early invasive strategy may be offered in hospitalised patients without contraindications for revascularisation** (*Level of Evidence: B*).

CABG = coronary artery bypass graft; CHF = congestive heart failure; EF = ejection fraction; LV = left ventricular; MR = mitral regurgitation; NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; TnI = troponin I; TnT = troponin T; UA = unstable angina.

physicians determines that they should be admitted and transferred for inpatient coronary angiography and revascularisation. For many patients, this is independent of whether or not they have ongoing symptoms. Not to do so puts them at high risk of a major adverse cardiac event.

Conclusions

NSTE ACS is associated with considerable morbidity and mortality, with a 30% rate of death, MI, refractory angina or readmission to hospital for unstable angina at six months. Contemporary trials show that the risk of further adverse cardiac events can be reduced by an early revascularisation strategy. The current evidence base determines that patients in the following categories benefit prognostically from early (ie inpatient) angiography and revascularisation:

- ongoing evidence of ischaemia
- elevated Tn regardless of ongoing symptoms
- ST depression regardless of ongoing symptoms.

In clinical practice, patients with ongoing chest pain self select for early coronary angiography. For other patients, their risk for further adverse cardiac events can be stratified on admission by Tn, ST segment changes and TIMI risk score. Medium and high risk patients benefit the most from an invasive strategy, while low risk patients achieve similar outcomes with either an early invasive or an early conservative strategy (Table 1).[18] For patients undergoing PCI, the treatment is extremely efficient, most going home the following day. More resources are needed to reduce the time it takes to get these patients to the catheterisation laboratory with an interventional cardiologist.

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