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Edited by Dr Chris Burrell, consultant cardiologist, Southwest Cardiothoracic Centre, Plymouth, UK and Plymouth Chair, British Cardiovascular Society, Communication and Education Committee, London, UK

Acute coronary syndrome: optimising management through risk assessment

Robert A Henderson, *consultant cardiologist*

Trent Cardiac Centre, Nottingham, UK

The term 'acute coronary syndrome' (ACS) covers a spectrum of conditions that present with acute myocardial ischaemia and range from non-ST-segment elevation ACS (NSTE-ACS, including non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina) to ST-segment elevation myocardial infarction (STEMI) (Fig 1). The management of patients with ACS presents a global challenge to clinicians and healthcare systems. Across Europe, the incidence of ACS is estimated to be between 1 in 80 and 1 in 170 per annum and, each year, approximately 1 in 330 of the population are hospitalised with suspected NSTE-ACS.[1–3]

Large patient registries have shown that patients with NSTE-ACS are at high risk of adverse cardiovascular events, with a 6-month mortality of 11% for patients with ST depression and 5% for patients without ST segment deviation. The hazard of death is greatest for the first few days after the index presentation, thereafter declining gradually over several weeks. Following this acute phase, the prognosis for patients with ST-segment depression is worse than for patients with STEMI, probably because patients with NSTE-ACS tend to be older, are more likely to be female and have a higher prevalence of diabetes and other vascular risk factors.[3,4] This article will focus on the role of risk assessment in patients with NSTE-ACS.

Risk assessment

Patients with NSTE-ACS are clinically heterogeneous and the risk of adverse cardiovascular events varies widely between individuals. Factors associated with increased cardiovascular risk in NSTE-ACS include:[5] increasing age, raised heart rate, low blood pressure, electrocardiogram (ECG) abnormality, elevated serum cardiac biomarker, arrhythmia, impaired left ventricular function, impaired renal function, diabetes, anaemia, and cerebrovascular and peripheral vascular disease.

To be clinically useful, potential markers of risk in patients with ACS must:[6] be statistically associated with the outcome of interest; predict the outcome in a prospective cohort; add incremental predictive value to established predictors of risk; have clinical utility (influence predicted risk sufficiently to change treatment recommendations); improve clinical outcomes; and be cost effective.

As yet, none of the factors associated with increased risk in patients with NSTE-ACS meet these stringent criteria for an ideal marker of risk. Moreover, single markers of risk do not provide a reliable indicator of risk in individual patients with NSTE-ACS. For example, patients with ST-segment deviation on the ECG at presentation are at high risk of death, but within this group, the risk of early mortality varies 40-fold between low- and high-risk patients and overlaps with risk in patients without ST-segment depression.[4] Similarly, patients with an elevated serum troponin level on admission to hospital are at increased risk of adverse cardiovascular outcomes relative to patients with a normal serum troponin level, but there is substantial overlap in risk between these two groups[7] (Fig 2). Hence, the widespread practice of stratifying patient risk on the basis of an elevated serum cardiac biomarker alone does not reliably identify high-risk patients.

Risk scores

Algorithms that combine several clinical variables into a single assessment of risk have been developed to overcome some of the limitations of single markers of risk. Some of these risk-scoring systems have been derived from randomised clinical trials,

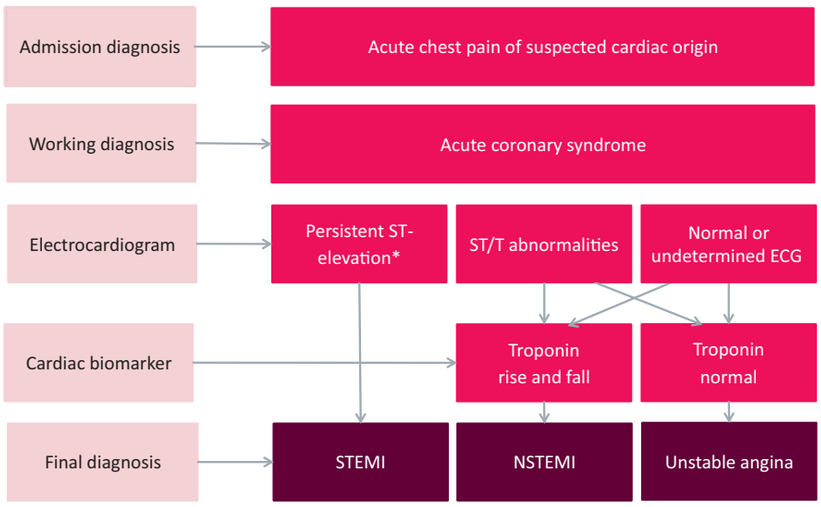

Fig 1. Classification of acute coronary syndromes. ECG = electrocardiogram; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction. The asterisk indicates that the patient should be immediately assessed for reperfusion therapy. Adapted and reproduced with permission from Hamm *et al* (2011).[1]

which generally exclude patients above the 50th centile of risk in unselected populations with ACS.[5] Other risk scores have been derived from large patient registries and are more representative of the wider population of patients with ACS (Table 1).

The Thrombolysis in Myocardial Infarction (TIMI) risk score was derived from patients with NSTE-ACS assigned to treatment with unfractionated heparin in the TIMI-11B trial. The TIMI risk score was developed to predict the occurrence of a composite endpoint (all-cause mortality, myocardial infarction, or urgent revascularisation) at 14 days, but has also been used to predict inhospital death and the composite of death and myocardial infarction.[5,8]

The Global Registry of Acute Coronary Events (GRACE) score was derived from a large multinational registry of patients with ACS to predict death or death and myocardial infarction, both inhospital and at 6 months.[9,10] The GRACE score has been validated in several data sets and predicts risk with high levels of discrimination and calibration.[11]

Risk-scoring systems in NSTE-ACS were comprehensively reviewed by the National Institute for Health and Care Excellence (NICE) Guideline Development Group.[5] Studies comparing risk scores generally suggest that the discriminatory performance of the GRACE score is superior or equal to that of other risk scores.[12–14] National and international guidelines recommend that all patients with NSTE-ACS should be assessed with an established risk-scoring system that takes account of multiple prognostic factors and that the risk assessment is used to determine the most appropriate treatment.[1,5,15]

Bleeding risk

Antithrombotic medication is administered to patients with NSTE-ACS to reduce the risk of ischaemic events, but increases the risk of bleeding. Major bleeding in patients with NSTE-ACS is associated with an adverse outcome, although a direct causal relation between bleeding and outcome has not been established.[16] A risk score to predict major inhospital bleeding in patients with NSTE-ACS has been developed from the large American CRUSADE registry (Table 1).[17]

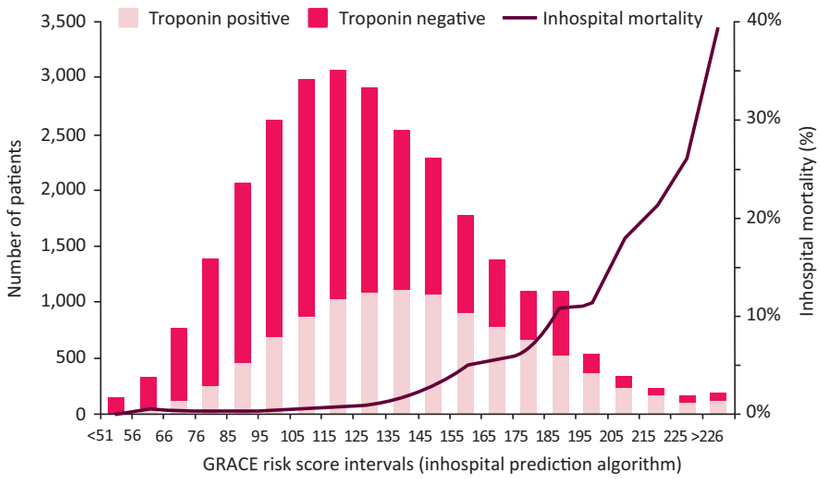

Fig 2. Relation between GRACE score and inhospital mortality for troponin-positive and troponin-negative patients. The bar chart shows the distribution (left axis) of troponin-positive and troponin-negative patients according to category of GRACE risk score among 27,406 patients with non-ST-segment elevation acute coronary syndromes. The curve (right axis) depicts the observed inhospital mortality rate. GRACE = Global Registry of Acute Cardiac Events. Adapted with permission from Steg *et al* (2009).[7]

Several of the variables that predict major bleeding also predict ischaemic events, but methods to integrate information from multiple risk scores in the care of patients with NSTE-ACS have not yet been developed. In practice, clinicians should take account of ischaemic and bleeding risk when deciding which treatments to offer to patients with NSTE-ACS.

Clinical utility of risk stratification

An intervention that has a consistent relative effect on an outcome will result in a greater absolute effect in those at highest risk of the outcome. For example, if the intervention reduces the relative risk of an adverse event by 20%, the absolute rate of the event might be reduced by 0.2% in those at low risk (1%), but by 2% in those at high risk (10%) (Fig 3). In this illustration, it would be necessary to treat 500 low-risk patients but only 50 high-risk patients to prevent one event and, therefore, the cost of preventing one event is likely to be lower in high-risk patients. Hence, accurate risk stratification can identify high-risk patients with NSTE-ACS in whom treatments are most likely to be both effective and cost effective.

In the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, addition of clopidogrel to treatment with aspirin in patients with NSTE-ACS was associated with a significant 20% relative reduction in the risk of the composite primary outcome of cardiovascular death, non-fatal myocardial infarction, or stroke.[18] In a post-hoc subgroup analysis, the rate of the primary outcome and the magnitude of the treatment benefit from clopidogrel increased proportionally with increasing TIMI risk score (Fig 4). Patients at lowest risk (TIMI risk score 0–1) did not gain any significant benefit from clopidogrel treatment[19] and, therefore, NICE guidance recommends that patients at low risk (with a predicted 6-month mortality of <1.5%) should not be offered clopidogrel.[5]

The role of a routine invasive strategy (routine early coronary arteriography and follow-on myocardial revascularisation if indicated) versus a selective invasive strategy in patients with NSTE-ACS has been assessed in several randomised trials. A pooled analysis of individual patient data from the three largest such trials demonstrated a 19% relative and 3.2% absolute reduction in the hazard of cardiovascular death or myocardial infarction over a 5-year follow-up.[20] When the patients were stratified according to baseline risk characteristics into low-, intermediate- and high-risk

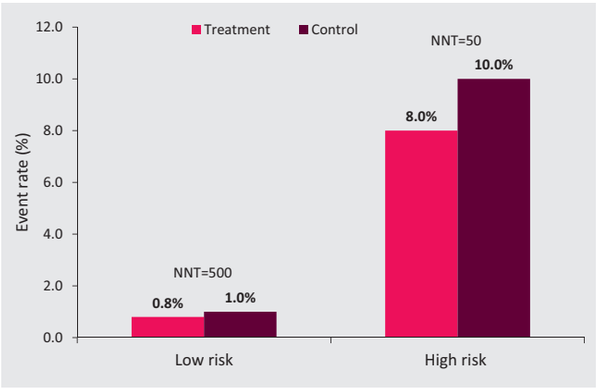

Fig 3. Impact of the underlying risk of an adverse event on the absolute benefit of treatment. If a treatment reduces an event rate by 20% relative to the control, the absolute reduction in event rate will be 0.2% in low-risk patients and 2% in high-risk patients. In low-risk patients, the number needed to treat (NNT) to prevent one event is 500, whereas in the high-risk group, it is 50 patients. Therefore, the cost of preventing one event is likely to be lower in high-risk patients.

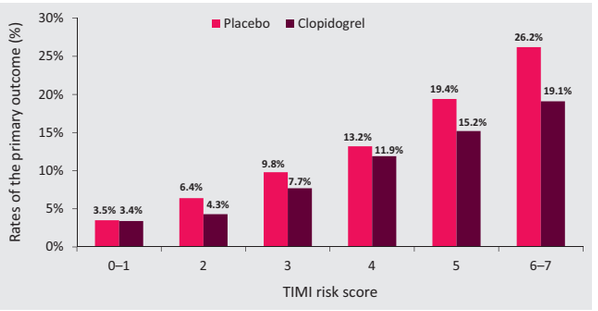

Fig 4. Subgroup analysis of the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial of clopidogrel versus placebo in patients with non-ST-segment elevation acute coronary syndrome. Rates of the primary outcome (cardiovascular death, myocardial infarction or stroke) in the clopidogrel and placebo groups are stratified by TIMI risk score. The greatest absolute benefit of clopidogrel treatment is seen in patients at highest risk (TIMI scores 5–7). T TIMI – thrombolysis in myocardial infarction. Reproduced with permission from Budaj *et al* (2002).[19]

subgroups, the absolute benefit of the routine invasive strategy was only 2% in those at lowest risk, but 11.1% in those at highest risk. These data support the role of risk stratification in the selection of patients with NSTE-ACS who are likely to benefit from a routine invasive strategy.

More recently, the Timing of Intervention in Acute Coronary Syndrome (TIMACS) trial assigned patients with NSTE-ACS to an early invasive (within 24 h of presentation) versus a delayed invasive management strategy (later than 36 h after presentation). The primary outcome of death, myocardial infarction, or stroke at 6 months

Table 1. Risk scores in acute coronary syndrome.

	Thrombolysis in Myocardial Infarction (TIMI)	Global Registry of Acute Cardiac Events (GRACE)	Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE)
Website	www.timi.org	www.outcomes-umassmed.org/grace	www.crusadebleedingscore.org
Derivation data source	TIMI 11b trial (1,957 patients with NSTE-ACS assigned to treatment with unfractionated heparin)[8]	GRACE registry (11,389 ACS patients for inhospital mortality;[9] 21,688 ACS patients for 6-month outcome)[10]	CRUSADE registry (71,277 patients with NSTEMI)[17]
Outcome	Death, MI or urgent revascularisation at 14 days	Death, and death or MI, both inhospital and at 6 months	Inhospital major bleeding
Variables			
1	Age 65 years or older	Age	Baseline haematocrit
2	At least three risk factors for CHD: family history of CHD, hypertension, hypercholesterolaemia, diabetes or current smoker	Serum creatinine	Creatinine clearance
3	Previous coronary stenosis of 50% or more	Heart rate	Heart rate
4	At least two anginal events over the previous 24 h	Systolic blood pressure	Systolic blood pressure
5	Use of aspirin during the previous 7 days	Killip class	Signs of CHF at presentation
6	ST-segment deviation	ST-segment deviation	Sex
7	Elevated serum cardiac markers	Elevated serum cardiac markers	Previous vascular disease*
8		Cardiac arrest at admission	Diabetes mellitus

ACS = acute coronary syndrome; CHD = coronary heart disease; CHF = congestive heart failure; MI = myocardial infarction; NSTE = non-ST-segment elevation; NSTEMI = non-ST-segment elevation myocardial infarction.
*Previous vascular disease is defined as a history of peripheral artery disease or previous stroke.

occurred in 9.6% of the early invasive group and 11.3% in the delayed invasive group, a non-significant 15% reduction in risk. In a pre-specified subgroup analysis, patients were stratified into tertiles of GRACE risk score. In the high-risk group, an early invasive strategy was associated with a significant 7.1% absolute reduction in the primary event rate, but in low- and intermediate-risk patients, there was no benefit from early intervention (Fig 5).[21]

Risk stratification and bleeding

In the CRUSADE registry, the use of multiple antithrombotic agents and an invasive management strategy both increased bleeding across the spectrum of bleeding risk. The magnitude of this effect was greatest in those at highest risk of bleeding, suggesting that careful treatment selection might reduce rates of bleeding, especially in those at high risk.

Treatment risk paradox

Evidence from several studies suggests that physicians often do not integrate the most important markers of risk into a clinical assessment of risk. In one study, several established determinants of risk (including age, haemodynamic status, serum creatinine and history of heart failure) appeared not to influence the treating physicians' assessment of risk, which correlated poorly with risk assessed by a validated risk score.[22] Patients judged to be at high risk by treating physicians are more likely to be offered antithrombotic medication and invasive management (coronary arteriography and myocardial revascularisation) than are patients judged to be at low risk. By contrast, when risk is assessed by a validated risk score, a treatment risk paradox is evident, such that patients at highest risk are less likely to be treated with evidence-based pharmacological interventions and undergo invasive management.[12,22–24] These data demonstrate that clinicians often do not assimilate all relevant determinants of risk into their overall assessment of patients with NSTE-ACS. Therefore, systematic application of validated risk scores is appropriate to identify patients at high risk who are at greatest need of treatment and who will obtain greatest benefit.

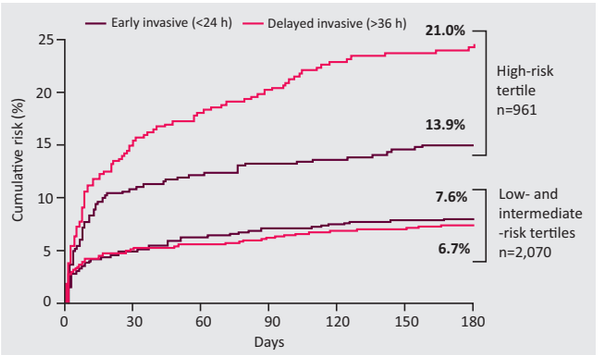

Fig 5. Cumulative risk of the primary outcome (death, myocardial infarction or stroke) in the Timing of Intervention in Acute Coronary Syndrome (TIMACS) trial, stratified by tertile of Global Registry of Acute Coronary Events (GRACE) risk score at baseline. Patients in the high-risk tertile benefitted from early intervention (<24 h), whereas patients in the low- and intermediate-risk tertiles did not benefit (>36 h). Reproduced with permission from Mehta *et al* (2009).[21]

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Key points

Patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACE) are at high risk of adverse cardiovascular outcomes

Numerous factors associated with high risk in patients with NSTE-ACS have been identified, but these factors are of limited value in determining risk in individual patients

In routine practice, treating physicians often do not integrate the most important markers of risk into a clinical assessment of individual patients with NSTE-ACS

Risk-scoring algorithms that combine several risk factors into an overall assessment of risk provide a reliable assessment of risk in individual patients with NSTE-ACS, but are underused in routine clinical practice

Available data suggest that risk stratification in patients with NSTE-ACS has clinical utility and can influence treatment decisions and clinical outcomes. Randomised trials of risk stratification in patients with NSTE-ACS are required to confirm these findings

KEY WORDS: Acute coronary syndrome, risk score, risk stratification, myocardial revascularisation

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Address for correspondence:
Dr RA Henderson, Trent Cardiac Centre, City Hospital Campus, Nottingham University Hospitals, Nottingham, NG5 1PB.
Email: robert.henderson@nuh.nhs.uk