Acute coronary syndromes

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Key points

- Coronary artery disease is a common condition and anaesthetists frequently encounter patients who have suffered or are at risk of suffering from acute coronary syndrome (ACS). A diagnosis of new or recent ACS carries important implications for anaesthetic and critical care management.
- ACS is categorized into two broad groups according to ECG appearance and evidence of myocardial necrosis by biochemical markers. This categorization determines immediate treatment priorities.
- Myocardial infarction and ischaemia can be difficult to diagnose in the perioperative period; most present without chest pain, and the pathophysiology of perioperative myocardial ischaemia is complex.
- Timing of elective surgery in patients with recent coronary stents is complex and requires a multi-disciplinary assessment of risks of in-stent thrombosis vs risks of perioperative bleeding.
- Starting beta-blockers prophylactically in the immediate preoperative period may increase mortality.

Coronary heart disease is the biggest killer in the UK, resulting in more than 80 000 deaths in 2010. Major non-cardiac surgery is associated with an incidence of perioperative cardiac death of 0.5–1.5%, and of major cardiovascular complications (e.g. myocardial infarction, heart failure and stroke) of 2–3.5%. This article provides a brief synopsis of the diagnosis and management of acute coronary syndrome (ACS). The recognition and implications of perioperative myocardial infarction are discussed, and the perioperative care of patients on anti-platelet therapy with coronary stents in situ is summarized.

Definitions

ACS refers to a spectrum of conditions of varying myocardial ischaemic states. It can be broadly categorized into two groups, depending on evidence of myocardial ischaemia on an electrocardiogram (ECG) and evidence of myocardial necrosis from serum levels of cardiac biochemical markers (e.g. troponin):

- ST-elevation myocardial infarction (STEMI)
- Non-ST elevation ACS (NSTE-ACS):
  - Non-ST-elevation myocardial infarction [NSTEMI] (associated troponin rise).
  - Unstable angina (no myocardial cell necrosis/troponin increase).

In general, STEMI is associated with more prolonged duration of ischaemia and a larger territory of myocardial necrosis (e.g. after a complete artery coronary occlusion) than NSTEMI. The short-term mortality from STEMI is marginally higher than that from NSTEMI, but the 4-yr mortality rate for patients with NSTEMI is twice that of STEMI patients. The incidence of STEMI has declined over the past 20 yr whereas the incidence of NSTEMI remains unchanged or has even increased. Improved quality and timeliness of treatment for ACS has resulted in a decrease in hospital mortality from around 20% to nearer 5% over the past 30 yr.

Risk factors

Non-controllable risk factors include: advancing age, male gender, family history of premature coronary artery disease (males <55 yr and females <65 yr), premature menopause and ethnicity (e.g. higher in those from the Indian subcontinent). Modifiable risk factors include smoking, diabetes mellitus, hypertension,
obesity, sedentary lifestyle, and high cholesterol—specifically a high ratio of low- to high-density lipoprotein.

**Presentation**

Patients usually present with central chest pain of >20 min duration, often radiating to the neck, left arm, or jaw. There may be associated dyspnoea, sweating, palpitations, dizziness, nausea, and vomiting. The character of the pain may be atypical, or chest pain may occasionally be absent. Silent myocardial ischaemia is more common in certain patient populations (e.g. in the perioperative and ITU setting) and in certain conditions (e.g. diabetes mellitus). The relief of chest pain by nitrates is unreliable as a diagnostic tool.

**Investigations**

**12-Lead ECG**

ST-segment elevation >1 mm in two consecutive limb leads, 2 mm in two consecutive chest leads (Fig. 1), or new onset left bundle branch block (LBBB) is indicative of STEMI, and should be promptly managed (see below). NSTE-ACS usually presents as ST-segment depression or T-wave inversion (Fig. 2). The ECG may be normal, especially if the pain has resolved.

**Biomarkers of myocardial necrosis**

The cardiac troponins (cTn) T and I are the most commonly used biomarkers of myocardial damage. They become elevated around 3–6 h, peak at around 12–24 h and can remain elevated for up to 2 weeks, dependent upon renal function. Abnormal levels of cTn are defined as those above the 99th percentile of the normal population or upper reference limit for that laboratory assay, and most local cardiology services will issue a ‘positive’ result range. If troponin levels are elevated, myocardial necrosis is likely, although there are many other non-ACS causes of an elevated cTn. These include severe congestive cardiac failure, dysrhythmia, myocarditis, pulmonary embolus, acute subarachnoid haemorrhage, severe sepsis, burns, rhabdomyolysis, and renal failure. Elevated levels of cTn must therefore be interpreted allowing for the clinical context. Serial cTn levels may aid diagnosis (e.g. a rapid increase within 24 h, peak levels >50× upper reference

Fig 1 Anteroseptal MI: ST elevation is maximal in the anteroseptal leads (V1–4). Q waves are present in the septal leads (V1–2). Less obvious ST elevation in I, aVL, and V5, with reciprocal ST depression in lead III.

Fig 2 ECG changes possible in NSTEMI: T-wave inversion in the anteroseptal chest leads.
limit, and rapid decrease of >50% within 72 h are indicative of acute myocardial infarction. In ACS, higher troponin levels (peak values and area under the cTn – time curve) correlate with infarct size and consequent risk of mortality and morbidity. In the postoperative population, an elevated troponin, peaking in the first 3 days after operation, is strongly associated with increased 30-day mortality.5

**Biomarkers to aid prognostication**

Various biomarkers have been evaluated for incremental prognostic indication. These include highly sensitive C-reactive protein, B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide. These are markers of left ventricular dysfunction and are correlated with the risk of death in patients with ACS.5

**Further investigations**

Echocardiography is mandatory in patients with a new myocardial infarction,7 to assess regional wall motion abnormalities, ventricular function, and valvular abnormalities and also contributing factors such as ventricular hypertrophy. A chest radiograph is prudent to assess complications such as pulmonary congestion, or prompt for differential diagnoses such as pneumonia, pneumothorax, and aortic dissection. Cardiac MRI and stress echocardiography are further modalities used non-acutely to assess perfusion, function, and scarring. Coronary artery angiography remains the gold standard for urgent assessment of coronary artery disease.

**Management of ACS**

**Immediate acute care**

All patients presenting with ACS should have their airway, breathing, and circulation assessed and stabilized. Hypoxaemia should be treated with supplemental oxygen. Aspirin 300 mg should be administered orally, and on-going chest pain should be managed with i.v. morphine and nitrates via the sub-lingual or i.v. routes. Patients with ACS are at high risk of early acute complications including ventricular fibrillation, pulmonary oedema (requiring CPAP), and cardiogenic shock (requiring inotropic support). They should be closely monitored (including continuous ECG) and managed in a cardiac high dependency environment, whilst awaiting definitive treatment.

**NSTE-ACS**

The National Institute for Health and Clinical Excellence (NICE) issued guidance on the management of unstable angina and NSTEMI in 2010.7 All patients presenting with NSTE-ACS should receive early scoring of their risk of death or complications from ACS. This information enables outcomes from large databases to guide subsequent treatment decisions for an individual patient. The 2010 NICE guidance (Fig. 3) advocates the use of the GRACE risk score (Global Registry of Acute Cardiac Events) to evaluate 6-month mortality risk. Points are allocated for patient factors including age, history of heart failure, and previous acute myocardial infarction and signs on admission including heart rate, systolic blood pressure, ECG changes, serum creatinine, and cardiac enzyme levels. In clinical practice, web-based or app-based calculators are widely used (http://gracescore.org). Subsequent treatment is then determined according to the predicted 6-month mortality risk derived from the score. The biomarkers to aid prognostication

**Angiography for NSTE-ACS**

All patients with NSTE-ACS whose GRACE score indicates intermediate to high risk (i.e. predicted 6-month mortality >3%) should undergo in-hospital angiography within 96 h. Where the risk is low (predicted 6-month mortality <3%), ischaemia testing should be performed first, unless there are other high-risk features (e.g. significant ECG changes) or the ischaemia is recurrent, in which case angiography is offered.7 The percentage of patients requiring CABG during their initial hospitalization is approximately 10%.5

**Cardiac medication**

Details of the main classes of medication used in the treatment of ACS are summarized in Table 1. Treatment of ACS usually requires the use of potent anti-platelet agents, so management strategies should be tailored according to an assessment of a patient’s bleeding risk. The NICE guidance highlights advanced age, renal impairment, female sex, low body weight and known bleeding tendency as known risk factors for bleeding. Scoring systems for bleeding risk, such as the CRUSADE score (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the NICE guidelines) have been created in an attempt to objectively assess bleeding risk, but these are not yet included in the NICE guidance.

**STEMI**

The National Institute for Health and Clinical Excellence issued guidance on the management of myocardial infarction with ST-segment elevation in July 2013 (Fig. 4). Coronary angiography and primary angioplasty are recommended for all patients with STEMI presenting within 12 h of onset of chest pain, or beyond this time if there is evidence of continuing myocardial ischaemia.

If PCI cannot be offered within 2 h of presentation, then fibrinolysis (tenecteplase or reteplase) should be offered in combination with anti-thrombin treatment (e.g. fondaparinux). After fibrinolysis, immediate rescue PCI is indicated for failed re-perfusion or for recurrent ischaemia. PCI is ideally performed within 24 h for all patients after successful fibrinolytic therapy to reduce re-infarction rates. Persistent unconsciousness after cardiac arrest secondary to an STEMI should not be used as a contraindication to PCI.

**Perioperative ACS and myocardial infarction**

Myocardial infarction and ischaemia can be difficult to diagnose in the perioperative period because most present without chest pain, and physiological signs consistent with myocardial ischaemia are common and non-specific in the perioperative and ICU setting.

Two mechanisms may lead to perioperative myocardial infarction (PMI):

1. **ACS due a primary coronary event**: occurs perioperatively when coronary plaques rupture or fissure leading to coronary thrombosis. Catecholamines and cortisol levels increase after surgery, especially in the presence of anaemia, hypothermia, or pain. The resultant tachycardia and hypertension may exert shear stresses leading to plaque rupture. In addition, a pro-coagulant and pro-thrombotic state develops.
Fig 3 NICE guidelines 2010: early management for unstable angina and NSTEMI.7
## Table 1 Drugs used in the treatment of ACS

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<th>Drug class</th>
<th>Mode of action</th>
<th>Usage</th>
<th>Note</th>
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| Aspirin                     | COX-1 inhibition. Irreversibly prevents Thromboxane A2 production in platelets | 300 mg loading dose to all patients with ACS. 75 mg daily dosage as effective in long term with fewer side-effects | Incidence of allergy <0.5% 
No use with NSAIDS – can block effects of aspirin and their COX-2 inhibition is pro-thrombotic  
No high-level evidence to show reduction in infarct size, major cardiac events, or outcome improvement.  
GRACE database suggests chronic use means less likelihood of STEMI vs NST-ACS, and less cTn release |
| Nitrates                    | Vasodilators—reduce cardiac preload, LV end-diastolic volume and thus myocardial oxygen demand. Dilate coronary arteries | For all patients with suspected coronary ischaemia, acute, and chronic use. I.V. more effective | 34% reduction in mortality in NSTE-ACS |
| Beta-blockers               | Reduce myocardial oxygen demand by reducing heart rate, blood pressure and contractility | Recommended for all patients with ischaemia without contraindications.  
However, no evidence exists to support their use in the first 8 h | Avoid combination of verapamil and beta-blockers: can precipitate profound AV node blockade |
| Calcium-channel blockers    | Vasodilatation including coronary arteries. Non-dihydropyridine (e.g. diltiazem, verapamil) slow atrio-ventricular conduction | Where beta-blockade contraindicated in myocardial ischaemia, especially where tachycardia |  |
| ACE inhibitors              | Inhibit conversion angiotensin-I to angiotensin-II, the latter being a potent vasoconstrictor and inducing aldosterone production. Beneficial effect on cardiac remodelling | Given to all patients with ischaemic heart disease. Should be started as an in-patient where possible | Reduce mortality in ischaemic heart disease |
| P2Y12 inhibitors            | Pro-drug, metabolized via two cytochrome P450 (CYP450) enzymes in liver to its active metabolite, thus genetic variability and affected by drugs interacting with CYP450 metabolism (e.g. proton pump inhibitors). Inhibits platelet aggregation by preventing ADP binding to its receptor on the platelet | Offered to all patients with a GRACE mortality >1.5%, or those likely to have PCI within 24 h. 300 mg loading dosage, 75 mg maintenance for 1 yr | Currently recommended by the NICE guidelines for the treatment of STEMI and NSTE-ACS; however, the European Society of Cardiology guidelines only recommend clopidogrel if prasugrel or ticagrelor are not available or contraindicated |
| Prasugrel                   | Similar with two step metabolism however first step is plasma esterase, second CYP450. So faster onset and more consistent than clopidogrel | Used in addition to aspirin for patients with STEMI undergoing immediate PCI, or in patients with previous stent thrombosis on clopidogrel | Longer duration of action than clopidogrel |
| Ticagrelor                  | Not a pro-drug, faster onset and more consistent than clopidogrel. Quicker offset than prasugrel | Used in patients with STEMI before angioplasty. May be continued up to 12 months | Higher efficacy with aspirin than clopidogrel with no increase in bleeding risk. Because of this it is the preferred agent in many centres in NSTE-ACS before PCI |
| Glycoprotein IIb/IIIa receptor inhibitors (GIIb/IIIai) | Inhibition of platelet aggregation by antagonizing their cross-linking | Eptifibatide or tirofiban: considered for all intermediate or high-risk patients if angiography scheduled within 96 h. Abciximab: for all intermediate/high-risk patients as adjuvant for PCI who are not already taking GIIb/IIIai | Increased risk of bleeding especially in the elderly |
| Anti-thrombin therapy       | Thrombin inhibition either indirectly (heparin) or directly (bivalirudin) | Fondaparinux: offered to all NSTE-ACS patients without high bleeding risk. If PCI anticipated within 24 h or renal impairment then unfractionated heparin should be used instead. Bivalirudin is alternative for patients not on GIIb/IIIai having PCI within 24 h | For all patients with ACS, a combination of anti-thrombin with anti-platelet therapy is superior to either therapy alone |
with elevated levels of fibrinogen, factor VIII, and von Willebrand factor, together with increased platelet activation and decreased levels of protein C and antithrombin. According to the universal classification of myocardial infarction, this is defined as a type 1 myocardial infarction.9

2. Reduced myocardial oxygen supply to demand ratio: this is known to be associated with intraoperative and postoperative hypotension, hypertension, tachycardia, anaemia, hypoxaemia, hypercarbia, and hypothermia. It represents a spectrum from minor myocardial ischaemia with low-level troponin increase to prolonged overt ischaemia in multiple ECG leads with significant myocardial necrosis and high troponin elevation. This is defined as a type 2 myocardial infarction.9

Most PMIs occur early after surgery, are asymptomatic, and most commonly preceded by ST-segment depression on ECG.10 ST-elevation is rare, accounting for <2% of cases of PMI. Nevertheless, histological studies reveal that both circumferential infarction (consistent with myocardial oxygen supply:demand mismatch) and transmural infarctions are both commonly found. Peak
postoperative troponin levels and adverse cardiac outcomes appear to correlate with the duration of ST depression.10

Treatment of PMI
Close maintenance of physiological stability to prevent myocardial oxygen supply:demand mismatch remains an integral part of preventing and treating myocardial ischaemia. Routine commencement of beta-blockers in the preoperative period has been shown by meta-analysis to increase overall mortality by 27%, associated with an increased rate of hypotension and stroke. However, beta-blockers should be continued if they are part of a patient’s regular medication for hypertension, angina, or arrhythmia.

Because of uncertainties in diagnosis and the varying underlying pathological processes, there is no consensus on the optimal management or drug treatment of PMI. The risks of anti-platelet and anti-thrombin therapies are generally greater in the perioperative and ITU populations. In particular the requirement for dual anti-platelet therapy (DAPT) after stent insertion makes the decision to proceed to PCI particularly complex. In most cases aspirin should be given to any patient suspected of PMI or perioperative ACS. However, even aspirin has been associated with significant harm in certain high-risk surgical procedures (e.g. intra-cranial and spinal canal surgery, posterior chamber ophthalmic surgery). Early mortality after PMI may be as high as 25% and therefore balancing the benefits of anti-platelet therapy and PCI against the risks of bleeding requires a high level of communication between anaesthetists, intensivists, surgeons, and cardiologists.

Management of anti-platelet therapy for coronary stents in the perioperative period
Coronary stents can be broadly divided into drug-eluting stents (DES) and bare-metal stents (BMS). In simple terms, stents may

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**Fig 5** Suggested algorithm for management of antiplatelet therapy for non-cardiac surgery in context of bleeding risk. Reproduced with permission from Oprea and Popescu. ASA, aspirin; PTCA, percutaneous trans-luminal coronary angioplasty; MI, myocardial infarction; BMS, bare metal stent; DES, drug-eluting stent; ST, stent thrombosis.
block after insertion because of thrombosis or re-stenosis, which are pathophysiologically distinct mechanisms. DAPT is required to prevent thrombosis until endothelialization of the stent occurs. Stent re-stenosis occurs as a result of over-growth of smooth muscle cells. BMS endothelialize quickly, reducing the risk of thrombosis but carry an increased risk of re-stenosis. DES release an anti-proliferative drug to inhibit smooth muscle cell proliferation, to reduce re-stenosis rates. Unfortunately this also slows stent endothelialization which results in a greater risk of thrombosis without DAPT. The Genous™ stent is a relatively new type of BMS which uses endothelial progenitor cell technology to encourage faster endothelialization aiming to reduce thrombosis risk.

BMS carry a risk of re-stenosis of approximately 14% per year (peaking at 4–9 months), whereas DES carry a re-stenosis risk of 3–4% over the first year. Certain patient populations carry increased risk of stent thrombosis. These include patients with stents for bifurcating lesions, multiple or over-lapping stents, stent length >25 mm, recent myocardial infarction, triple vessel disease, left ventricular ejection fraction <30%, diabetes mellitus, and renal insufficiency. Stent thrombosis is a serious and life-threatening complication, carrying an associated mortality of up to 45%.13

Guidelines vary on the recommended duration for continuing DAPT after the insertion of coronary stents.5,14,15 There is little controversy on the duration required after simple balloon angioplasty without stent insertion (2-week DAPT), although this is rarely performed in modern cardiological practice. There is minor variation in recommendations for minimum duration of DAPT with standard BMS (30–45 days). Genous™ BMS may permit temporary cessation of DAPT after 15 days. There remains significant uncertainty regarding DES, with some guidelines recommending 6 months and others 12 months before DAPT can be safely stopped.5,15

In patients with DES, the decision to continue or stop DAPT in the perioperative period must weigh a number of conflicting and complex risks. These include the risk of stent thrombosis, of surgical bleeding, of possibly delaying surgery till DAPT is no longer required, and of precluding certain types of anaesthesia (e.g. central-neuraxial blockade). This usually requires an individualized approach, with specialist input from cardiologist, surgeon, and anaesthetist.

The complex decisions regarding the management of antplatelet therapy in the perioperative period have been simplified into a decision algorithm produced by Oprea and Popescu.13 The algorithm balances the evaluation of the risk of bleeding, the urgency of surgery, the type of stent, and duration since insertion (Fig. 5). The most difficult patient group to manage are those with coronary stents that are at high risk of thrombosis, who require urgent surgery that cannot be delayed for more than a few days to weeks, and in whom there is a high risk of perioperative bleeding. This group of patients will usually require intravenous short-acting bridging anticoagulant (e.g. heparin) or anti-platelet therapy (e.g. Ticofiban) to cover temporary cessation of their DAPT. These patients should always be managed in close consultation with a cardiologist. Most patients with coronary stents should continue aspirin throughout the perioperative period.

Conclusion
Coronary artery disease is a common condition and anaesthetists frequently encounter patients who have suffered, or are at risk of suffering from ACS. The evidence-base and treatment options for the management of ACS are large and ever-expanding. Treatment of ACS results in a considerable reduction in mortality and morbidity, but can carry significant risk of bleeding in the surgical population. The timing of pharmacological and interventional therapy needs to be considered on an individual bases and in a multi-disciplinary setting.

MCQs
The associated MCQs (to support CME/CPD activity) can be accessed at www.access.oxfordjournals.org by subscribers to BJA Education.

References
4. NICE clinical guidance: myocardial infarction with ST-segment elevation. NICE 2013 (CG167)
7. NICE clinical guidance: unstable angina and NSTE MI. NICE 2010 (CG94)