REVIEW

Contemporary management of acute coronary syndrome

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This review focuses on the modern management of the non-ST elevation acute coronary syndromes (unstable angina and non-ST elevation myocardial infarction). Patients with these syndromes are at varying degrees of risk of (re)infarction and death. This risk can be reliably predicted by clinical, electrocardiographic, and biochemical markers. Aspirin, clopidogrel, heparin (unfractionated or low molecular weight), and anti-ischaemic drugs should be offered to all patients, irrespective of the predicted level of risk. Patients at high risk should also receive a glycoprotein IIb/IIIa receptor inhibitor and should undergo early coronary arteriography with a view to percutaneous or surgical revascularisation. Lower risk patients should undergo non-invasive testing. When inducible myocardial ischaemia is exhibited coronary arteriography should follow. When non-invasive testing is negative, a conservative management strategy is safe.

Acute coronary syndrome (ACS) is a broad term that encompasses a range of acute clinical manifestations of coronary atherosclerosis. It has become convention to divide acute coronary syndrome patients into two groups according to whether or not initial 12 lead electrocardiograms show persistent ST-segment elevation (fig 1). Its presence correlates well with acute and complete epicardial coronary artery occlusion¹ and predicts benefit from urgent reperfusion therapy with fibrinolytic drugs² or percutaneous coronary intervention.³ In the absence of persistent ST-segment elevation reperfusion therapy confers no benefit and may even be harmful.² In this setting other therapeutic strategies are effective and the purpose of this review is to précis the evidence that underlies the contemporary management of ACS without persistent ST-segment elevation.

RISK STRATIFICATION

The rate of death, myocardial (re)infarction, or recurrent severe ischaemia early after non-ST elevation acute coronary syndrome (NSTEMACS) varies but may be as high as 41%.⁴ The primary goal of therapy is reduce this risk. It has been shown that higher risk demands more aggressive management⁵⁻⁷ and so, achieving this goal first requires an estimate to be made of the absolute level of risk. Thereafter a "package" of treatment can be assembled and offered, which is appropriate for the degree of hazard. There is an abundance of clinical study data to guide the clinician risk stratifying the NSTEMACS patient. In

addition a number of national and international guideline documents have been published to facilitate the process.⁸⁻¹¹ The thrombolysis in myocardial infarction (TIMI) risk scoring system is a risk stratification tool that can easily be applied at the bedside of the NSTEMACS patient (box 1). This risk score, developed by Antman *et al*,⁴ was derived by multivariate logistic regression analysis of the TIMI 11B trial dataset.¹² In this and most other risk stratification algorithms, three groups of variables have been used; clinical, electrocardiographic, and biochemical.

Clinical risk stratification

A number of clinical features have been identified as conferring increased risk of adverse outcome.¹³ The most important are age >75 years, rest pain (lasting >20 minutes), haemodynamic instability, pulmonary congestion, a new or worsening mitral regurgitant murmur, and the presence of a third heart sound.^{14 15} Presentation with NSTEMACS in the early aftermath of myocardial infarction (within two weeks) is an additional ominous feature.¹⁶

Electrocardiographic risk stratification

A 12 lead ECG is usually the earliest investigation undergone by patients presenting with suspected ACS. Often it serves to confirm the clinical suspicion but its utility reaches further than diagnosis alone. ST-segment depression (or transient ST segment elevation) in particular, demarcates patients at highest risk of adverse outcome and is predictive of three vessel or left main stem coronary disease, or both.^{17 18} Furthermore, there seems to be a direct correlation between the extent of ST segment shift and increased risk.¹⁹ In comparison, T wave inversion without ST segment shift implies an intermediate level of risk and the finding of a normal 12 lead ECG on admission to hospital is a marker of a favourable immediate prognosis.^{18 20}

Biochemical risk stratification

Central to the biochemical risk stratification of NSTEMACS patients are the cardiac troponin assays. The cardiac troponins (T and I) are both highly specific and sensitive markers of myocardial necrosis²¹ and in its absence they are undetectable in serum. Patients with suspected NSTEMACS in whom an increase in serum cardiac troponins is detected fair worse than those in whom it is not. Troponin increase is predictive of

Abbreviations: ACS, acute coronary syndrome; NSTEMACS, non-ST elevation acute coronary syndrome; TIMI, thrombolysis in myocardial infarction risks scoring system; CABG, coronary artery bypass grafting; UFH, unfractionated heparin; LMWH, low molecular weight heparin

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reinfarction and cardiac death.^{22–24} Even the smallest detectable elevations are indicative of increased risk and it has been shown that the level of risk is directly proportional to the degree of increase.²⁵ Furthermore, it has become apparent that troponin “positivity” identifies patients who benefit most from treatment with low molecular weight heparins,⁶ platelet glycoprotein IIb/IIIa receptor inhibitors,²⁶ and speedy revascularisation.⁷ An important caveat for the clinician to bear in mind regarding the use of cardiac troponin assays relates to the time course of their release from the cytosolic pool. The release kinetics of troponins are such that after myocardial necrosis their appearance in peripheral blood is delayed by three to four hours. It is therefore imperative to appreciate that a single negative troponin assay at the time of a patient’s admission cannot always be relied upon to exclude myocardial infarction. In this setting, it is recommended that the test be repeated 6 to 12 hours after admission and after any further episode of chest pain. The practice of omitting immediate troponin estimation on admission (to cut cost) has the potential for delaying the identification of high risk patients and is therefore inappropriate.

Evidence is emerging that “newer” biomarkers may provide prognostic information additional to that available from cardiac troponin assays. Data have been published showing that B type natriuretic peptide (a neurohormone synthesised in ventricular myocardium),²⁷ fibrinogen,^{28–29} C reactive protein,^{30–32} and soluble CD40 ligand (a marker of platelet activation)³³ are all markers of increased risk in the NSTEMI patient. Although yet to be widely adopted into routine practice, the apparent value of these novel markers in predicting recurrent events in troponin negative patients may define their future niche.

DRUG THERAPY

Antiplatelet and anticoagulant drugs

The efficacy of aspirin in NSTEMI is well established and has been verified repeatedly in large, randomised, controlled trials.^{34–35} It reduces rates of death and myocardial

infarction.³⁶ Accordingly, immediate treatment with aspirin in a dose of 300–325 mg followed by a maintenance dose of 75–150 mg daily is required in all cases of suspected ACS unless there is an absolute contraindication.

In the recent CURE study of 12 562 NSTEMI patients,³⁷ the ADP receptor antagonist clopidogrel was shown to reduce the rate of a combined end point of cardiovascular death, non-fatal MI, or stroke from 11.4% to 9.3%, after a median treatment period of nine months. It is noteworthy that, in contrast with most of the other proven therapies for NSTEMI, the benefit seen with clopidogrel was seen in patients at all levels of baseline risk, including those who were troponin negative and those without ST segment depression on ECG.³⁸ As a result it has been recommended that short term treatment with 300 mg of clopidogrel followed by 75 mg daily for at least nine months be offered in all cases of NSTEMI. Some concerns have arisen regarding the finding of an increased risk of major bleeding with clopidogrel in CURE study patients undergoing coronary artery bypass grafting (CABG) within five days of stopping the drug. This has led to the recommendation that clopidogrel be withheld for at least five days before CABG surgery. The need for expedited surgery is the exception rather than the rule and if this is anticipated (because of refractory ischaemia with widespread ST segment shift on ECG or haemodynamic instability) it is reasonable to withhold clopidogrel. If, after subsequent coronary arteriography, a “non-surgical” management strategy is chosen treatment with clopidogrel can be started.

Having been shown to reduce the risk of peri-procedural death and myocardial infarction in patients undergoing percutaneous intervention,^{39–44} inhibitors of the platelet glycoprotein IIb/IIIa receptor have subsequently been extensively studied in patients with acute coronary syndromes. In a meta-analysis, Boersma *et al* studied a total of 30 402 patients with NSTEMI enrolled in six randomised controlled studies.⁴⁵ It was found that early treatment with GPIIb/IIIa inhibitors was associated with an absolute risk reduction in the 30 day rate of

Figure 1 The use of 12 lead electrocardiography and cardiac troponins in the diagnostic evaluation of suspected acute coronary syndrome. *It is unusual to find serial negative troponins in suspected acute coronary syndrome patients whose electrocardiograms show persistent ST segment elevation.

Box 1 The seven predictor variables of the thrombolysis in myocardial infarction (TIMI) risk scoring system for NSTEMI*

- Age >65 years
- Three or more "conventional" risk factors for coronary arteriosclerosis (dyslipidaemia, diabetes mellitus, hypertension, smoking, positive family history)
- Known prior coronary stenosis of 50% or more
- ST-segment deviation on electrocardiogram at presentation
- At least two anginal events in prior 24 hours
- Use of aspirin in prior seven days
- Raised serum cardiac markers

*For each variable score one point. Rates of adverse outcomes (all cause mortality, myocardial infarction and severe recurrent ischaemia) at 14 days increase with TIMI risk score (4.7% for a score of 0/1; 8.3% for 2; 13.2% for 3; 19.9% for 4; 26.2% for 5; and 40.9% for 6/7).

death or myocardial infarction of 1% ($p = 0.015$) but at the expense of an increase in the rate of major bleeding complications (2.4% compared with 1.4%; $p < 0.0001$). Separate subgroup analyses showed that benefit from treatment was largely confined to patients who underwent early revascularisation and that troponin negative patients did not benefit. Current guidelines recommend the "upstream" use of intravenous small molecule GPIIb/IIIa inhibitors (eptifibatide or tirofiban) in high risk patients who should also be destined to undergo early coronary arteriography and revascularisation. Benefit is not restricted to patients who undergo percutaneous intervention and is also observed in patients who subsequently undergo CABG.^{46,47} Eptifibatide and tirofiban have comparatively short half lives but should be stopped at least four hours before surgery to avoid bleeding complications. Abciximab is not recommended for "upstream" use because in the 7800 patient, GUSTO-IV ACS study its use did not favourably influence the rate of the primary end point of death or myocardial infarction at 30 days.⁴⁸ Moreover, the mortality rate at 48 hours was significantly higher in patients treated with abciximab.

Historically, unfractionated heparin (UFH) has gained widespread acceptance as one of the cornerstone treatments for NSTEMI and its use has been recurrently advocated in published guideline documents. Surprisingly however, the evidence base to support the routine use of UFH in addition to aspirin is limited to a meta-analysis of six randomised controlled studies showing an absolute reduction in risk of death or myocardial infarction of 2.4%, an effect that failed to reach conventional criteria for statistical significance.⁴⁹ The data to support routine use of low molecular weight heparins (LMWH) are more robust. Firstly, a single study has shown the superiority of a LMWH (dalteparin) to placebo in NSTEMI patients.⁵⁰ Secondly, theoretical advantages of LMWH over UFH have been confirmed in clinical end point studies. Two large randomised controlled trials have shown the superiority of enoxaparin to UFH^{51,52} and a meta-analysis of both confirmed a significant reduction in risk of death or myocardial infarction attributable to the use of enoxaparin therapy.⁵² Current guidelines recommend the use of UFH or LMWH in all cases of NSTEMI irrespective of level of risk.

Anti-ischaemic drugs

Relief of the symptoms of acute myocardial ischaemia requires the use of drugs that correct the imbalance that

exists between myocardial oxygen supply and demand. In the absence of contraindications β adrenergic block should be first line anti-ischaemic therapy and should be given intravenously in high risk patients, particularly if ischaemia is ongoing. The reasons for this are twofold. Firstly, these agents have a confirmed track record as antianginal agents and secondly, unlike the other groups of antianginals, there is some evidence that their use in NSTEMI may favourably affect prognosis. A meta-analysis of three randomised clinical trials comparing β block with placebo in unstable angina showed a significant reduction in rates of progression to acute myocardial infarction but not death, by active treatment.⁵³ In addition, extrapolation of data from trials of β block in patients with acute or recent myocardial infarction, in which significant reductions in mortality were seen, supports its early use in NSTEMI.

There are no randomised, placebo controlled trials investigating the effect of nitrates on symptoms or prognosis in NSTEMI. A number of small, uncontrolled datasets have been published^{54,55} but the routine use of this group of drugs is almost entirely based on anecdotal experience of their efficacy in relieving symptoms. Two large randomised controlled trials have studied the impact of nitrate therapy on outcome in acute coronary syndrome associated with persistent ST segment elevation and in both, no significant benefit from treatment was shown.^{56,57} It is recommended then that sub-lingual glyceryl trinitrate be given in all cases where ischaemic chest discomfort is present at the time of initial clinical assessment. If symptoms are not relieved rapidly thereafter and after administration of intravenous β block, an intravenous nitrate infusion should be started.

Randomised studies of calcium channel blockers in NSTEMI have shown their efficacy in relieving symptoms.^{58,59} In addition, diltiazem may have a protective effect^{60,61} and there is strong evidence that immediate release nifedipine (a dihydropyridine) increases mortality rate, particularly if given without β block.^{62,63} Current guidelines recommend reservation of the dihydropyridine calcium antagonists for use as second or third line therapy after β block and nitrates whereas the rate limiting, non-dihydropyridine agents (diltiazem and verapamil) may be reasonable alternatives when β block is contraindicated.

The potassium channel activator nicorandil reduced the rate of a combined end point of cardiovascular death, non-fatal myocardial infarction, and unplanned hospitalisation for angina in a recent study of 5126 patients with stable angina.⁶⁴ Patel *et al* reported a smaller study showing that nicorandil significantly reduced the rate of transient myocardial ischaemia or tachyarrhythmias in patients with unstable angina.⁶⁵ This study was not powered to detect differences in clinical outcomes and to date there have been no large randomised controlled studies of this agent in NSTEMI.

CARDIAC CATHETERISATION AND REVASCULARISATION

An important recent advance in the management of NSTEMI has been the recognition that high risk patients benefit from early (before discharge) invasive investigation and coronary revascularisation compared with a more conservative, "ischaemia guided" strategy, whereby coronary arteriography and revascularisation are reserved for patients with ischaemia refractory to drug therapy or with evidence of inducible ischaemia on early non-invasive testing. Five prospective randomised studies have investigated this issue. The earliest, the TIMI IIIb trial, showed no difference between strategies in terms of rates of myocardial infarction and mortality.⁶⁶ Hospital readmission was significantly reduced by the invasive approach. The veterans affairs

Figure 2 Algorithm to guide the management of patients with non-ST elevation acute coronary syndrome. *Glycoprotein IIb/IIIa.

non-Q-wave infarction strategies in hospital (VANQWISH) investigators reported an increased risk of death or non-fatal myocardial infarction with an early invasive strategy.⁶⁷ This may be explained by the unusually high 30 day mortality rate after CABG in this study (12%).

Both the TIMI IIIB and VANQWISH trials were conducted before the routine use of stents and GPIIb/IIIa inhibitors during percutaneous coronary intervention. As such, the results have to be interpreted with caution in the current day. Three subsequent studies have all shown superiority of early, “modern” invasive management. The fragmin and fast revascularisation during instability in coronary artery disease (FRISC) II study showed a significant reduction in all cause mortality and myocardial infarction at one year follow up, attributable to an invasive strategy.⁶⁸ The TACTICS-TIMI 18 investigators randomised 2220 patients to early coronary arteriography followed by revascularisation as appropriate or a more conservative strategy in which catheterisation was only performed for recurrent ischaemia or positive stress

testing.⁷ All patients received tirofiban for 48 hours before randomisation and cardiac catheterisation was carried out comparatively early (at a mean interval of 22 hours after randomisation) compared with the FRISC II study (mean interval six days). Again a benefit in favour of the invasive strategy was found with an absolute risk reduction of 3.5% in the rate of the primary end point (death, non-fatal myocardial infarction, or rehospitalisation for ACS). Of note, this benefit was restricted to high risk patients—that is, those with TIMI risk score ≥ 3 , raised troponins, or ST segment deviation. Most recently, Fox *et al* published the results of the randomised intervention trial of unstable angina (RITA) 3 study.⁶⁹ All 1810 patients studied were treated with subcutaneous enoxaparin and in the invasive arm, cardiac catheterisation took place at a mean of two days after enrolment. A primary end point of death, (re)infarction, or refractory angina at four months was prespecified and was observed in 9.6% of patients in the invasive arm compared with 14.5% of those in the conservative arm ($p = 0.001$).

Box 2 Key points

- Patients presenting with NSTEMI are at varying degrees of risk of myocardial (re)infarction and death.
- Early risk stratification is central to the choice of appropriate treatments.
- High risk is demarcated by clinical (age >75 years, rest pain, haemodynamic instability, pulmonary congestion, new or worsening mitral regurgitation, third heart sound, or recent myocardial infarction), electrocardiographic (ST segment shift), and biomarker (troponin positivity) abnormalities.
- Patients at all levels of risk should be treated with aspirin, clopidogrel, heparin (unfractionated or low molecular weight), and anti-ischaemic drugs.
- High risk patients should receive a small molecule, IIb/IIIa inhibitor (eptifibatide or tirofiban) and should be offered early (in-patient) coronary arteriography with a view to a revascularisation procedure.
- Patients at lower risk should undergo early, non-invasive testing with coronary arteriography reserved for those in whom inducible myocardial ischaemia is unveiled.

The remarkably consistent results observed by the FRISC II, TACTICS-TIMI 18, and RITA 3 investigators form a large, concrete evidence base on which it is recommended that in-patient coronary arteriography and revascularisation should be made available to all high risk NSTEMI patients. Low risk patients can be safely managed with an initial conservative approach with cardiac catheterisation reserved for those who develop recurrent ischaemia or who subsequently have a positive stress test.

CONCLUSIONS AND RECOMMENDATIONS

Figure 2 shows a suggested algorithm to guide the management of suspected NSTEMI. Aspirin, clopidogrel, heparin (UFH or LMWH), and a β blocker should be on offer to all patients. Aspirin should be continued indefinitely and clopidogrel for at least nine months. Early risk stratification should guide the choice of further therapies. High risk status demands an aggressive management strategy including treatment with a small molecule GPIIb/IIIa inhibitor followed by coronary arteriography and revascularisation. Patients at lower risk should undergo early, non-invasive testing for inducible myocardial ischaemia, followed by coronary arteriography when such testing is positive. Finally, the secondary preventative advice and interventions that apply in general to patients with any clinical manifestation of coronary arteriosclerosis should be made available to all ACS patients. Advice regarding smoking cessation, diet, and exercise should be given. In most cases, additional therapy with lipid lowering agents (statins) and an angiotensin converting enzyme inhibitor will also be required.

Conflicts of interest: none.

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