Non-ST-elevation acute coronary syndromes

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Rupture of an inflamed, metabolically active, non-flow-limiting thin-capped coronary fibroatheroma with superimposed thrombosis causes most acute coronary syndromes.[1] The interplay of local factors and systemic conditions, including plaque composition and location, thrombus burden, the competing efficiencies of endogenous fibrinolysis versus haemostasis, and the effectiveness of a preformed collateral circulation, in concert with pre-existing comorbidities (eg, left ventricular dysfunction and diabetes) will determine whether the patient with atherosclerotic plaque disruption presents with sudden cardiac death, transmural or non-transmural myocardial infarction, unstable angina, or minimum or atypical symptoms, or remains asymptomatic (though often with underlying plaque progression).

Patients with evolving ST-segment-elevation myocardial infarction (STEMI) are best managed with prompt primary percutaneous coronary intervention, supported with unfractionated heparin, aspirin, clopidogrel (and in most patients, glycoprotein IIb/IIIa inhibitors).[2] Conversely, the best approach for patients with non-ST-segment-elevation myocardial infarction and unstable angina (nSTE-ACS) is less certain.

For patients with nSTE-ACS, the fundamental decision is whether to proceed with invasive or conservative revascularisation. The invasive approach uses coronary angiography after initial medical stabilisation, followed by percutaneous coronary intervention, coronary artery bypass surgery, or medical therapy, depending on individual circumstances. A conservative approach emphasises medical stabilisation only, with angiography reserved for patients with significant breakthrough symptoms or ischaemia on an exercise test. The invasive approach aims for early revascularisation in as many patients as appropriate, in an attempt to "cure" the underlying lesion before it progresses. By contrast, the conservative approach seeks to stabilise plaques by intensive antithrombotic and antiplatelet medication, because the atherosclerotic lesion underlying the coronary thrombus is typically non-obstructive.[1] However, in theory and practice, these approaches are not always distinct, which is important when interpreting studies that have compared these two strategies.

Two meta-analyses examining the pooled results from ten randomised trials in nearly 11 000 patients with nSTE-ACS in which the routine invasive and conservative approaches were compared have been published.[3,4] In Mehta and colleagues' overview,[3] at a mean follow-up 17·3 months, the primary composite endpoint of death or myocardial infarction was reduced from 14·4% with the conservative approach to 12·2% with the invasive approach (odds ratio reduction 18%, 95% CI 7–28% reduction), due to a significant decrease in myocardial infarction and a reduction in death that did not reach statistical significance. In Bavry and colleagues' overview of more contemporary trials,[4] at a mean follow-up of 2 years, mortality was reduced from 6·5% with the conservative approach to 4·9% with the invasive approach (relative risk reduction 25%, 95% CI 10–37% reduction), and myocardial infarction was decreased with the invasive approach from 9·1% to 7·6% (17%, 4–28% reduction). The difference in the rates of revascularisation by percutaneous coronary intervention or surgery before hospital discharge in the invasive and conservative arms varied from 44% and 33%, respectively, in the VANQWISH trial (an absolute difference of only 11%), compared with 71% and 9%, respectively, in FRISC-II (an absolute difference of 62%), possibly explaining the differences in mortality and myocardial infarction observed between studies.[3,4] Both meta-analyses showed that the invasive strategy resulted in a lower rate of recurrent severe angina and rehospitalisation.

Are these beneficial findings sustained beyond 2 years? In today's *Lancet*, the long-term results from the 1200-patient ICTUS trial are reported.[5] ICTUS was notable for enrolling only troponin-positive patients, and for using intensive lipid-lowering therapy in all patients. There was no difference in mortality at 4 years between the patients randomised to an early invasive compared with a conservative strategy (7·9% *vs* 7·7%), possibly due to the fact that the use of percutaneous coronary intervention or coronary artery bypass at 3 years was not that different between the two groups (81% *vs* 58%). Of concern in ICTUS, the 3-year rate of myocardial infarction was higher in the invasive group because of procedural-related infarcts. However, the liberal definition of periprocedural myocardial infarction in ICTUS has been controversial, and the occurrence of inhospital myocardial infarction (most of which were

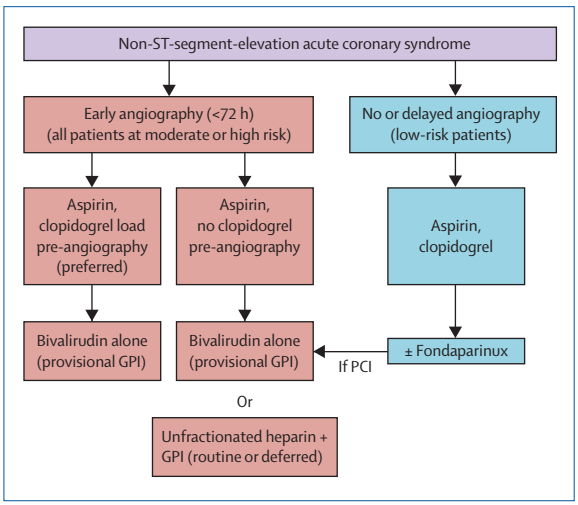

Figure: **Treatment algorithm for non-ST-segment-elevation acute coronary syndromes**
Stratified by decision to use early invasive approach (recommended either in all patients, or in those with moderate-risk and high-risk characteristics), or a conservative approach (in lower-risk patients or in those with atypical symptoms). GPI=glycoprotein IIb/IIIa inhibitor, PCI=percutaneous coronary intervention.

small) did not predict subsequent mortality. By contrast, 5-year follow-up after randomisation to invasive or conservative treatment strategies in patients with nSTE-ACS in the larger RITA-3 (n=1810) and FRISC-II (n=2457) trials showed a durable long-term reduction in composite death and myocardial infarction in patients treated invasively, with cardiovascular mortality also reduced in RITA-3.[6,7] In both FRISC-II and RITA-3, but not in ICTUS, higher-risk patients benefited most from the invasive approach. These trials were done before the introduction of drug-eluting stents, which might further reduce rehospitalisation and revascularisation rates.[8]

The results of ten randomised trials thus collectively show a significant improvement in survival free from myocardial infarction, recurrent ischaemia, rehospitalisation, and subsequent revascularisation procedures in patients with nSTE-ACS treated invasively rather than conservatively. The selection of an adjunct drug regimen should be tailored to the risk profile of the patient. Antiplatelet agents in combination with an antithrombin are typically used to stabilise the disrupted plaque. Benefits of these agents must be weighed against their potential haemorrhagic complications (especially when used in combination), the occurrence of which has been strongly associated with early and late mortality in acute coronary syndromes and with percutaneous coronary intervention.[9–11]

The best drug regimen in nSTE-ACS patients will depend on the local approach. A recommended treatment algorithm based on recent contemporary randomised trial data is shown in the figure. In patients managed with an early invasive approach, current evidence supports the use of aspirin, clopidogrel (with full loading before angiography), and bivalirudin monotherapy, with glycoprotein IIb/IIIa inhibitors reserved for breakthrough ischaemia.[12] Heparin and glycoprotein IIb/IIIa inhibitors may be considered for the patient not loaded with clopidogrel, which might decrease ischaemic events at the expense of increased major bleeding.[12]

Finally, if a conservative approach is used (which may be reasonably considered in lower-risk patients with nSTE-ACS in some health-care systems, or in those with atypical symptoms), the use of aspirin, clopidogrel, and fondaparinux (if an antithrombin agent is required) would be expected to minimise ischaemic and haemorrhagic complications,[13] thereby optimising outcomes in patients with an otherwise favourable prognosis. Catheter-related thrombus, however, precludes this as a standalone regimen for patients undergoing percutaneous coronary intervention.[13] Given the frequency of acute coronary syndromes (more than 896 000 hospital discharges for myocardial infarction and 669 000 for unstable angina in the USA alone in 2004),[14] nSTE-ACS remains a fertile area for investigation.

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Can we RESOLVE the treatment of sepsis?

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In today's *Lancet*, Simon Nadel and colleagues[1] report the much anticipated results of the RESOLVE (REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspectiVE) trial, in which they assessed activated drotrecogin alfa (recombinant human activated protein C) in children with sepsis. In this double-blind placebo-controlled international trial, the investigators randomly assigned children with severe sepsis to a 4-day course of drotrecogin alfa or placebo (intravenous saline). The primary endpoint was a composite score for resolution of organ failure; secondary endpoints were all-cause mortality up to 28 days after treatment and safety. The overall results are unexpected and profoundly disappointing: no efficacy signal was detectable from any of the endpoints, and the survival graphs look much the same for both treatment groups.

Children with sepsis should be an ideal population to test the efficacy of new antisepsis agents because these patients commonly have acute life-threatening infection without major underlying comorbidities. Furthermore, children have a greater capacity for tissue repair than do adults, and such physiological reserve should translate into a greater potential for reversal of severe sepsis. However, the favourable outlook for children with sepsis creates an unintended but major impediment to the development of new antisepsis drugs. A low number of deaths in placebo groups forces investigators to do very large studies to identify significant differences in outcome, or to have no mortality endpoints and rely on measurement of morbidity for drug efficacy.

Several scoring systems to assess morbidity in children with sepsis have been proposed, the most recent of which[2] was used in RESOLVE. However, these scores generate abstract numbers that lack clear clinical applicability, and they are substantially affected by early mortality events and by the particular management of organ dysfunction (eg, ventilator-weaning protocols, use of blood product, removal of renal replacement therapy). Without specific protocols that standardise the management of organ support in these children, the heterogeneity of the population and the widely disparate management strategies make it difficult to find a signal of modest efficacy with any antisepsis drug.

RESOLVE has some intriguing findings. First, patients with sepsis who had the most severe coagulation abnormalities seemed to benefit from drotrecogin alfa. Similar findings, independent of APACHE (Acute Physiology And Chronic Health Evaluation) II score, have been recorded for adults with sepsis who were treated with activated protein C[3,4] or with antithrombin in the