

Acute coronary syndrome

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ABSTRACT The term ‘acute coronary syndrome’ encompasses STEMI, NSTEMI, and UA. The electrocardiogram identifies those with STEMI. An elevated troponin level measured at least 12 hours after the onset of pain distinguishes NSTEMI from UA. However, the separation of NSTEMI and UA is somewhat artificial, as the management of individual patients is based on their risk score, with troponin being only a small part of the equation. Patients at moderate to high risk of death, MI, or subsequent admission to hospital should be offered early coronary arteriography with a view to revascularisation. The CLARITY and COMMIT studies, when added to the CURE study, support the early use of clopidogrel in all patients with ACS, irrespective of age.

KEYWORDS Angioplasty, clarity, commit, NSTEMI, STEMI, thrombolysis

LIST OF ABBREVIATIONS Acute coronary syndrome (ACS), American College of Cardiology (ACC), Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY), Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE), glycoprotein (GP), myocardial infarction (MI), non-ST-elevation myocardial infarction (NSTEMI), percutaneous coronary intervention (PCI), ST-elevation myocardial infarction (STEMI), thrombolysis in myocardial infarction (TIMI), tissue plasminogen activator (tPA), tPA with multiple-point mutations to enlarge the molecule (TNK-tPA), Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS), unstable angina (UA)

DECLARATION OF INTERESTS No conflict of interests declared.

ACUTE CORONARY SYNDROME – WHAT DOES IT MEAN?

When a patient is admitted to hospital with cardiac chest pain and a normal electrocardiogram, does a small rise in troponin 12 hours post-admission constitute an MI? Within the North American Guidelines and within the European Guidelines, the answer would be ‘yes’. However, in the UK there has been ongoing debate and the use of confusing terms such as ‘acute coronary syndrome with myocardial necrosis’. What follows is a practical guide for the non-specialist physician, based on the North American and European Guidelines.

The term acute coronary syndrome can be sub-divided into STEMI, NSTEMI, and UA. The common link is that the physician believes that the patient has experienced cardiac chest pain at rest or on minimal exertion.

ST-ELEVATION MYOCARDIAL INFARCTION

Patients presenting with STEMI are recognised by their ECG. The gold standard therapy is primary PCI within 90 minutes of first medical contact. Within the first three hours following the onset of STEMI, thrombolysis and PCI have similar effects on reducing mortality but with an excess of

strokes in patients receiving thrombolysis. In patients presenting more than six hours from the onset of cardiac chest pain, PCI has a clear advantage over thrombolysis with improved survival and reduced rate of stroke. The most recent guidance from the European Society of Cardiology supports a strategy of PCI in ACS with ST-segment elevation. A meta-analysis of 23 randomised trials included 7,739 patients and concluded that primary PCI was superior to thrombolytic therapy in short-term (defined as 4–6 weeks) death (7.0% vs 9.3%, $p=0.0002$), non-fatal re-infarction (2.5% vs 6.8%, $p=0.0004$), and total stroke (1.0% vs 2.0%, $p=0.0004$). A significant proportion of patients who receive thrombolysis will undergo coronary angiography and percutaneous intervention in the days or weeks following their initial presentation. Indeed, often patients who are exposed to the risks of thrombolysis fail to reperfuse the infarct-related artery and are increasingly offered rescue angioplasty. In patients who reperfuse with thrombolytic therapy but subsequently re-infarct, prompt PCI is preferable to repeat thrombolysis.

The logistics of expanding primary PCI within the UK are complex and expensive in time and money. In economies such as Denmark and the Czech Republic, national primary PCI programmes have been possible and affordable. However, in the UK the present strategy is one of aspirin

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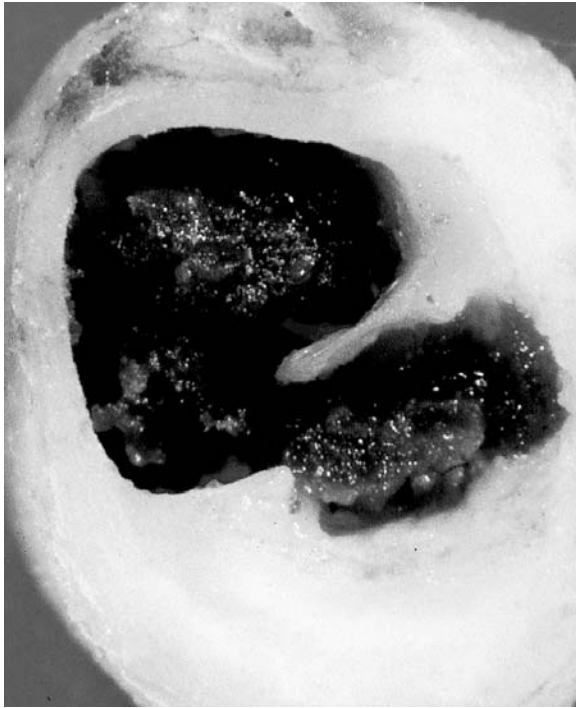


FIGURE 1 Occluded coronary artery in a patient admitted with STEMI. Reproduced by kind permission of the *BMJ*.

and prompt thrombolysis, with coronary arteriography offered at a later and more logistically convenient time.

An example of an occluded coronary artery in a patient with STEMI is shown in Figure 1.

Improving thrombolytic therapy

With the current situation, improvements in the efficacy of thrombolytic therapy may provide the most practical step forward. However, in the 12 years since accelerated tPA was shown to improve survival compared with streptokinase, there have been many unsuccessful attempts with medical therapy to improve vessel patency rates and survival, without increasing major bleeding complications. Double-bolus tPA, TNK-tPA, rPA (a deletion mutant of wild-type tPA), nPA (a deletion and point mutant of wild-type tPA), GP IIb/IIIa inhibitors as an adjunct to thrombolytic therapy, and oral GP IIb/IIIa inhibitors have all failed to demonstrate a mortality advantage over tPA.

It was with this background that the first major advance in the treatment of STEMI in 12 years was announced at the ACC meeting in March 2005. Two studies, CLARITY and COMMIT, with a total of nearly 50,000 patients investigated the effect of adding clopidogrel to standard medical therapy, including aspirin, in patients presenting with STEMI.

CLARITY-TIMI 28

The CLARITY study was a double-blind, randomised comparison of clopidogrel and placebo in 3,491 patients

(aged 18–75 years) presenting within 12 hours of the onset of STEMI. Patients randomly received placebo or clopidogrel 75 mg daily (after a 300 mg loading dose), in addition to a fibrinolytic agent, aspirin, and, when appropriate, heparin. All patients were scheduled to undergo angiography within 48–192 hours of starting the study medication. This was a mechanistic study to test the hypothesis that clopidogrel would increase infarct-vessel patency rates. The primary endpoint was a composite of infarct vessel patency on angiography, or re-infarction, or death before angiography could be performed. The primary safety endpoint was the rate of major bleeding by the end of the calendar day after angiography.

The median time between onset of symptoms and administration of the fibrinolytic agent was 2.7 hours and the median time from administration of the fibrinolytic agent and clopidogrel or placebo was only ten minutes. The results indicate that the use of dual antiplatelet therapy after acute STEMI improves the patency of the infarct-related artery, with an absolute reduction of 6.7% (36% odds reduction) in the rate of re-occlusion, death, or recurrent MI (event rate with placebo 21.7%, with clopidogrel 15.0%, $p < 0.001$). This increased vessel patency was associated with reduced thrombus in the culprit vessel. Furthermore, in the 57% of patients who underwent PCI and continued on aspirin and clopidogrel, the benefit was maintained, with a 20% reduction in the odds of cardiovascular death, recurrent MI, or need for urgent revascularisation by 30 days (14.1% vs 11.6%, $p=0.03$). Importantly, the rate of major bleeding was not increased with the addition of clopidogrel (placebo 1.1%, clopidogrel 1.3%, $p=0.64$).

Thus, CLARITY indicates that dual antiplatelet therapy for acute MI is effective at preventing re-occlusion. However, the study was not designed to assess the effect of combination antiplatelet treatment on mortality. This was addressed in the COMMIT trial.

COMMIT

The COMMIT trial was a collaboration between a group in Oxford, UK and a group in Beijing, China. Some 45,852 patients in over 1,250 centres in China were included in this study. COMMIT was designed to evaluate clopidogrel when added to aspirin and other standard treatments during the acute phase of MI, but it differed from CLARITY in that there was no upper age limit and no loading dose of clopidogrel was used. The primary endpoint (death, recurrent non-fatal MI, or stroke before hospital discharge – up to four weeks) was also quite different to that used in CLARITY. Standard ECG criteria for STEMI were used. The study included patients up to 24 hours after onset of cardiac chest pain and therefore only half of those enrolled received thrombolytic therapy.

There was a relative risk reduction of 9% (9.2% vs 10.1%, $p=0.002$) in the composite endpoint, and an absolute

Historical	Points	Risk of cardiac events (%) by 14 days in TIMI IIB*		
		Risk score	Death or MI	Death, MI or urgent revasc.
Age \geq 65	1			
\geq 3 CAD risk factors (FHx, HTN, \uparrow chol, DM, active smoker)	1	0/1	3	5
Known CAD (stenosis \geq 50%)	1	2	3	8
ASA use in past 7 days	1	3	5	13
Presentation		4	7	20
Recent (\leq 24 hour) severe angina	1	5	12	26
\uparrow cardiac markers	1	6/7	19	41
ST deviation \geq .5 mm	1			

Risk score = total points (0–7)

* Entry criteria: UA or NSTEMI defined as ischemic pain at rest within past 24 hours, with evidence of CAD (ST segment deviation or + marker).

Antman EM, Cohen M, Bernink PJ et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA* 2000; **284**:835–42.

TABLE 1 TIMI risk score for NSTEMI/UA.

reduction in mortality of 0.6% (7.5% with clopidogrel vs 8.1% with placebo; relative risk reduction 7%, $p=0.03$). This, remarkably, was after a mean duration of treatment of only 16 days. Six lives could be saved per 1,000 patients treated at a relatively modest additional drug cost of less than £3,400 per life saved. More importantly, this benefit was achieved with no increase in major bleeding rate or haemorrhagic stroke (placebo 0.54%, clopidogrel 0.58% for any major bleed in hospital). Timing of clopidogrel treatment seemed to be important because the risk reduction in the composite endpoint was 17% for those treated six hours or less after the event, 10% for those treated 7–12 hours after the event, and no significant benefit for those treated 13–24 hours after the event.

Discussion

The results from the CLARITY study, in which clopidogrel and aspirin were given after onset of symptoms and before angiography was performed, are probably the most relevant to UK practice. It is not surprising that in thrombolised patients, the addition of clopidogrel to aspirin should be associated with increased infarct-vessel patency at day three after MI – the additive effects of these two agents has been well demonstrated before in NSTEMI. What is surprising is that there was no price to pay, as seen with the increased rates of stroke or major bleeding with GP IIb/IIIa inhibitors. The explanation may lie in the fact that the maximal antiplatelet effect of the 300 mg loading dose of clopidogrel is reached 15 hours after ingestion by which time the thrombolytic effect has waned. However, in practice, a loading dose of 600 mg of clopidogrel is increasingly used in patients who undergo elective angiography. This higher dose is known to cause effective platelet inhibition within two hours, and so may have a different safety profile.

Another factor that may affect the loading dose of clopidogrel is the age of the patient. Thrombolytic trials

have consistently demonstrated increased intra-cranial bleeding rates in patients over 75 years of age. In the CLARITY study, patients over the age of 75 years were excluded. In COMMIT, on the other hand, there was no upper age limit but a loading dose of clopidogrel was not given. Therefore, in patients older than 75 years who receive thrombolysis, caution should be exercised: the safety and efficacy of a 300 mg loading dose of clopidogrel is untested and unknown.

NON-ST-ELEVATION MYOCARDIAL INFARCTION

Patients with NSTEMI present with cardiac chest pain but often have no ECG changes or only minor ST-depression. Only beyond 12 hours following the onset of pain does a troponin test reliably distinguish NSTEMI from unstable angina. The six-month mortality rate for patients with NSTEMI is often greater than that of patients with STEMI who survive to hospital. It is on the basis of their future risk of death, further MI, or admission with unstable angina that these patients deserve the diagnosis 'myocardial infarction'. Unlike patients with STEMI, these patients are not immediately identifiable on admission and are often triaged through the medical receiving unit to a variety of specialty wards. Thrombolysis has no role in the treatment of these patients. Standard care for these patients is aspirin 300 mg loading, 75 mg od indefinitely, clopidogrel 300 mg loading followed by 75 mg od for 12 months, enoxaparin 1 mg/kg bd (reduced to od if renal impairment), beta-blocker, and statin. Intravenous nitrate can be used for ongoing ischaemic pain. Within the UK, small-molecule GPIIb/IIIa antagonists such as tirofiban are used in particularly unstable patients as a bridge to cardiac catheterisation where immediate transfer to a cardiac catheterisation laboratory is not practicable.

The key to effective management of these patients is one of early identification of those at high risk. Although not the most accurate, the most easily

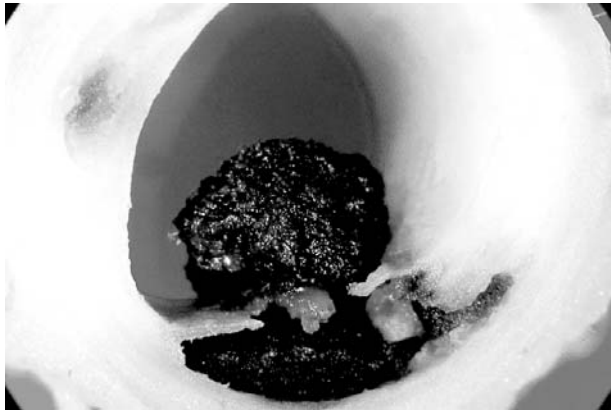


FIGURE 2 Thrombus in coronary artery of a patient with NSTEMI. Reproduced by kind permission of the BMJ.

applicable risk stratification score is the TIMI score (see Table 1). It is recommended that intermediate to high-risk patients be considered for early coronary arteriography with or without percutaneous intervention. The low-risk group should undergo an in-patient exercise tolerance test.

A thrombus in a coronary artery of a patient with NSTEMI is shown in Figure 2.

FURTHER READING

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UNSTABLE ANGINA

Unstable angina is the ‘Cinderella’ of the acute coronary syndromes. Although the risk of death, MI, or readmission to hospital at six months is half that of NSTEMI patients, it can be seen from the TIMI risk score that a proportion of these troponin-negative patients will have other risk predictors which may justify an early invasive strategy.

KEYPOINTS

- Acute coronary syndrome encompasses STEMI, NSTEMI, and UA.
- Aspirin, clopidogrel, and enoxaparin are recommended in NSTEMI and UA.
- The TIMI risk score is better than troponin alone in identifying high risk patients for NSTEMI and UA.
- The gold standard of primary PCI for STEMI is not widely available.
- The CLARITY and COMMIT studies support the addition of clopidogrel in STEMI patients treated with thrombolysis.

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