Acute coronary syndromes

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Acute coronary syndrome (ACS) refers to the aggregate of symptoms and signs resulting from acute myocardial ischaemia and encompasses:

- ST elevation myocardial infarction
- non-ST elevation myocardial infarction (NSTEMI), and
- unstable angina.

The focus of this review will be on patients who fall into the two last groups. NSTEMI is diagnosed when sufficient myocardial ischaemia occurs to release detectable quantities of a marker of myocardial injury, most commonly troponin I (TnI), troponin T (TnT) or creatine kinase-myocardial bound (CKMB). If no marker of myocardial injury is released, the patient is diagnosed as having unstable angina.

Coronary heart disease is the most common cause of death in the UK (1 in 4 men and 1 in 6 women died from the disease in 2001). Data from the PRAIS-UK registry (see end of text for explanation of acronyms) demonstrated a rate of death or myocardial infarction (MI) of 12.2% at six months for ACS patients.[1] However, a strategy which incorporates risk stratification with newer pharmacological agents and revascularisation (percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)) can improve both immediate and long-term outcomes.[2,3]

Pathophysiology

ACS is due to an acute or subacute primary reduction of myocardial oxygen supply, most commonly caused by non-occlusive thrombus formation on a disrupted atherosclerotic plaque. This tends to occur in plaques with:

- a large lipid core
- low smooth muscle density
- high macrophage density, and
- a thin fibrous cap.

Most lesions rupture at the sites of greatest mechanical stress (junction of plaque cap and adjacent normal intima).[4] In addition, within the plaque, interplay between macrophages and T cells leads to production of proteolytic enzymes (matrix metalloproteinase) that degrade the fibrous plaque resulting in erosion and favouring rupture. Exposure of the thrombogenic lipid-rich core and the high tissue factor expression brought about by inflammatory mediators[5] leads to thrombus formation. The resulting transient occlusion or subocclusion and embolisation to downstream arterioles cause myocardial necrosis in the absence of complete occlusion of the epicardial coronary artery.

Diagnosis and risk stratification

The common clinical presentations of ACS are prolonged anginal pain at rest (>20 min), new onset severe angina or recent destabilisation of previously stable angina. The history, physical examination, ECG and biochemical marker measurements in patients with symptoms suggestive of ACS at initial presentation can be integrated into an estimation of the risk of death and further cardiac events. Dividing patients into high- and low-risk groups will then guide management and further investigation.

High risk

Numerous clinical studies have been carried out to identify factors that place patients at high risk (Table 1). Patients show progressively increasing benefit from more aggressive medical or invasive strategies with increasing TIMI risk score.[2,6] The two most important factors (used clinically) that place patients at high risk of death or MI are acute ST segment alteration on the ECG and elevated cardiac troponins (cTn).

ST depression. In the FRISC II ECG study, patients with ST depression ($\geq$0.05 mV) had significantly higher risk of death or MI (75% increase, p <0.001) and three vessel/left main stem disease (100% increase, p <0.001) than those without ST depression.[7] They also

Key Points

To reduce death and myocardial infarction, risk stratification is essential in acute coronary syndrome patients in order to target treatment appropriately according to the level of risk

Patients at high risk include those with anginal symptoms at rest, ST segment depression, elevated troponin, recurrent ischaemia or postinfarction angina, diabetes mellitus, haemodynamic instability, or age over 65 years

Patients at low risk are those below 65 years, with no recurrent chest pain or ST segment depression, negative troponin and haemodynamically stable

High-risk patients should receive routine medical treatment (aspirin, clopidogrel, heparin), with an early small-molecule glycoprotein IIb/IIIa inhibitor and urgent angiography, with or without revascularisation

Low-risk patients should receive routine medical treatment (discontinue heparin if troponin negative) and be further risk stratified by exercise or pharmacological stress testing, with or without myocardial scintigraphy or 2D-echocardiography

KEY WORDS: acute coronary syndrome; non-ST elevation myocardial infarction, unstable angina

Table 1. Features that indicate a patient with acute coronary syndrome is at high risk of myocardial infarction or death.

- Rest angina >20 min
- ST segment depression or transient ST elevation
- Elevated cardiac biomarkers and/or inflammatory markers (cTnI/T, CKMB, hsCRP, BNP, CD40 ligand)
- Recurrent ischaemia
- Postinfarction angina
- Diabetes mellitus
- Haemodynamic instability
- Ventricular tachyarrhythmia associated with chest pain
- TIMI risk score ⩾3

BNP = B-type natriuretic peptide; CKMB = creatine kinase-myocardial bound; cTnI/T = cardiac troponins I and T; hsCRP, = highly selective C-reactive protein; TIMI = Thrombolysis in Myocardial Infarction [trial].

Table 2. The seven-point Thrombolysis in Myocardial Infarction (TIMI) risk score.

1	Age ⩾65 years
2	⩾3 Coronary artery disease risk factors (↑ cholesterol, diabetes mellitus, hypertension, smoking, family history)
3	⩾50% Coronary stenosis on angiography
4	>0.5 mm ST segment deviation
5	⩾2 Anginal episodes in previous 24 hours
6	Elevated biochemical markers of myocardial necrosis (cTnI, cTnT or CKMB)
7	Use of aspirin in last 7 days

CKMB = creatine kinase-myocardial bound; cTnI/T = cardiac troponins I and T.

obtained much greater benefit from revascularisation.

Troponins. Troponins are myocardial proteins that regulate the calcium dependent interaction between actin and myosin.[4] They are not detected in the blood of healthy persons. High troponin levels (cTnT >0.01 ng/ml or cTnI >0.1 ng/ml)[8] 6-12 hours after symptom onset are diagnostic of myocardial necrosis. High troponin levels allow detection of myocardial damage in a further 30% of patients presenting with ACS who do not have elevated CKMB.[9] Despite this, the recently published Euro Heart Survey of ACS revealed that troponins were measured in only 63% of patients and that many clinicians continue to diagnose MI only when there is a substantial rise in cardiac markers.[10,11] Troponins provide an incremental marker of risk of death and MI and identify patients who will benefit from treatment with low molecular weight heparins, glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors and an early invasive strategy.[2,12–14] However, raised troponin levels may occur in other disorders that can present with chest pain and cTnT elevation, including pulmonary embolism, dissecting aortic aneurysm and pericarditis. The diagnosis of NSTEMI should therefore be made with cTnI/T elevation in conjunction with the clinical presentation and/or the ECG.

New markers. Because of the improved understanding of the pathophysiology of ACS, new markers, based on neurohormonal activation and inflammation, can refine risk stratification. B-type natriuretic peptide, a neurohormone synthesised in the ventricular myocardium, and the inflammatory markers, C-reactive protein and soluble CD40 ligand (released from activated lymphocytes and platelets, promoting inflammation and coagulation), have been identified as markers of adverse outcome. Furthermore, elevated levels of these markers are associated with increased risk of recurrent events in patients without evidence of myocardial necrosis (ie troponin negative).[15,16] It has thus been suggested that using both established and new markers for risk assessment and decision making has the potential substantially to improve the outcomes in ACS patients.[17]

In summary, high-risk patients are identified by their history and clinical characteristics, although the two most important features indicating patients at high-risk are ST segment depression on the initial 12-lead ECG and elevation of cTnI/T (Tables 1 and 2).

Low risk

The low-risk group for MI or death are patients under 65 years who are haemodynamically stable, with a normal ECG, negative cTnI/T and no recurrent chest pain. Further risk stratification, in the form of stress testing, is indicated for most patients. Exercise ECG stress testing is recommended in low-risk patients who have a resting ECG that is interpretable for ST segment shifts. Patients with inconclusive results, those unable to exercise or who have an uninterpretable baseline ECG should be considered for pharmacological stress testing, either with nuclear perfusion or 2D-echocardiography,[9] which assists not only in diagnosis but also for prognosis.

Chest pain clinics were devised to facilitate more definitive evaluation of ACS. They can identify high-risk patients, while significantly reducing the number of unnecessary hospital admissions of low-risk patients and of inappropriate discharge of high-risk patients.[18] Rapid-access chest pain clinics are cost saving compared with in-hospital evaluation of ACS.[19]

Management of patients

ACS patients who suffer an MI during the first 72 hours after presentation are at significantly increased risk of death over the following six months. To reduce risk of long-term mortality, it is thus important to consider therapies that reduce the risk of *early* MI.[20] The current recom-

TRIAL ACRONYMS

CURE	Clopidogrel in Unstable angina to prevent Recurrent Events
FRISC II	Fast Revascularisation during Instability in Coronary Artery Disease
PRAIS-UK	Prospective Registry of Acute Ischaemic Syndromes in the UK
TACTICS-TIMI	Treat Angina with aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy – Thrombolysis in Myocardial Infarction

mendations for all patients are prompt initiation of:

- aspirin
- low molecular weight/unfractionated heparin
- clopidogrel, and
- anti-ischaemic therapy with nitrates, beta-blockers and angiotensin-converting enzyme inhibitors.

High-risk patients should receive a small molecule GPIIb/IIIa inhibitor with early referral for cardiac catheterisation and consideration of revascularisation.[4]

Clopidogrel

The CURE study[21] examined the use of clopidogrel in combination with aspirin in 12,562 patients with non-ST-elevation ACS. The primary end-point (composite of cardiovascular death, non-fatal MI or stroke up to 12 months) was significantly reduced from 11.4% to 9.3% (p <0.001) by the addition of clopidogrel. The benefit of clopidogrel was evident by 24 hours, with a 21% relative risk reduction in the primary end-point ($p = 0.003$) at 30 days and 18% ($p = 0.009$) at one year.[22] The benefit was demonstrated in both high- and low-risk groups, with greatest benefit in the former.[23]

Glycoprotein IIb/IIIa inhibitors

Activation of GPIIb/IIIa receptors on platelets is the final common pathway that leads to platelet aggregation, thrombus formation and myocardial ischaemia. Many trials have investigated the role of intravenous GPIIb/IIIa inhibitors in ACS both as primary therapy and as an adjunct to PCI (Table 3).[24–29] Are the benefits of GPIIb/IIIa inhibitors limited to those receiving interventional treatment? In a meta-analysis of six randomised trials (31,402 patients) of the clinical efficacy of GPIIb/IIIa inhibitors in patients with ACS, GPIIb/IIIa inhibitors were associated with a highly significant absolute reduction in death or MI at 5 days (1.2%, $p = 0.0003$) and a 1% absolute reduction at 30 days ($p = 0.015$).[30] The benefit was greatest in higher-risk patients such as those with ST depression on the initial ECG, diabetics and troponin-positive patients.[30,31] No benefit was seen in the troponin negative group.

Patients undergoing early PCI have a significant reduction in preprocedural events with GP IIb/IIIa inhibitors.[30] In the TACTICS-TIMI 18 trial, all patients received aspirin, heparin and tirofiban and were randomised to early invasive (within 48 hours) or conservative strategy. It has been postulated that the routine use of GPIIb/IIIa inhibitors in the invasive arm may have eliminated the excess risk of early (within seven days) MI present in FRISC II and other trials in which there was no routine 'upstream' use of GPIIb/IIIa inhibitors.[9] In the subgroup of patients in the meta-analysis[30] undergoing PCI within five days, GPIIb/IIIa inhibitors had a strong treatment effect with a 23% relative risk reduction of death or MI at 30 days. A significant benefit has also been seen in NSTEMI patients treated early with GPIIb/IIIa inhibitors who subsequently underwent CABG.[32,33]

Thus, early use of GPIIb/IIIa inhibitors is recommended in the management of patients with ACS who are at high risk of subsequent death or MI. The 2002 National Institute for Clinical Excellence guidelines state that, whilst it is recognised that an early invasive strategy is desirable for these patients, in situations where PCI is or is not immediately

Table 3. Overview of multicentre trials of glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes.

Study	Ref.	Year	No. of patients	Drug	Primary end-point	Primary end-point: results	Death or MI at 30 days
CAPTURE	24	1997	1,265	Abciximab vs placebo	Death/MI/urgent PCI at 30 days	11.3% vs 15.9% ($p = 0.012$)	9.0% vs 4.8% ($p = 0.003$)
PRISM	25	1998	3,232	Tirofiban vs heparin	Death/MI/ischaemia at 48 hours	3.8% vs 5.6% ($p = 0.01$)	5.8% vs 7.1% (NS)
PRISM-PLUS	26	1998	1,915	Tirofiban + heparin vs heparin	Death/MI/ischaemia at 7 days	12.9% vs 17.9% ($p = 0.004$)	8.7% vs 11.9% ($p = 0.03$)
PURSUIT	27	1998	10,948	Eptifibatide vs placebo	Death/MI at 30 days	14.2% vs 15.7% ($p = 0.04$)	14.2% vs 15.7% ($p = 0.04$)
PARAGON B	28	2002	5,225	Lamifiban vs placebo	Death/MI/ischaemia at 30 days	11.8% vs 12.8% (NS)	10.6% vs 11.5% (NS)
GUSTO IV	29	2001	7,800	Abciximab for 48 hours vs 24 hours vs placebo	Death/MI at 30 days	9.1% vs 8.2% vs 8.0% (NS)	8.2% vs 8.0% (NS)

MI = myocardial infarction; PCI = percutaneous coronary intervention.

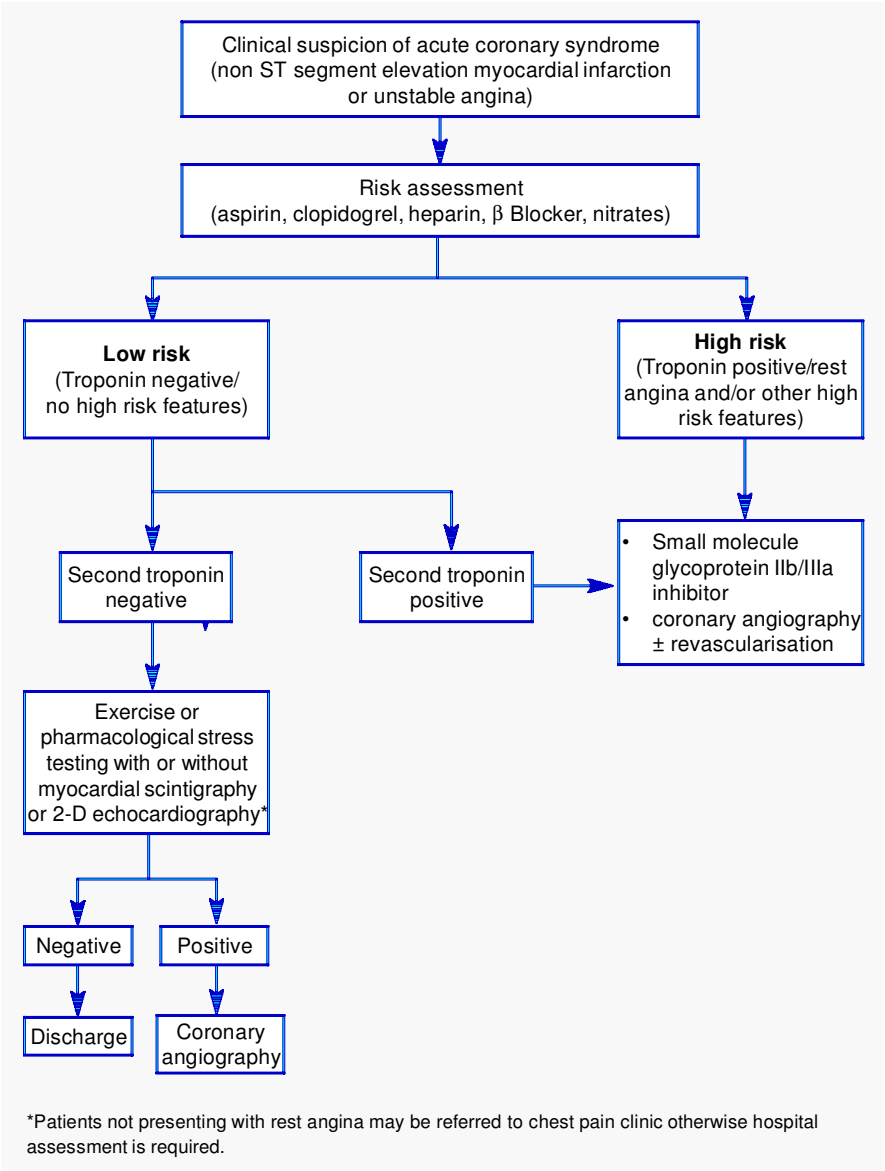

Fig 1. Algorithm outlining strategy for management of patients with acute coronary syndrome.

available, initial medical management with GPIIb/IIIa inhibitors is still recommended.[34]

Conclusions

There is substantial variation in the risk of death and MI in patients presenting with NSTEMI ACS. Early risk stratification is essential in order appropriately to target pharmacological treatment and the use of coronary angiography/ revascularisation depending on the level of risk. Fig 1 summarises the recommended strategy for management of ACS patients.

All patients suspected of ACS (high or low risk) should receive aspirin, clopidogrel (300 mg loading then 75 mg daily), heparin (low molecular weight or unfractionated), beta-blocker and nitrates. Clopidogrel should be continued for 12 months. High-risk patients should receive 'upstream' a small molecule GPIIb/IIIa inhibitor and an early invasive strategy.

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