Adam D. Timmis 16.13.4 Management of acute coronar

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section 16 Cardiovascular disorders 3626 NICE (2011). Management of stable angina. Clinical guideline. https:// www.nice.org.uk/guidance/cg126 NICE (2016). Chest pain of recent onset: assessment and diagnosis. Clinical guideline. https://www.nice.org.uk/guidance/cg95 Rapsomaniki E, et al. (2014). Prognostic models for stable coronary artery disease based on electronic health record cohort of 102,023 patients. Eur Heart J, 35, 844–52. Sekhri N, et al. (2007). How effective are rapid access chest pain clinics? Prognosis of incident angina and non-cardiac chest pain in 8762 consecutive patients. Heart, 93, 458–63. Sekhri N, et al. (2016). A 10-year prognostic model for patients with suspected angina attending a chest pain clinic. Heart, 102, 869–75. 16.13.4 Management of acute
coronary syndrome Rajesh K. Kharbanda and Keith A.A. Fox ESSENTIALS Acute coronary syndrome (ACS) is precipitated by an abrupt change in an atheromatous plaque and/or thrombotic occlusion. This re- sults in increased obstruction to perfusion and ischaemia or in- farction in the territory supplied by the affected vessel. The clinical consequences of plaque rupture can range from a clinically silent episode, through to unstable symptoms of ischaemia without in- farction, to

profound ischaemia complicated by progressive infarc- tion, heart failure, arrhythmia, and risk of sudden death. Clinical presentation with an ACS identifies a patient at high risk of further cardiovascular events requiring a defined acute and long-term management strategy. The choice and timing of acute management strategy is critic- ally dependent on the extent and severity of myocardial ischaemia, with the spectrum of ACS broken down into three elements: (1) Unstable angina: typical ischaemic symptoms without ST elevation on ECG and without elevated biomarkers of necrosis. (2) Non-ST- elevation myocardial infarction (NSTEMI): typical ischaemic symp- toms without ST elevation on ECG but with biomarkers of necrosis above the diagnostic threshold. (3) ST-elevation myocardial infarc- tion (STEMI): typical ischaemic symptoms with ST elevation on ECG and with biomarkers of necrosis above the diagnostic threshold. An acute reperfusion strategy (primary percutaneous coronary intervention (PCI) or thrombolysis) is of proven benefit only in ST-segment elevation infarction (or MI with new bundle branch block). Prompt relief of pain is important, not only for humanitarian reasons, but also because pain is associated with sympathetic ac- tivation, vasoconstriction, and increased myocardial work. Effective analgesia is best achieved by the titration of intravenous opioids, with concurrent administration of an antiemetic. High-flow oxygen is re- commended for symptom relief in those patients with evidence of desaturation, particularly in those who are breathless or who have features of heart failure or shock. The management of prehospital cardiac arrest requires special attention: at least as many lives can be saved by prompt resuscita- tion and defibrillation as by reperfusion. Patients may also require management of arrhythmic and haemodynamic complications, including heart failure. Acute coronary syndromes without ST elevation
(unstable angina/non-ST elevation MI) Risk stratification and initial management Patients without ST elevation or left bundle branch block can be tri- aged into low, intermediate, and high-risk categories. (1) High-risk— patients with typical clinical features of ischaemia and ST-segment depression or transient ST-segment elevation, or with troponin eleva- tion and a high-risk score (risk calculator downloadable from http:// www.gracescore.org/ or http://www.timi.org/). Patients are also at high risk when ischaemia provokes arrhythmias or haemodynamic compromise. (2) Intermediate or low risk—patients with clinical fea- tures of ACS and nonspecific ECG changes (e.g. T-wave inversion,
T-wave flattening, minor conduction abnormalities). (3) Low risk or an alternative diagnosis—patients with a normal ECG, normal bio- markers, normal cardiac examination, and normal echo. Patients at high risk—(1) high-risk patients with acute ischaemia at initial presentation, or those who develop such features after hospital admission, and especially those with haemodynamic compromise, re- quire emergency assessment for revascularization and dual antiplatelet therapy. (2) Those proceeding to emergency revascularization should receive (a) aspirin; (b) P2Y12 receptor inhibitor; (c) unfractionated or low molecular weight heparin (LMWH), or a direct thrombin inhibitor, and (d) if required for bail-out, glycoprotein IIb/IIIa inhibition. (3) In addition to anti-ischaemic therapy, additional therapy may be re- quired: antiarrhythmic management, or haemodynamic support to reduce ischaemia and stabilize the patient for revascularization. Where the clinical features support a diagnosis of ACS, patients developing ST elevation require emergency assessment with cor- onary angiography and where appropriate reperfusion by primary PCI, or—when a primary angioplasty service is not available—by thrombolysis (see next). Patients at intermediate or low risk—patients with non-ST-elevation ACS and an intermediate risk score require dual antiplatelet therapy (aspirin plus P2Y12 receptor inhibitor, e.g. ticagrelor or prasugrel; if neither available, clopidogrel) plus parenteral anticoagulation.

They are candidates for an early elective revascularization strategy (within c.72 h). Clinically stable patients with minor or nonspecific ECG abnor- malities and a low risk score (including negative repeat troponin) are at very low risk for in-hospital, major cardiac events. Such patients may, nevertheless, have significant underlying coronary artery dis- ease. They require assessment of the cardiovascular risk and non- invasive ischaemia testing to identify the presence and extent of inducible ischaemia, ideally prior to discharge. Specific pharmacological therapies Anti-ischaemic therapies—(1) nitrates—effective in reducing ischaemia in the in-hospital management of non-ST-elevation ACS, but there is no evidence that they improve mortality; (2) β-blockers—patients with suspected acute coronary syndromes should be initiated on
β-blocker therapy unless contraindicated; (3) dihydropyridine cal- cium entry blockers—should only be employed with β-blockers in

16.13.4 Management of acute coronary syndrome 3627 ACS to avoid reflex tachycardia. In patients unable to tolerate β- blockers, a heart-rate-slowing calcium antagonist (e.g. diltiazem or verapamil) may be appropriate. Short-acting dihydropyridines should not be used in isolation in ACS. Antiplatelet therapies—(1) aspirin 75–325 mg daily—indicated in all patients with ACS unless there is good evidence of aspirin allergy or evidence of active bleeding; (2) P2Y12 receptor inhibitor—patients with non-ST-elevation ACS should be given a loading dose of either ticagrelor 180 mg, prasugrel 60 mg (once anatomy is defined), or clopidogrel 300–600 mg (if neither ticagrelor nor prasugrel are avail- able), followed by continued treatment, in combination with aspirin. Dual antiplatelet therapy should be maintained for 12 months, unless the risks of bleeding exceed potential benefits. Certain patients may benefit from more prolonged duration of dual antiplatelet therapy. (3) GPIIb/IIIa inhibitors (e.g. abciximab, eptifibatide, tirofiban) can be used in patients requiring urgent percutaneous intervention for non-ST-segment elevation ACS and in those at intermediate to high risk. Current indications for treatment with GPIIb/IIIa inhibitors are mainly as a bail-out at PCI. Anticoagulation—this is required in addition to antiplatelet therapy. Indirect thrombin inhibitors: low molecular weight heparin is better than unfractionated heparin and is most commonly used. In the ab- sence of an urgent/early invasive strategy, fondaparinux (a synthetic pentasaccharide that selectively binds antithrombin and causes in- hibition of factor Xa) has the most favourable efficacy/safety pro- file. Bilvalirudin is the only direct thrombin inhibitor currently used in ACS management. ST-segment-elevation myocardial infarction Patients with clear-cut evidence of ST-elevation infarction (STEMI) re- quire immediate triage to reperfusion therapy. ‘Fast-track’ systems have been developed to minimize in-hospital delay to reperfusion: these aim to achieve clinical assessment and electrocardiography within 15 min of arrival and rapid transfer for PCI or the institution of thrombolytic therapy within 30 min. Audit programmes and continuous training are necessary for centres to achieve this 30-min median ‘door-to-needle’ time. PCI—randomized clinical trials of primary PCI vs. thrombolysis have shown consistent findings: primary PCI is better, providing more effective restoration of vessel patency, achieving better ven- tricular function, and improving important clinical outcomes with lower rates of death, reinfarction, stroke, major bleeding, and re- current ischaemia. Particular gains are seen in haemodynamically compromised patients. In consequence, primary PCI is the preferred therapeutic option in national and international guidelines. Thrombolysis—prehospital thrombolysis is the next best option if a primary PCI programme is not available, or if transfer times are suffi- ciently prolonged that reperfusion may not be achieved within 120 min of patient call. The current reference standard for the comparison of fibrinolytic agents is the accelerated infusion regimen of alteplase (tPA), or—for simplicity—the single-bolus administration of tenecteplase (TNK), which does not require an

infusion pump or refrigeration and hence is particularly suited for prehospital administration. Internationally, streptokinase remains the most widely used fibrinolytic agent, prin- cipally because it is relatively inexpensive. If timely primary PCI is not available, a pharmaco-invasive strategy (thrombolysis and subsequent revascularization) may provide similar benefit to primary PCI, but requires further testing. Antiplatelet agents and anticoagulants—(1) aspirin 75–325 mg daily—indicated in all patients with ACS unless there is good evi- dence of aspirin allergy or evidence of active bleeding. (2) P2Y12 receptor inhibitors should be given to all patients, continuing for at least 1 month in patients managed with fibrinolysis (or as deter- mined by the type of stents implanted). (3) Anticoagulants—heparin or bivalirudin are indicated in patients managed with primary PCI. Patients treated with fibrinolytic therapy should receive low mo- lecular weight heparin or fondaparinux. (4) GPIIb/IIIa inhibitors may be used in patients managed with primary PCI (mainly for bail-out), but not in those managed with fibrinolysis. Secondary prevention measures in patients with ACS Patients require advice and help regarding cessation of smoking (including the avoidance of passive smoking), dietary modification, exercise, rehabilitation, and management of obesity. The following therapies have been shown to reduce the risk of subsequent cardiovascular events: (1) antiplatelet therapy—aspirin in a dose of 75 mg/day, clopidogrel 75 mg/day. Certain subgroups may benefit from prolonged dual antiplatelet therapy—aspirin and ticagrelor 60 mg/bd or aspirin and clopidogrel; (2) β-blockers in those without contraindications; (3) lipid lowering with 3-hydroxy-3- methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins); (4) angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers, especially in those with left ventricular dysfunction and heart failure, and benefit is also possible in other patients with vas- cular disease; (5) aldostrone blockade (e.g. eplerenone) in those with left ventricular ejection fraction (LVEF) less than 35% and diabetes or clinical features of heart failure. Introduction The term ‘acute coronary syndrome’ (ACS) describes the clinical manifestations of a heterogeneous spectrum of conditions that share key pathophysiological features: disruption or erosion of coronary atheromatous plaque, changes in vascular tone, and a variable extent of thrombotic occlusion. The clinical presentation is determined by the extent of coronary obstruction, the volume of ischaemic myocardium, and timing of the atherothrombotic disease process. ACS occurs in patients with underlying symp- tomatic or occult coronary artery disease, and flow-limiting or non-flow-limiting atheromatous plaques in the coronary arterial wall (Fig. 16.13.4.1). The ACS is precipitated by an abrupt change in an atheroma- tous plaque, resulting in increased obstruction to perfusion and ischaemia or infarction in the territory supplied by the affected (culprit) vessel. For discussion of the mechanisms involved, see Chapter 16.13.1. The pattern and severity of clinical manifestations are dependent not only on the degree of obstruction to perfusion, but also on the presence or absence of collateral perfusion, the ex- tent and distribution of fragmented microthrombi, and myocardial oxygen demand in the perfused territory. Thus, the clinical conse- quences of plaque rupture can range from an entirely silent episode, through to unstable symptoms of ischaemia without infarction, to profound ischaemia complicated by progressive infarction, heart failure, arrythmia, and risk of sudden death.

 The goals of early management of ACS are to relieve ischaemia (by reducing myocardial oxygen demand, inhibiting thrombotic occlu- sion, and reducing coronary obstruction), to prevent further throm- botic occlusion, and to prevent or manage complications. The choice and timing of management strategy, including pharmacological treat- ment and percutaneous or surgical revascularization, is critically de- pendent on the extent and severity of myocardial ischaemia. Despite sharing key pathophysiological mechanisms across the

spectrum of ACS, ST-segment-elevation acute myocardial infarction (STEMI) and non-ST-elevation ACS (unstable angina and non-STEMI) need to be considered separately because an acute reperfusion strategy (primary percutaneous coronary intervention (PCI) or thrombolysis) is of proven benefit in STEMI (or MI with new bundle branch block), but not in the remainder of the syndrome. Thus, although the manage- ment of STEMI differs, the remainder of the ACS should be managed as a continuous spectrum, but influenced by risk stratification. Clinical presentation and definition of ACS The ACS may present de novo (as new-onset angina), with typ- ical ischaemic discomfort at rest (rest angina) or on minimal exer- tion. Alternatively, a previously stable pattern of angina may change, resulting in episodes of typical rest angina or angina provoked by minor exertion (crescendo angina). New-onset exertional angina has not pre- viously been recognized as part of 'acute coronary syndrome', but the outcomes are similar—c.7% develop nonfatal MI and 4% die, and a further 19% require revascularization within 15 months—and such patients may fulfil the clinical and ECG/biomarker characteristics of the syndrome (EuroHeart survey, GRACE, and CRUSADE registries). There are three components to the clinical diagnosis of ACS: the symptom description, the ECG, and biomarker evidence of myocyte necrosis. The symptoms must be distinguished from noncardiac pain, and from stable angina. To improve the specificity of diagnosis, clinical trials use a more restricted definition, requiring at least 15 to 20 min of typical ischaemic discomfort or two 5-min episodes at rest. The specificity is further improved when the definition requires objective evidence of ischaemia or evidence of underlying coronary artery disease. ST-segment depression on the ECG, especially in as- sociation with typical pain, is highly predictive, whereas the less spe- cific ECG abnormalities, including T-wave inversion, are less strong predictors. Markers of myocardial damage (troponins or cardiac en- zymes) are powerfully predictive, in the presence of a typical clinical syndrome. ST elevation or depression on the ECG and elevated bio- markers of necrosis are markers of higher risk and adverse outcome (Table 16.13.4.1). In the absence of such markers, documented Spectrum of acute coronary syndrome unstable angina ST elevation myocardial infarction Marker: Tn & CK-MB undetectable troponin elevated +/− CK-MB troponin elevated +/− CK-MB Non-ST elevation myocardial infarction myocardial infarction Fig. 16.13.4.1 The spectrum of acute coronary syndromes. Table 16.13.4.1 Prognostic value of admission ECG for early risk stratification in 12 142 patients with an acute coronary syndrome Outcome ST elevation + ST depression (n = 15) ST elevation (n = 28) ST depression (n = 35) T-wave inversion (n = 23) p Acute infarction on admission (%) 87 81 47 31 <0.0001 Death (%) 6.8 5.0 5.0 1.8 <0.001 (Re) infarction (%) 6.9 5.1 6.7 4.3 <0.001 Death and reinfarction at 30 days follow-up. Data from the GUSTO IIb trial.

16.13.4 Management of acute coronary syndrome 3629 evidence of underlying coronary artery disease (prior infarction or angiographically demonstrated coronary disease) helps to confirm the diagnosis. In brief, the three components of ACS are: • unstable angina—typical ischaemic symptoms without ST eleva- tion on ECG and without elevated biomarkers of necrosis • non-STEMI—typical ischaemic symptoms without ST elevation on ECG but with biomarkers of necrosis above the diagnostic threshold • STEMI—typical ischaemic symptoms with ST elevation on ECG and with biomarkers of necrosis above the diagnostic threshold. The definition of MI has been revised by a global task force of the European Society of Cardiology, the American College of Cardiology, the American Heart Association (AHA), and others and has identified five subtypes of MI (Box 16.13.4.1). Universal definition of acute myocardial infarction This requires a combination of criteria including an increase and/or decrease of a cardiac biomarker (preferably high-sensitivity troponin) and at least one of:

1. Symptoms of ischaemia
2. New significant ST-T-wave changes or LBBB
3. Development of pathological Q waves
4. Imaging evidence of new loss of viable myocardium or regional wall motion abnormality
5. Intracoronary thrombus detected on angiography or autopsy Outcome of acute coronary syndrome Trial data and large-scale observational registry studies Overall, based upon large-scale registries with consistent dis- ease definitions, there are approximately two patients with non- STEMI ACS for each patient with STEMI. Previously, inclusion of patients with chest pain, but without diagnostic features of acute ischaemia, under the term ‘unstable angina’ may have masked the true hazards of the syndrome. Comparisons between studies may be confounded by different disease definitions and varying use of more sensitive markers of myocyte necrosis (troponins), but on the basis of data from randomized trials and prospective registry studies there is no doubt that patients with ACS (with or without persistent ST elevation) are at substantial risk of sub- sequent cardiac events despite current therapy. About 9 to 11% suffer death or MI in the first 6 months following presentation, and almost half of this risk is within the first 7 days (GUSTO IIb, OASIS registry, and GRACE registry). Whereas patients with STEMI are most at risk of death, especially in the first hours of symptom onset, those with non-STEMI ACS are at higher risk after discharge (Fig. 16.13.4.2 and Table 16.13.4.2). These ob- servations highlight the need for treatment of both the acute and longer-term phases of ACS. The clinical syndrome and outcome The Braunwald classification categorizes unstable angina according to the mode of onset and time course (Table 16.13.4.3). It was empir- ically based, but has been validated by prospective studies. Patients Box 16.13.4.1 Universal classification of myocardial infarction • Type 1—spontaneous MI related to ischaemia due to a primary cor- onary event such as plaque fissuring, erosion or rupture, or dissection • Type 2—MI secondary to oxygen demand and supply imbalance un- related to acute coronary athero-thrombosis (e.g. coronary spasm or embolism, anaemia, arrhythmias, hypertension, or hypotension) • Type 3—sudden unexpected cardiac death, including cardiac arrest with symptoms suggestive of myocardial ischaemia, accompanied by new ST elevation, or new left bundle branch block, or definite new thrombus by coronary angiography (death before blood samples obtained) or in the lag phase of cardiac biomarkers • Type 4—(a) MI associated with PCI; (b) MI related to stent thrombosis • Type 5—MI associated with CABG ST elevation ACS ST depression ACS No ST shift Death rate 0.13 0.12 0.11 0.10 0.09 0.08 0.07 0.06 0.05 0.04 0.03 0.02 0.01 0.00 0 10 20 30 40 50 60 70 80 90 Days from presentation 100 110 120 130 140150 160 170 180 Fig. 16.13.4.2 Mortality over the first 180 days following presentation with ACS: patients stratified according to ST shift on presentation to hospital. Reproduced from Bassand J-P, et al. (2007). Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J, 28, 1598–660, by permission of Oxford University Press.

section 16 Cardiovascular disorders 3630 with unstable ischaemic pain at rest and those with ST depression have the highest risk of an adverse cardiac event. Similarly, those with unstable angina following acute myocardial infarction (MI) are at an increased risk. Although the classification is useful, many of the patients that present with ACS are in Braunwald class 3B and additional methods of risk characterization are required to optimize management. A diagnostic triage system can be developed for patients with sus- pected ACS (see ‘Emergency department—triage and

establishing a working diagnosis’). This is based on ECG changes, biomarker re- lease, and stress or perfusion testing. Patients with evolving STEMI are identified, and those with higher risk separated from those with lower risk. The respective categories of patients require different management strategies. The ECG and outcome The 12-lead ECG (performed on admission) provides direct prognostic information (Table 16.13.4.1). The greatest risk of death and subsequent MI is seen in patients with simultaneous ST elevation and depression; the next highest risk is seen in those with transient ST-segment elevation or ST-segment depression (defined as being >0.5 mm in thrombolysis in mycocardial in- farction (TIMI) score); isolated T-wave inversion carries a lower risk. The number of leads demonstrating ST deviation also yields prognostic information: among those with ST deviation in the anterior leads a rate of death or MI of 12.4% was seen at 1 year—higher than seen with similar changes in other locations (TIMI III trial). Patients with a left main and three-vessel coronary artery disease may show a combination of ST-segment elevation and depression. Ambulatory ST-segment recording can identify patients with unstable angina and either silent or symptomatic myocardial is- chaemia with an increased risk for major subsequent cardiac events. However, conventional ambulatory monitoring usually requires offline analysis and is not suitable for the prediction of imminent events. Computer-assisted, continuous, multilead, ECG monitoring techniques have become available for real-time ECG and ST-segment monitoring. The occurrence and extent of ischaemic territory identified by such continuous recordings can provide additional prognostic information over and above the ad- mission ECG. The information can be combined with biomarkers and, together, they provide additional prognostic information (FRISC study). Biochemical markers and outcome Markers of myocardial damage Biomarkers of necrosis are gradually released into the systemic cir- culation following complete or transient occlusion of the coronary artery, or fragmentation of a thrombus and embolization. Following total occlusion of the vessel, troponins and creatine kinase (or more specifically CK-MB) are released and are detectable at clearly ab- normal levels about 6 to 8 h after the event unless there is extensive collateral perfusion. The cardiac isoforms of troponin I and troponin T are exclusively expressed in cardiac myocytes and provide specific evidence of myo- cardial damage. Following infarction, troponins are released from the cytosolic pool and first appear in the circulation in detectable concentrations between 3 and 4 h after the ischaemic event, reaching diagnostic concentrations at 6 to 8 h. Troponin release is evidence of myocardial injury and carries prognostic significance: the greater the troponin release, the greater the risk of subsequent MI and death. High-sensitivity or ultrasensitive assays have a 10-to 100-fold lower limit of detection than current assays, allowing detection of MI more frequently and earlier (within 1 hour), but it is important to recognize that other causes of myocyte necrosis can give rise to detectable troponin concentrations in the circulation, hence the diagnosis of ACS requires an appropriate clinical context. A clinical assessment of the reasons for troponin detection in the circulation is vital for determination of the correct diagnosis (Fig. 16.13.4.3 and Table 16.13.4.4). When should the cardiac enzymes be measured? The time course of the release of troponins (or enzymes) from myocardium is such that diagnostic concentrations may not be achieved until some time after an ischaemic event, depending on Table 16.13.4.2 Mortality in hospital and at 6 months in low-, intermediate-, and high-risk categories in registry populations according to the GRACE risk score Risk category (tertiles) GRACE risk score In-hospital deaths (%) Low ≤108 <1 Intermediate 109–140 1–3 High

140 3 Risk category (tertiles) GRACE risk score Post-discharge to 6 months deaths (%) Low ≤88 <3 Intermediate 89–118 3–8 High 118 8 The Global Registry of Acute Coronary Events (GRACE) risk score, assigns risk on the basis of the following patient characteristics on admission: age, heart rate, systolic blood pressure, serum creatinine, evidence of congestive heart failure, also the presence/ absence of cardiac arrest, ST-segment deviation, and elevated cardiac enzymes/markers. For calculations, see http://www. outcomes.org/grace.
Table 16.13.4.3 Classification of unstable angina (Braunwald) Class A: Secondary unstable angina (e.g. anaemia, hypoxia) B: Primary unstable angina
C: Postinfarction (<2 weeks) unstable angina I New-onset, severe or accelerated angina IA IB IC II Subacute rest angina (>48 h since last pain) IIA IIB IIC III Acute rest angina (<48 h since last pain) IIIA IIIB IIIC Braunwald E (1989). Unstable angina. A classification. Circulation, 80, 410–14.

16.13.4 Management of acute coronary syndrome 3631 the assays employed. Thus, a normal value for a patient on arrival within a short duration of time after the event does not exclude infarction or unstable angina, but an elevated value is highly pre- dictive of subsequent infarction. Troponins should be measured on arrival depending upon the clinical presentation, and may re- quire a second sample. The timing of the second sample depends upon the troponin assay. The latest generation of high-sensitive troponin assays increase diagnostic performance and improve the early diagnosis of MI regardless of the time of chest-pain onset, and re-test within 3 hours maybe feasible. Implementation of a sensitive troponin assay, and lowering the diagnostic threshold for MI, reduces recurrent MI and death in patients with suspected ACS. Among those with persistently negative troponins and without significant ECG changes, there is a very low risk of subsequent infarction and death (provided that severe underlying cor- onary artery disease is excluded). Such patients should undergo predischarge risk assessment and stress testing. The best tests are myocardial perfusion scanning or stress echocardiography, but treadmill ECGs on exercise are more widely available. Rule-in and rule-out pathways The specific pathway depends upon the biomarker and assay system used. With the use of high-sensitivity troponins a 0 h/3 h pathway is suggested, although future refinements may endorse a 0 h/1 h pathway. Current guidelines advocate a pathway as illus- trated in Fig. 16.13.4.4. Follow optimised pathways for acute coronary syndrome Presentation in the context of another acute illness SERIAL TROPONIN MEASUREMENT at least one value >99th centile INVESTIGATION RESULTS ACUTE CHRONIC CLINICAL ASSESSMENT CLINICAL ASSESSMENT SYMPTOMS OR SIGNS OF MYOCARDIAL ISCHAEMIA Significant change in troponin concentration Oxygen supply-demand imbalance? No Consider invasive coronary angiography Consider no further investigation Consider invasive or CT coronary angiography No further cardiac investigation Consider echocardiography or cardiac MRI scan No known CAD Known CAD Yes Coronary artery disease with plaque rupture Obstructive coronary artery disease No coronary artery disease eg sustained hypotension, tachycardia, hypoxaemia No significant change in troponin concentration Known structural heart disease or clear alternative pathology* Yes No No Yes 1 1 2 Injury Injury Fig. 16.13.4.3 Algorithm for the investigation of patients with elevated cardiac troponin concentration on serial measurements is used to identify patients with acute and chronic myocardial injury. The definition of significant change in cardiac troponin will be dependent on the particular assay used and should be consistent with the local pathway for the assessment of

patients with an isolated presentation with acute coronary syndrome. CAD, coronary artery disease. * alternative pathologies that can lead to troponin elevation are shown in Table 16.13.4.4. Adapted from Chapman AR, Adamson PD, Mills NL (2017). Assessment and classification of patients with myocardial injury and infarction in clinical practice. Heart, 103, 10–18. Table 16.13.4.4 Causes of elevation of serum troponins Cause Example Cardiac Cardiac contusion Cardiac failure Cardiac interventions/surgery Cardiac toxins, e.g. cocaine, anthracyclines Cardiac tumour Cardiomyopathies Cardioversion Myocardial infarction Myocarditis (Myo)pericarditis Cardiovascular Aortic dissection Pulmonary embolism Neurological Stroke Subarachnoid haemorrhage Other Acute kidney injury Sepsis Chronic kidney disease

section 16 Cardiovascular disorders 3632 Markers of left ventricular wall stress and inflammation Natriuretic peptides such as brain natriuretic peptide (BNP) or its N-terminal prohormone fragment (NT-proBNP) are associated with left ventricular dysfunction and elevated levels are associated with adverse prognosis; however, current management protocols are not determined by BNP levels. Inflammatory changes in the vessel wall promote plaque fis- suring or erosion, and inflammatory changes also follow episodes of minor myocardial damage. In ACS there is evidence that inflam- matory markers, such as C-reactive protein (CRP) and interleukins IL-6 and IL-1, are independently associated with adverse outcome. After the acute phase, continuing inflammation (e.g. with elevated CRP) occurs in one-half of those whose levels are acutely elevated and identifies a category of patients at increased risk. However, al- though inflammatory mechanisms are implicated in plaque growth and plaque destabilization, specific anti-inflammatory therapies have not yet been demonstrated to improve outcome, and measure- ment of CRP or other inflammatory markers is not part of routine clinical practice. Noninvasive imaging and outcome Transthoracic echocardiography is useful to identify regional wall motion abnormality and assess LV function, in addition to detecting other important pathology associated with chest pain such as aortic dissection, pericardial effusion, valve disease, or right ventricular strain suggestive of pulmonary embolism for example. Noninvasive assessment of ischaemia can be performed in low risk patients using stress echo, cardiac magnetic resonance, or nuclear perfusion techniques. Multidetector computed tomography (MDCT) allows for visual- ization of the coronary arteries. It may be applied to assess certain ACS patients but requires a high level of expertise and is not yet rou- tinely available. Risk characterization in ACS The timing and the nature of key management decisions in ACS are dependent upon risk estimation. For example, the choice of reperfusion therapy in ST elevation may be influenced by the pres- ence of comorbidity, bleeding risk, and time delay from symptom onset. Similarly, in non-STEMI ACS, ongoing ischaemia with ST depression or the presence of hypotension or a high-risk score may initiate very early revascularization. Specific pharmacological (e.g. glycoprotein IIb/IIIa inhibitors) or interventional therapies (PCI) have demonstrated benefit in high-or moderate-risk patients but not in low-risk patients (5-year outcome: RITA 3, FRISC-II). In patients with ACS, risk can be separated into two compo- nents: ‘prior risk’ and ‘acute ischaemic risk’. Prior risk is determined by patient characteristics (age and gender), prior ischaemic heart disease (MI, heart failure, prior angina), and systemic factors that influence risk (hypertension, diabetes, renal dysfunction, and other life-threatening systemic disorders). These can be considered as the background level of risk that the patients bring with them to the point of presentation. Although several of the individual risk com- ponents may not be modifiable, the combined impact of prior risk influences the balance between benefit and risk for each of the thera- peutic strategies in ACS. Thus, prior risk sets the baseline for risk– benefit decisions. By contrast, ‘acute ischaemic risk’ is potentially modifiable and determined by the

severity of coronary obstruction and the extent of the territory affected. Collateral perfusion, embolization, myo- cardial oxygen demand, and cytoprotection mechanisms all influ- ence the extent of ischaemia. Patients with similar clinical features may have experienced transient complete occlusion, or severe sub- total occlusion complicated by distal embolization of fragments of a platelet-rich thrombus, and altered vascular tone in the distal terri- tory. Clinical markers of acute ischaemic risk include ECG changes, Fig. 16.13.4.4 0 h/3 h rule-out algorithm of non-ST elevation coronary syndromes using high-sensitivity cardiac troponin assays. From Roffi M, et al. (2016). 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J, 37, 267–315, by permission of Oxford University Press.

16.13.4 Management of acute coronary syndrome 3633 release of biomarkers of necrosis into the systemic circulation, and mechanical and arrhythmic complications of the ischaemic episode. Simplistically, prior risk can be regarded as the ‘baggage’ that the patient carries with them, and acute ischaemic risk as an ‘acquired hazard’ arising from the new ischaemic event. The distinction is im- portant because management strategies for prior risk aim to treat heart failure, underlying coronary and systemic disease, and risk factors. The management of acute ischaemic risk aims to reverse the impact of acute coronary obstruction and thrombosis and is the first priority in the management of patients with ACS. Assessment of the extent and impact of underlying coronary artery disease (e.g. with stress testing) and assessment of left ventricular function can take place later in the management of these patients (Box 16.13.4.2), and are important determinants of the longer-term outcomes. In summary: (1) A diagnosis of ACS is a clinical diagnosis based on the suspicion that coronary ischaemia due to atherothrombosis is responsible for the patient’s presentation; (2) clinical examination and ECG provide early and rapid assessment tools; (3) patients with STEMI require consideration of emergency reperfusion therapy, and those without require further risk assessment to guide the ongoing management (Table 16.13.4.5). Management of ACS without ST elevation (unstable angina/non-STEMI) Anti-ischaemic therapy Anti-ischaemic therapy can decrease myocardial oxygen consump- tion by reducing heart rate, lowering blood pressure, or depressing left ventricular contractility, and may also act by inducing vaso- dilatation. In consequence, anti-ischaemic therapy can limit the progression of occlusion and improve perfusion and improve the supply–demand imbalance. Mechanical revascularization (PCI and coronary bypass surgery) also aims to relieve obstruction and re- duce a patient’s susceptibility to ischaemia and its complications— these interventions will be considered separately (see later section of this chapter and Chapter 16.13.5). Nitrates Nitrates act by venodilatation and—in higher dose—by arteri- olar dilatation, and hence reduce preload and afterload, thereby decreasing oxygen demand. In addition, nitrates can also induce coronary vasodilatation. They are effective in relieving symptoms of ischaemia. In the acute phase of the syndrome, where dose titra- tion is required, they are most conveniently administered intraven- ously. Once dose titration is no longer required, oral administration is feasible. However, continuous nitrate administration can induce tolerance, hence oral nitrates should be prescribed with appropriate nitrate-free intervals when symptoms are controlled. An alternative is to use drugs with nitrate-like properties but with out the same problems of tolerance, such as a potassium channel activator (see ‘Potassium channel activators and other antianginals’). Large outcome trials have been conducted with nitrates in acute STEMI but not in other ACS. However, patients without ST-segment elevation or bundle branch block were randomized within the ISIS- 4 trial: their mortality was 5.3% for nitrate treatment and 5.5% for placebo treatment, a nonsignificant difference. Nitrates are effective Box

16.13.4.2 Practical steps to assess risk (in addition to clinical symptoms) • 12-lead ECG—obtained directly after first medical contact, repeated after recurrent symptoms • Troponin estimation (cTnT or cTnI)—repeated if the initial test is negative • Apply a risk score (such as GRACE, TIMI—see Table 16.13.4.2 and http://www.outcomes.org/grace) • An echocardiogram may be required to rule in/out alternative diag- noses and assess left ventricular function • In patients with no recurrence of pain, normal ECG, and no troponin elevation, a noninvasive stress test or coronary imaging may be required Table 16.13.4.5 Recommendations for diagnosis and risk stratification in patients with suspected non-ST-segment elevation acute coronary syndromes Recommendations Class of recommendation Level of evidence Diagnosis and risk stratification It is recommended to base diagnosis and initial short-term ischaemic and bleeding risk stratification on a combination of clinical history, symptoms, vital signs, other physical findings, ECG, and laboratory results. I A It is recommended to obtain a 12-lead ECG within 10 min after first medical contact and to have it immediately interpreted by an experienced physician. It is recommended to obtain an additional 12-lead ECG in case of recurrent symptoms or diagnostic uncertainty. I B Additional ECG leads (V3R, V4R, V7–V9) are recommended if ongoing ischaemia is suspected when standard leads are inconclusive. I C It is recommended to measure cardiac troponins with sensitive or high-sensitivity assays and obtain results within 60 min. I A A rapid rule-out protocol at 0 h and 3 h is recommended if high-sensitivity cardiac troponin tests are available. I B A rapid rule-out and rule-in protocol at 0 h and 1 h is recommended if a high-sensitivity cardiac troponin test with a validated 0 h/1 h algorithm is available. Additional testing after 3–6 h is indicated if the first two troponin measurements are not conclusive and the clinical condition is still suggestive of ACS. I B It is recommended to use established risk scores for prognosis estimation. I B Modified from Roffi M, et al. (2016). 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J, 37, 267–315, by permission of Oxford University Press.

section 16 Cardiovascular disorders 3634 in reducing ischaemia in the in-hospital management of non-ST- elevation ACS, but there is no evidence that they improve mortality. β-Blockers β-Adrenoceptor antagonists reduce heart rate and blood pressure and myocardial contractility and hence decrease myocardial oxygen consumption. They are primarily employed to reduce ischaemia in ACS. Large-scale trials have not been conducted in patients with non- ST-elevation ACS. However, in the context of acute STEMI treated by thrombolysis, β-blockers reduce mortality by approximately 10 to 15% (ISIS-1 study). They may act by reducing ventricular arrhyth- mias, reinfarction, and myocardial rupture. However, this trial was conducted before the widespread use of reperfusion therapy and the findings may not be relevant to contemporary practice. More re-cently the large COMMIT/CCS study demonstrated that immediate intravenous (metoprolol 5–15 mg) followed by oral metoprolol 200 mg daily had no effect on mortality, with reductions in recurrent MI and cardiac arrest offset by increased cardiogenic shock. A meta- analysis of 27 trials showed a 13% relative risk reduction of mor- tality in the first week after MI. Patients with significantly impaired atrioventricular conduction or asthma or acute left ventricular dys- function should not receive β-blockers. Although β-blockers may exacerbate acute heart failure, extensive trials have produced strong evidence of a benefit for the gradual introduction of β-blockers in ambulant patients with heart failure (see Chapter 16.5.3). In the absence of bradycardia or hypotension, patients with suspected ACS should be initiated on β-blocker therapy unless contraindicated. Calcium entry blockers These agents inhibit the slow inward current induced by the entry of extracellular calcium through the cell membrane, especially in car- diac and arteriolar

smooth muscle. They act by lowering myocardial oxygen demand, reducing arterial pressure, and reducing contract- ility. Calcium channel blockers can provide symptom relief in pa- tients already receiving nitrates and β-blockers, and may be useful in patients with contraindications to β-blockade. Some agents induce a reflex tachycardia (e.g. nifedipine, nicardipine, amlodipine) and are best administered in combination with a β-adrenoceptor antagonist. By contrast, diltiazem and verapamil are suitable for patients who cannot tolerate a β-blocker because they inhibit conduction through the atrioventricular node and tend to cause bradycardia. All calcium antagonists reduce myocardial contractility and may aggravate heart failure. Calcium entry blockers have been demonstrated to reduce the frequency of angina in patients with variant angina. A meta-analysis of calcium entry blockers in ACS indicates a non- significant trend towards a higher mortality in treated vs. control pa- tients (5.9% vs. 5.2%, in 7551 patients). In individual trials, diltiazem has been compared with propranolol, and both agents produced a similar reduction in anginal episodes. Dihydropyridine calcium entry blockers should be employed with β-blockers in ACS to avoid reflex tachycardia. In patients unable to tolerate β-blockers, a heart- rate-slowing calcium antagonist may be appropriate. Short-acting dihydropyridines should not be used in isolation in ACS. Potassium channel activators and other antianginals These agents (e.g. nicorandil) have arterial and venous dilating prop- erties, but do not exhibit the tolerance seen with nitrates. They have been shown to be better than placebo in relieving the symptoms of angina. A randomized trial of nicorandil (a combined nitrate-like and potassium channel activator) suggested benefit on a composite clinical endpoint (IONA study), and this drug may be considered as an alternative to nitrate administration. Ivabradine selectively inhibits the primary pacemaker current in the sinus node and maybe used in selective patients with contraindi- cations to β-blockers. Ranolazine inhibits the late sodium current, and can reduce recurrent ischaemia in non-ST-elevation ACS. The recommendations in Box 16.13.4.3 are based on current clinical and trial evidence. Antiplatelet therapy Aspirin Exposure of the contents of atheromatous plaque to circulating blood triggers platelet activation by several different pathways. Aspirin is a potent and irreversible inhibitor of platelet cyclooxygenase, blocking the formation of thromboxane A2 and inhibiting platelet aggrega- tion. Although the effects of aspirin can be overcome in the presence of potent thrombogenic stimuli, nevertheless the benefits of aspirin treatment in unstable angina are clearly defined and substantial. The Antiplatelet Trialists Collaboration demonstrated a reduction of 36% in death or MI with antiplatelet treatment (predominantly as- pirin) vs. placebo in unstable angina trials. Aspirin treatment signifi- cantly reduces subsequent MI, stroke, and vascular death, with the largest reductions seen among patients at highest risk. In patients with unstable angina, four key studies have demonstrated that as- pirin significantly reduces the risk of cardiac death or nonfatal MI by approximately 50%. The efficacy of lower-dose aspirin (75 mg/day) therapy has been demonstrated in several studies, including those of Wallentin and colleagues where long-term effects were evaluated in men under 70 years of age with unstable coronary artery disease. After 6 and 12 months of aspirin treatment, the risk of MI or death was reduced by 54% and 48%, respectively (risk ratio 0.52 with 95% confidence intervals 0.37–0.72). The strength of evidence and magnitude of benefit demonstrated with aspirin treatment in non-ST-segment elevation ACS is such that aspirin is indicated in all patients with ACS, unless there is a clear contraindication. Nevertheless, pa- tients with ACS remain at significant risk despite aspirin therapy. In prospective registry studies of unstable angina/non-STEMI, and Box 16.13.4.3 Recommendations for anti-ischaemic therapy • Anti-ischaemic therapy should be administered in conjunction with antithrombotic and interventional therapy (see next), with the overall strategy guided by risk evaluation of the patient (see risk stratification) • Patients with suspected ACS should be initiated

on nitrate and β-blocker therapy, unless there are contraindications to the use of β-blockers • In patients with contraindications to β-blockers, heart-rate slowing calcium antagonists should be employed • The combination of a calcium antagonist and β-blocker is superior to either agent alone • Angiography and revascularization should be considered in patients with recurrent or persistent ischaemia, or patients with troponin ele- vation (including non-STEMI). The timing of angiography should be guided by the risk status of the patient

16.13.4 Management of acute coronary syndrome 3635 in spite of aspirin treatment in more than 80% of patients, the risk of death or MI is approximately 10% at 6 months and the risk of death/MI or refractory angina is approximately 22 to 33% over the same period (OASIS registry, PRAIS registry). Aspirin treatment (75–325 mg daily) is indicated in all patients with ACS unless there is good evidence of aspirin allergy or evidence of active bleeding. P2Y12 receptor inhibitors Ticlopidine and clopidogrel are ADP receptor antagonists, and they block the ADP-induced pathway of platelet activation by inhibiting the P2Y12 ADP receptor. Clopidogrel replaced ticlopidine on account of a superior safety profile and has been tested in a large-scale trial of patients with un- stable angina/non-STEMI (n = 12 562, CURE trial). The agent was used on top of existing therapy, and in addition to aspirin. It reduced death, nonfatal MI, and stroke from 11.4 to 9.3% (95% confidence interval 0.72–0.90, p <0.001). For every 1000 patients treated, there were 28 fewer major cardiovascular complications but six more transfusions. Importantly, benefits were seen across risk groups (dia- betics, hypertensives, biomarker elevation or not, revascularization or not). In a substudy (PCI-CURE), clopidogrel also reduced death and MI in those undergoing percutaneous revascularization (2.9% clopidogrel vs. 4.4% for placebo). Thus, with the combination of clopidogrel and aspirin, there is evidence of early and sustained reductions in the risks of death and MI in patients that present with ACS. Several smaller studies have used higher loading doses of clopidogrel (usually 600 mg), and these show more rapid inhib- ition of platelet aggregation than that achieved with 300 mg. The CURRENT-OASIS 7 trial assessed the effects of double-dose (600 mg loading, 150 mg for 1 week, then 75 mg daily) vs. standard dose (300 mg loading, then 75 mg daily) clopidogrel in patients with ACS and intended early revascularization. The double-dose clopidogrel regimen was associated with a reduction in cardiovas- cular events and stent thrombosis compared with the standard dose in patients who underwent PCI. Long-term clopidogrel administration was tested in the CHARISMA study of 15 603 patients with documented vascular disease or risk factors for vascular disease. Overall, there was no difference in the primary endpoint of cardiovascular death, MI, or stroke. However, in the subgroup of patients with documented car- diovascular disease, the same endpoint was significantly reduced with dual antiplatelet therapy (DAPT), when compared with aspirin (6.9 vs. 7.9%, relative risk 0.88, 95% confidence interval 0.77–0.99). Thus, longer-term treatment with DAPT should only be considered in those in whom the risk of ischaemic events exceeds the risk of bleeding complications. Prasugrel is a more potent thienopyridine with faster onset than clopidogrel. Similar to clopidogrel, prasugrel is a prodrug that re- quires metabolism by enzymatic hydrolysis in the liver for activation. In moderate–high-risk patients with ACS scheduled to undergo PCI, prasugrel (60 mg loading dose, 10 mg maintenance) compared to clopidogrel (300 mg loading dose, 75 mg maintenance), reduced MI and stent thrombosis, particularly in diabetic patients, but with an increased risk of major bleeding, including fatal bleeding. Prasugrel should therefore be avoided in patients older than 75 years, with pre- vious intracerebral bleeding or transient ischaemic attack, or who weigh less than 60 kg. Prasugrel is approved for use in patients with ACS undergoing PCI. Ticagrelor is a reversible inhibitor of the platelet P2Y12 re- ceptor and belongs to a new class of antiplatelet agents, the

cyclopentyltriazolopyrimidines. It does not require hepatic metab- olism to an active form and therefore has a rapid onset with more predictable platelet inhibition. The PLATO study demonstrated that ticagrelor (180 mg loading dose, 90 mg twice daily there- after) as compared to clopidogrel (300–600 mg loading dose, 75 mg daily thereafter) reduced cardiovascular death, MI, and stent thrombosis without increasing the rate of major bleeding in pa- tients with ACS. This was the first study to demonstrate a mor- tality benefit with the addition of an antiplatelet agent to aspirin in patients with ACS. The PEGASUS study examined the role of extended aspirin and ticagrelor in a high-risk group following MI and showed a reduction in CV death, MI, or stroke with extended dual antiplatelet therapy. The DAPT trial failed to show a benefit of extended dual antiplatelet therapy. ACS patients, however, rep- resent a higher-risk group and current guidelines do suggest that prolonged therapy may be considered after assessment of the is- chaemic and bleeding risk. Cangrelor is an intravenous P2Y12 inhibitor with a short plasma half-life. It may have a role in patients undergoing PCI, particularly where there are difficulties with prior antiplatelet loading. Guidelines for antiplatelet therapy are listed in Table 16.13.4.6. Glycoprotein IIb/IIIa inhibitors Platelet adhesion is the initial step in haemostasis after disruption of an atheromatous plaque. It is triggered by damage to the vessel wall and exposure of the subendothelium and is followed by platelet acti- vation and aggregation. Regardless of the agonist, the final common pathway leading to the formation of a platelet aggregate is mediated by the glycoprotein (GP) IIb/IIIa receptor. GPIIb/IIIa receptor ant- agonists inhibit platelet aggregation irrespective of the agonist, and they prevent binding of fibrinogen to its receptor on the platelet surface. Three GPIIb/IIIa receptor antagonists have been approved for clinical use: abciximab, eptifibatide, and tirofiban. They all require intravenous administration. Abciximab is a chimeric human– murine monoclonal antibody that binds with high affinity to the re- ceptor: it has a long biological half-life of 6 to 12 h, and low levels of receptor occupancy are detected even 2 weeks after treatment. Eptifibatide is a synthetic cyclic heptapeptide with high affinity for the arginine–glycine–aspartic acid ligand-adhesion site of the IIb/ IIIa receptor. It inhibits platelet aggregation in a dose-dependent manner and is readily reversible due to competitive binding and a short half-life of approximately 2.5 h. Tirofiban is a nonpeptide tyro- sine derivative which also binds to the arginine–glycine–aspartic acid site with high specificity. It inhibits platelet aggregation in a dose- and concentration-dependent manner and is rapidly revers- ible, with platelet function approaching normal levels in 90% of pa- tients within 4 to 8 h. Although it is convenient to group glycoprotein IIb/IIIa receptor antagonists together, and undoubtedly there is evidence of a class effect, there are biological and pharmacological differences be- tween the agents. It is also important to note that there are limited data about the use of combination GPIIb/IIIa and the newer P2Y12 receptor inhibitors.

 Trials of GPIIb/IIIa inhibitors More than 32 000 patients have been randomized in clinical trials involving GPIIb/IIIa inhibitors (16 trials). A highly significant ($p < 0.001$) benefit is observed for the combined endpoint of death or MI at 48 to 96 h, 30 days, and 6 months. At 30 days the odds ratio is 0.76, or 20 fewer events per 1000 patients treated, and a highly sig- nificant benefit is observed for the combined endpoint of death/MI or revascularization at all time points. By contrast, mortality benefits are seen only at 48 to 96 h, with no significant benefit at 30 days or 6 months. A pooled analysis of abciximab trials has revealed a net mortality benefit, but there is no evidence of benefit for abciximab in medically treated patients (GUSTO-4-ACS). The impact of GPIIb/IIa inhibitors is influenced by the risk status of the patient and whether administered in the context of percutaneous coronary intervention (PCI). In a meta-analysis of 29

570 patients, there was a 9% reduction in relative risk overall, but with no significant benefit in those who were medically man- aged (death and MI at 30 days of 9.3% for IIb/IIIa vs. 9.7% placebo, OR 0.95, 95% confidence interval 0.86–1.04). Significant benefit was observed when GP IIb/IIIa inhibitors were maintained during PCI (10.5 vs. 13.6%, OR 0.74, 95% confidence interval 0.57–0.96). The EARLY-ACS study demonstrated that the use of eptifibatide 12 h or more before coronary angiography was not superior to pro- visional use after angiography, and early use was associated with more nonfatal bleeding. Similarly, there is no convincing evi- dence of benefit in low-risk patients, irrespective of interventional strategy. However, there are limited data on the use of GPIIb/IIIa in the context of newer DAPT regimens, and the value of upstream GPIIb/IIIa inhibition is uncertain. Current indications for treatment with GPIIb/IIIa inhibitors are mainly as a bail-out at PCI when there is large thrombus burden or evidence of no-reflow. Anticoagulant therapy for non-ST-elevation ACS is summarized in Box 16.13.4.4. Anticoagulant therapy Unfractionated heparin Unfractionated heparin is widely used for the treatment of non-ST- elevation ACS, but the evidence on which this is based is less ro- bust than for other widely adopted treatment strategies. In practice, unfractionated heparin is difficult to control because of its unpre- dictable levels of binding to plasma proteins, and this may be amp- lified by the acute-phase response. In addition, heparin has reduced effectiveness against platelet-rich and clot-bound thrombin. Oler and colleagues conducted a meta-analysis of the influence of adding heparin to aspirin in the treatment of patients with unstable angina. Only six randomized trials were available, with 1353 patients included: there were 55 deaths or MIs in the aspirin plus heparin arm and 68 in the aspirin-alone arm, giving a risk reduction of 0.67 and a 95% confidence interval of 0.44 to 1.02. These results do not produce conclusive evidence of benefit from adding heparin to as- pirin, but it must be stressed that appropriately powered, larger-scale trials have not been conducted. Nevertheless, clinical practice has Table 16.13.4.6 Recommendations for platelet inhibition in non-ST-segment elevation acute coronary syndromes Recommendation Class of recommendation Level of evidence Oral antiplatelet therapy Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (in aspirin-naïve patients) and a maintenance dose of 75–100 mg/day in long-term regardless of treatment strategy. I A A P2Y12 inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds. • Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications, for all patients at moderate-to-high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started). • Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication. • Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation. I A I B I B I B P2Y12 inhibitor administration for a shorter duration of 3–6 months after drug-eluting stent implantation may be considered in patients deemed at high bleeding risk. IIb A Long-term P2Y12 inhibition P2Y12 inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient. IIb A Modified from Roffi M, et al. (2016). 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J, 37, 267–315, by permission of Oxford University Press. Box 16.13.4.4 Anticoagulation for non-ST-elevation ACS • Anticoagulation is required in addition to antiplatelet therapy • Anticoagulant options include unfractionated heparin, LMWH, fondaparinux, and bivalirudin, with choice dependent on the initial strategy (early invasive, or not) and the bleeding risk • With an urgent invasive strategy,

unfractionated heparin, enoxaparin, or bivalirudin are treatment options • In the absence of an urgent/early invasive strategy, fondaparinux (2.5 mg SC) has the most favourable efficacy/safety profile • If fondaparinux is not available enoxaparin (1 mg/kg twice daily) is recommended • Bivalirudin with bail-out GPIIb/IIIa are recommended as an alterna- tive to UFH/GPIIb/IIIa in patients with intended invasive manage- ment and high bleeding risk

16.13.4 Management of acute coronary syndrome 3637 adopted unfractionated heparin treatment with aspirin as a prag- matic extrapolation of the available evidence. Low molecular weight heparin Trials vs. placebo The FRISC trial tested dalteparin against placebo in aspirin- treated patients with unstable angina/non-STEMI. Some 1506 pa- tients were randomized to receive dalteparin (twice daily for the first 6 days and then once daily at a lower dose for approximately 6 weeks), and the trial showed a highly significant reduction in the frequency of death or new MI at 6 days (1.8% vs. 4.8%, with a risk ratio of 0.37). The effects were sustained to 42 days, but were attenuated at 6 months, the differences no longer maintaining sig- nificance. Nevertheless, this trial clearly showed the benefit of low molecular weight heparin (LMWH) over placebo in the presence of aspirin. Trials vs. unfractionated heparin LMWH possesses enhanced anti-Xa activity in relation to anti-IIa (antithrombin) activity, compared with unfractionated heparin. It also exhibits decreased sensitivity to platelet factor 4 (PF4), more predictable anticoagulant effect, and lower rates of thrombocyto- penia. In view of its enhanced bioavailability, it offers the substantial practical advantage of subcutaneous administration based on a dose per kilogram of body weight and without the need for laboratory monitoring. Acute-phase treatment (c.2–8 days) In the FRIC trial, dalteparin was tested against unfractionated hep- arin in 1400 patients with unstable angina: it had limited power to show a difference, and no significant difference was seen between unfractionated heparin and dalteparin. The ESSENCE trial was double-blinded and placebo-controlled and tested enoxaparin against unfractionated heparin. The treat- ments were given for 2 to 8 days (median 2.6 days) and the pri- mary endpoints were death, MI, or recurrent angina. Enoxaparin reduced the primary endpoint from 19.6% to 16.6% at 14 days (odds ratio 0.80 and confidence intervals 0.67–0.98; see Fig. 16.13.4.5). A similar and significant odds ratio was maintained at 30 days and 1 year. At 1 year, there were 3.7 fewer events/100 patients ($p = 0.022$). The study was not powered for death/MI alone, but demonstrated corresponding trends for these endpoints. The TIMI 11b trial was also double-blinded and tested enoxaparin vs. unfractionated heparin, but additionally it examined 72 h of treat- ment vs. 43 days of treatment. The results up to 14 days mirrored those seen in the ESSENCE trial: at 14 days the primary outcome occurred was 16.6% (heparin) vs. 14.2% (enoxaparin), risk ratio 0.85 ($p = 0.03$). A combined analysis of ESSENCE and TIMI 11b indi- cated an absolute reduction of 3.1 per 100 for death/MI/refractory angina, and showed a similar risk ratio of 0.79 (confidence interval 0.65–0.96) for death and MI. Taken together, these findings indicate that short-term treatment with enoxaparin results in about 3 per 100 fewer major cardiac endpoints compared to unfractionated heparin treatment, and this is achieved without additional major bleeding. Prolonged outpatient treatment The FRAXIS trial tested fraxiparin, for 6 or 14 days, against unfractionated heparin in 3468 patients; no difference was seen in efficacy, but there was a significant excess of major bleeds with longer-term outpatient treatment. In TIMI 11b, the curves remained separated over the succeeding treatment interval: at 43 days there were 19.6% events (heparin) vs. 17.3% (enoxaparin) ($p = 0.049$), with no evidence of a further separation of the curves. There was 1.4% absolute excess in major bleeds over the chronic phase. ESSENCE ‘97 3171 s d e elb r oja M s y a d 0 3 ta l M r o h ta e D e ziS TIMI-11B ‘99 3910 A to Z ‘04 3620 INTERACT ‘03 746 ACUTE-II ‘02 525 SYNERGY ‘04 9974 All 21946 LMWH+ 0%

10% 0% 0.1 0.5 1 2 10 10% 5% 20% Incidence 10.1 vs. 11.0% Odds ratio and 95% CI 0.91 (0.83–0.99) NNT and 95% CI 113 (61–1438) Incidence 3.9 vs. 3.7% Odds ratio and 95% CI 1.1 (0.96–1.3) 0.5 1 2 1 1 10 10 102 102 ∞ LMWH+ + H F U + H F U + H F U LMWH+ Fig. 16.13.4.5 Death, MI, and major bleeds at 30 days in randomized trials of enoxaparin (filled bars) vs. unfractionated heparin (open bars). NNT, number of patients who needed to be treated to avoid one event. Reproduced from Bassand J-P, et al. (2007). Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J, 28, 1598–660, by permission of Oxford University Press.

section 16 Cardiovascular disorders 3638 Conclusions from the LMWH studies There is convincing evidence in aspirin-treated patients (heparin or LMWH is not indicated in the absence of antiplatelet therapy) that LMWH is better than placebo (FRISC trial). The two trials using enoxaparin have provided consistent data in favour of LMWH over unfractionated heparin when administered as an acute regimen. The other trials have produced a similar outcome for the acute phase of treatment and it can be concluded that acute treatment is at least as effective as unfractionated heparin There is no convincing evidence to support longer-term treatment with LMWH. The use of the Xa antagonist fondaparinux is now preferred to LMWH in high risk ACS (see next). Anti-Xa inhibitors Fondaparinux is a synthetic pentasaccharide that selectively binds antithrombin and causes inhibition of factor Xa. In the OASIS-5 study, 20 078 patients with non-ST-elevation ACS were randomized (double-blind design) to receive 2.5 mg subcutaneous fondaparinux once daily vs. subcutaneous enoxaparin 1 mg/kg twice daily for up to 8 days. Fondaparinux was noninferior at 9 days (the primary endpoint), but subsequently those randomized to fondaparinux had reduced mortality and approximately half the rate of major bleeding. In those undergoing PCI, there was an excess of catheter- related thrombi, and administration of this agent requires additional antithrombin therapy (the excess thrombi were not seen when com- bined with unfractionated heparin and there was no evidence of ex- cess bleeding with this combination). Direct thrombin inhibitors Direct thrombin inhibitors (e.g. hirudin, bivalirudin) bind directly to thrombin (factor IIa) and inhibit thrombin-induced conversion of fibrinogen to fibrin. They bind to and inactivate fibrin-bound thrombin as well as thrombin in the circulation. They do not bind to plasma proteins or interact with PF4, and hence their anticoagulant effect is predictable. Hirudin has been tested in large-scale trials (e.g. OASIS-1, OASIS- 2, TIMI 9b, GUSTO IIb) against heparin and a combined analysis suggests a 22% relative risk reduction in cardiovascular death or MI at 72 h, 17% at 7 days, and 10% at 35 days. This combined analysis is significant at 72 h and 7 days but not beyond. Hirudin is licensed for heparin-induced thrombocytopenia but not for ACS. Bivalirudin was tested in the open-label randomized ACUITY trial in 13 819 patients with moderate-to high-risk non-ST-elevation ACS with a planned invasive strategy. The composite endpoints in- cluded death, MI, or unplanned revascularization for ischaemia, major bleeding (noncoronary artery bypass graft (CABG)-related), and net clinical outcome (composite ischaemia or major bleeding). Bivalirudin plus GPIIb/IIIa had similar outcomes (noninferior) to heparin/LMWH plus GPIIb/IIIa and similar rates of bleeding. Bivalirudin alone had similar outcome (noninferior composite) to heparin/LMWH plus GPIIb/IIIa, but had superior safety (less bleeding). An interaction with the effects of clopidogrel was evident; benefits were seen with clopidogrel but not without. The HORIZON- AMI trial tested a bilvalirudin strategy in PPCI for ST-elevation ACS and showed superiority over GPIIb/IIIa/UFH (unfractionated hep- arin), primarily driven by a reduction in bleeding. A reduction in cardiovascular mortality was found at 30 days and 3 years. However, recent larger trials in contemporary practice have suggested that the major benefit of reduction in bleeding is related to

use of the femoral access route. With increasing use of the radial access route, the bene- ficial effect of bivalirudin is attenuated. Oral antithrombotics Certain oral factor Xa inhibitors (e.g. rivaroxaban, apixaban, and otamixaban) have been assessed in dose-ranging and safety phase II trials of patients with ACS. An efficacy study of apixaban in pa- tients with ACS (APPRAISE 2) was stopped due to excess bleeding. The ATLAS 2 study assessed the effect of rivaroxaban in addition to DAPT (aspirin and clopidogrel) and showed a significant re- duction in cardiovascular death at a dose of 2.5 mg/bd. A recent metanalysis concluded that the addition of new oral anticoagulants to antiplatelet therapy was associated with a modest reduction in cardiovascular events but a substantial increase in bleeding. These agents may be considered in patients with a high ischaemic risk and low bleeding risk. Further studies using single agents or shorter dur- ation of therapy are underway. Oral platelet thrombin receptor ant- agonists (TRA) are currently under evaluation in a phase III clinical trial programme (TRA 2 degrees P-TIMI 50). Vorapaxar selectively inhibits the cellular actions of thrombin via the protease-activated receptor 1 (PAR-1) on the surface of platelets. Given that the gen- eration of fibrin by thrombin is not affected by PAR-1 inhibition, it is anticipated that this molecule will have potent antithrombotic effects with less bleeding than other antiplatelet agents. Antiplatelet and oral anticoagulant therapy In the setting of ACS, the evidence to guide the best approach in patients who require oral anticoagulation therapy is limited. If the indication for oral anticoagulation is strong, triple therapy with as- pirin, clopidogrel and oral anticoagulation may be considered for a short time (1–6 months depending upon the bleeding risk) and dual therapy with an oral anticoagulant and aspirin or clopidogrel for 12 months, followed by monotherapy with anticoagulant long- term. The duration of therapy and choice of agent is a complex de- cision and should be personalized to the patient’s ischaemic and bleeding risk. Revascularization The aim of revascularization in non-ST-elevation ACS is to relieve angina, to alleviate myocardial ischaemia, and to prevent progres- sion to MI or death. The indications for myocardial revascularization are dependent on the risk status of the patients and the presence or absence of evidence of ongoing myocardial ischaemia and/or evi- dence that the ischaemia has resulted in mechanical or electrical complications. Following angiography, the choice of PCI or cor- onary artery bypass grafting (CABG) is dependent on the extent and severity of angiographic stenoses and the comorbidity of the pa- tient. Angiographic analyses from the TIMI-3B and FRISC-2 studies demonstrate that about 30 to 38% of patients with non-ST-elevation ACS have single-vessel disease and 44 to 60% have multivessel dis- ease (>50% diameter stenosis). Observational studies Large-scale observational studies have demonstrated wide vari- ations between countries in the use of cardiac catheterization and

16.13.4 Management of acute coronary syndrome 3639 revascularization for patients with acute ischaemic syndromes, and a paradox whereby lower-risk patients are less likely to re- ceive aggressive antithrombotic and interventional treatment than moderate-or higher-risk patients. Similar findings have been ob- served in the United States of America in the CRUSADE registry. Nevertheless, there is clear evidence over time of increasing use of guideline-indicated therapies (especially class 1 indicated treat- ments) in non-ST-elevation ACS, including angiography and inter- ventional procedures. Overall, the changing pharmacological and interventional therapies have been associated with striking im- provements in outcome, including a halving of new heart failure and a reduced risk of death. Higher rates of revascularization have been associated with an increased frequency of procedural complications, including stroke and major bleeding. Definitive assessment of the impact of revascularization on outcomes requires randomized trials and longer- term follow-up. Randomized trial data Several smaller and older trials (including TIMI 3B and

VANQWISH) tested the impact of a routine invasive strategy in ACS. These largely predated modern antithrombotic therapy, interventional tech- nology (including PCI and stents), and the use of radial access. The FRISC-II trial compared an invasive strategy with a conser- vative strategy in patients who were initially stabilized with approxi- mately 6 days of treatment with LMWH. Coronary angiography was performed within the first 7 days and revascularization performed in 71% of those in the invasive arm and 9% of those in the noninvasive arm within 10 days. This was, therefore, the first trial to achieve sub- stantial separations in delivery of intended treatment and to include an appropriately powered population. After 6 months, death or MI occurred in 9.4% of the invasive group compared with 12.1% of the noninvasive group (a risk ratio of 0.78, p = 0.031) and the results remained significant at 1 year, but the mortality and the death or MI outcomes were no longer significant at 5 years. However, the re- sults at 5 years clearly demonstrate that most benefit was seen in higher-risk patients, with no evidence of benefit in low-risk patients. A similar relationship between patient risk status and long-term outcome had been demonstrated in the RITA-3 trial. The FRISC-II and the RITA-3 trials demonstrated that invasive therapy was associated with an excess early (within 30 days) rate of death or MI due to periprocedural complications. Overall, there was a consistency of benefit (for the efficacy endpoints) across the FRISC-II, TACTICS, and RITA-3 trials. RITA-3 demonstrated that most benefit in the first year was in preventing refractory angina, but over 5 years there was a significant benefit in death or MI, and in preventing cardiovascular death, in those randomized to interven- tion. The more recent ICTUS trial was smaller and had a high rate of intervention in the 'selective invasive' arm of the trial, about as high as the intervention arm in RITA-3 and only modestly lower than in the intervention arm of FRISC-II. ICTUS employed a high rate of adjunctive therapies (including GPIIb/IIIa inhibitors), and the trial did not show an overall benefit for intervention. Differences in trial design, in the risk status of the trial populations, and in the defin- itions of MI in the respective trials must be taken into consideration. Nevertheless, a pooled analysis of all the trials is likely to represent the most reliable interpretation of all of the randomized trial data. Several meta-analyses have been published recently. In a meta-analysis of eight trials, there was clear evidence for overall benefit on the outcomes of death, MI, or ACS in men and biomarker-positive women for a routine invasive strategy. A meta-analysis of FRISC- II, ICTUS, and RITA-3 confirmed that a routine invasive strategy reduced 5-year cardiovascular death and MI (17.9% vs. 14.7%, OR 0.83 (CI 0.710–.93), p = 0.002), with most benefit in the highest risk group. Risk stratification of patients with non-ST-elevation ACS Risk stratification is required to guide management and therapeutic decisions in patients with non-ST-elevation ACS. Some patients are clearly at high risk at the time of initial presentation (e.g. those with typical ongoing ischaemic pain and ST depression on the ECG and elevated biomarkers). However, for the remainder it may not be possible to identify higher-risk patients on the basis of biomarkers and ECG findings alone. Additional clinical criteria such as diabetes, renal insufficiency, impaired LV function, early post-MI angina, recent PCI, prior CABG are important high-risk factors. Several studies have demonstrated that simple risk scores can accurately pre- dict short-and longer-term outcome, not only in those with defined characteristics of ACS, but also in patients with suspected cardiac chest pain (GRACE and TIMI risk scores). Using a handheld device, a computer, or a scorecard, risk status can be calculated in less than a minute (risk calculator downloadable from http://www.outcomes. org/grace or http://www.timi.org/, Table 16.13.4.2). International comparisons have demonstrated superior predictive accuracy for the GRACE score and the European Society of Cardiology (ESC) guidelines for non-ST-elevation ACS recommend this score. The ESC guidelines also recommend that risk status be re-evaluated, es- pecially if clinical or biochemical features change. Troponin (cTnT or cTnI) measurement should be performed at pres-

entation (on the basis that those with elevated markers of necrosis on arrival are at increased risk) and repeated if the initial test is negative. Echocardiography may be required to demonstrate the presence or ab- sence of contractile dysfunction or to rule out alternative diagnoses. There is a substantial late mortality in non-STEMI that is cur- rently underrecognized, with 5-year death rates equivalent to pa- tients with STEMI. Although the GRACE risk score was derived and validated for in-hospital and 6-month outcomes, this analysis demonstrates that it has similarly high predictive accuracy for long- term outcomes. The late consequences of presentation with ACS, in terms of death, MI, and stroke, are substantially greater than those seen during the initial in-hospital phase and novel approaches to di- minish long-term risk are required. An integrated approach to the patient with non-ST-elevation ACS Patients with ACS may present to primary care physicians or dir- ectly to emergency hospital services. In addition, 15 to 20% of those presenting directly to chest pain clinics have ACS. Among patients presenting with an ACS, approximately 40% have evidence of prior coronary artery disease (e.g. MI, angiographically demonstrated disease, documented angina with a positive stress test). The evaluation of patients with suspected ACS needs to be con- sidered in a stepwise approach, proceeding from initial assessment and formulation of a working diagnosis (on the basis of clinical evaluation and the results of immediately available diagnostic tests) to confirmation of the diagnosis and stratification of the patients for emergency, urgent, and elective management.

section 16 Cardiovascular disorders 3640 Emergency department—triage and establishing a working diagnosis Acute chest pain is a common reason for presentation to the emer- gency room, and ACS is only one of several possible explanations. Other serious conditions such as aortic dissection, pulmonary em- bolus and bowel perforation must be considered in the differential diagnosis (see Chapter 16.2.1). Hence, for the patient with chest pain, two issues must be resolved urgently. First, is the chest pain/ discomfort thought to be of cardiac origin? This is a clinical judge- ment and requires prompt and skilled assessment. Secondly, in those with suspected cardiac pain, is there evidence of evolving infarction? Patients with evolving infarction (ST-segment elevation or bundle branch block and clinical features of infarction) require emergency reperfusion with primary angioplasty, or if unavailable, thromb- olysis (see next). Patients without ST elevation or left bundle branch block can be triaged into low, intermediate, high-risk and very high risk categories (Box 16.13.4.5): • Very high-risk ACS—patients with haemodynamic instability, ongoing chest pain, arrhythmia, or cardiac arrest, acute heart failure, recurrent dynamic ECG changes, mechanical complica- tion of MI. These patients require early invasive assessment and management similar to that for those with STEMI. • High-risk ACS—patients with typical clinical features of ischaemia and ST-segment depression or transient ST-segment-elevation, or with troponin elevation and a high- risk score (e.g. GRACE >140 and/or one high risk feature—see Table 16.13.4.2). Patients are also at high risk when ischaemia provokes arrhythmias or haemo- dynamic compromise. These patients should have early invasive assessment (i.e. within 24 h). • Intermediate or low-risk ACS—patients with clinical features of ACS and nonspecific ECG changes (e.g. T-wave inversion, T- wave flattening, minor conduction abnormalities). • Patients with a normal ECG, normal biomarkers, normal cardiac examination, and normal echo are potentially low-risk ACS; how- ever, an alternative diagnosis should be actively sought in this group. Management of patients with non-ST-elevation ACS and very high or high-risk status Very high-risk patients have been excluded from RCT. They have a poor short- and long-term prognosis if left untreated, and very early invasive assessment and treatment is recommended, similar to reperfusion pathways for STEMI patients. High-risk patients with acute ischaemia at initial presentation, and especially those with

haemodynamic compromise, require emergency assessment for revascularization (Fig. 16.13.4.6). Those proceeding to emergency revascularization should receive (1) as- pirin, (2) P2Y12 receptor inhibitors, (3) Fondaparinux, LMWH, or bivalirudin, and (4) consideration of GPIIb/IIIa inhibition, depending on the timing of planned invasive assessment. In add- ition, patients should receive anti-ischaemic therapy (see earlier) and some patients require antiarrhythmic management or haemo- dynamic support (e.g. intra-aortic balloon pump to reduce is- chaemia and stabilize the patient for revascularization). Management of patients with non-ST-elevation ACS at intermediate or low risk Patients without high-risk features on initial presentation re- quire further assessment to guide management (Fig. 16.13.4.7). Application of a risk score will reveal that a significant propor- tion have unsuspected higher risk (approximately one-third based on registry studies). Such patients require monitoring and repeat ECGs (ideally ST-segment continuous analysis) and evaluation in a dedicated chest pain, cardiac, or combined assessment unit (while awaiting the results of biomarker and other investigations). • Patients who develop high-risk features after initial presentation should be considered for urgent angiography and revascularization (within 24–72 h). See Table 16.13.4.6. Those developing ST eleva- tion require emergency reperfusion (by primary PCI or—if PCI not available—by thrombolysis). • Patients with non-ST-elevation ACS and an intermediate risk score require DAPT plus anticoagulation (heparin, LMWH, fondaparinux, or bivalirudin). All patients at intermediate and high risk are candidates for an early elective revascularization strategy (within c.72 h). • Clinically stable patients without further chest pain, heart failure, no evolving ECG changes, and biomarker negative are at very low risk for in-hospital major cardiac events. Such patients may, nevertheless, may have significant underlying coronary artery dis- ease. They require further assessment of cardiovascular risk and stress testing or perfusion scanning, ideally prior to discharge. Box 16.13.4.5 Risk criteria mandating an invasive strategy in non-STEMI Very high risk criteria • Haemodynamic instability or cardiogenic shock • Recurrent or ongoing chest pain refractory to medical treatment • Life-threatening arrhythmias or cardiac arrest • Mechanical complications of MU • Acute heart failure • Recurrent dynamic ST-T-wave changes, particularly with intermittent ST elevation High-risk criteria • Rise or fall in cardiac troponin compatible with MI • Dynamic ST- or T-wave changes (symptomatic or silent) • GRACE score >140 Intermediate-risk criteria • Diabetes mellitus • Renal insufficiency (eGFR <60 ml/min/1.73 m2) • LVEF <40% or congestive heart failure • Early post-infarction angina • Prior PCI • Prior CABG • GRACE risk score >109 and <140 Low-risk criteria • Any characteristics not mentioned above CABG, coronary artery bypass graft; eGFR, estimated glomerular filtra- tion rate; GRACE, Global Registry of Acute Coronary Events; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; MI, myocardial infarction. Modified from Roffi M, et al. (2016). 2015 ESC guidelines for the manage- ment of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J, 37, 267–315, by permission of Oxford University Press.

16.13.4 Management of acute coronary syndrome 3641 Other considerations Coronary artery bypass surgery As demonstrated by the FRISC-II study, those with three-vessel or left main coronary artery disease and an ACS can be stabilized in the acute phase with antiplatelet and anticoagulant therapy and can proceed to coronary artery bypass surgery with a low perioperative and postoperative morbidity and mortality in experienced centres (c.2%, 30-day mortality). Based on the findings of the CURE study, bleeding risk is minimized if the thienopyridine (clopidogrel) is stopped for 5 or more days prior to surgery. Patients at high risk for thrombotic events in the presurgery phase may require an Symptom onset PCI center Risk stratification Therapeutic

strategy Immediate invasive (<2 hr) Early invasive (<24 hr> Invasive (<72 hr> Noninvasive testing if appropriate Very high High High Intermediate Intermediate Transfer Transfer optional EMS = emergency medical services; PCI = percutaneous coronary intervention. Low Low Very high Immediate transfer to PCI center Same-day transfer EMS or Non-PCI center First medical contact non-STEMI diagnosis Fig. 16.13.4.6 Treatment strategy and timing according to initial risk stratification in non-STEMI. EMS, emergency medical service; PCI, percutaneous coronary intervention. Modified from Roffi M, et al. (2016). 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J, 37, 267–315, by permission of Oxford University Press. High-risk non-ST elevation ACS Clinically stable and no evidence of continuing ischaemia Haemodynamically unstable or continuing ischaemia Elective in-patient angiography Emergency/urgent angiography PCI or CABG Secondary prevention Low or uncertain risk Non-ST elevation ACS Clinically stable • No ST shift • Troponin negative Haemodynamically unstable or continuing ischaemia or ST shift or Troponin elevation • Reconsider diagnosis • Pre-discharge stress test for underlying CAD • Elective angiography • Revascularization if indicated • Secondary prevention No stress induced ischaemia Non CAD diagnosis Stress induced ischaemia Manage as for high-risk non-ST elevation ACS Fig. 16.13.4.7 Flow chart to indicate the key management steps for patients with non-ST elevation acute coronary syndromes. CABG, coronary artery bypass grafting; CAD, coronary artery disease; PCI, percutaneous coronary intervention.

section 16 Cardiovascular disorders 3642 intravenous small molecule GP IIb/IIIa inhibitor (to provide more potent but reversible platelet inhibition up until the time of surgery). See Chapter 16.13.6 for further discussion. Antiplatelet and LMWH therapy in patients on warfarin. There is continuing debate concerning the use of dual antiplatelet therapy in patients undergoing stent implantation for ACS who are on warfarin. Bleeding risk is increased in patients on triple therapy, and this has to be balanced against the risk of stent thrombosis with a single antiplatelet agent. Dual antiplatelet therapy is gener- ally recommended for at least 4 weeks for bare metal stents and for 6 months in patients with drug-eluting stents. Where the indication for warfarin is atrial fibrillation alone, oral anticoagulation is often discontinued for this period if the embolic risk is low. There is in- sufficient evidence to provide firm recommendations regarding pa- tients on NOAC’s at present. A standard approach to antithrombotic strategy in patients with nonvalvular atrial fibrillation is shown in Fig. 16.13.4.8. Secondary prevention All patients with ACS require cardiovascular secondary preven- tion measures (Table 16.13.4.7) including lifestyle modification (smoking cessation, diet, exercise), oral pharmacological therapy (antiplatelet, cholesterol-lowering, ACE inhibitor/ARB) and the Fig. 16.13.4.8 Antithrombotic strategies in patients with non-STEMI and nonvalvular atrial fibrillation. Modified from Roffi M, et al. (2016). 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J, 37, 267–315, by permission of Oxford University Press.

16.13.4 Management of acute coronary syndrome 3643 management of established and newly detected comorbidities (e.g. diabetes, hypertension, renal dysfunction, heart failure). These are the same in patients with non-ST-elevation ACS as they are for those with STEMI. ST-segment elevation myocardial
infarction (STEMI) Outcome in STEMI is critically determined by the extent and severity of myocardial ischaemia, and the extent of prior disease including prior myocardial function. In addition, the eventual extent of irrevers- ibly injured myocardium is influenced by residual

myocardial perfu- sion (via collaterals or subtotal coronary occlusion) and the duration of myocardial ischaemia. As a result, the clinical consequences of abrupt coronary occlusion can range from an entirely silent episode, to profound ischaemia with major cardiac rhythm disturbances (ven- tricular fibrillation or asystole), to acute mechanical decompensation with heart failure or cardiogenic shock. The outcome is influenced by the extent to which ischaemia is modified by prompt and effective reperfusion and the presence or absence of significant complications, especially arrhythmias (ventricular tachycardia, ventricular fibril- lation, and asystole) and acute heart failure. Prompt and successful reperfusion (e.g. within the first hour of symptom onset, may 'abort' or greatly attenuate the eventual extent of MI). Importantly, prompt and effective resuscitation for early ventricular arrhythmias (espe- cially ventricular fibrillation) may have a big impact on survival and freedom from cardiac complications. The priorities in the management of STEMI are to manage acute life-threatening complications (resuscitation), relieve acute dis- tress, limit the extent of infarction, and treat complications. Beyond the acute phase, attention focuses on secondary prevention and rehabilitation. Outcome in STEMI Historically, community-based studies in various populations dem- onstrated that the case fatality from acute MI, prior to the advent of resuscitation and reperfusion and other modern therapies, was approximately 50% by 1 month after the onset (MONICA studies). About one-half of those deaths were within the first 2 h of symptom onset. However, the risk of death, prior to hospitalization, varies with age: 80% of those above 85 years die before reaching hospital but only 40% of those below 55 years. Before the introduction of cardiac care units in the 1960s, in-patient mortality was in the range of 25 to 30%, and in the 1980s—before the introduction of reperfusion—in- patient mortality averaged about 18%. More recently, the MONICA study from five cities has indicated that the 28-day mortality for pa- tients admitted to hospital with a MI ranged from 13 to 27%, and other studies have provided figures of 10 to 20%. There is a marked discrepancy between mortality figures from randomized clinical trials and those from observational studies. Publications reporting the outcome for individuals ineligible for in- clusion in trials have demonstrated substantially higher death rates than seen in those entered into contemporaneous trials in the same centres. Clinical trials can provide accurate information on what is possible in defined populations (often excluding patients with im- portant comorbidity), and carefully conducted registries can pro- vide an accurate reflection of 'real-world' clinical practice. Both approaches are required. The multinational GRACE registry has demonstrated a decline in in-hospital mortality from 8.4 to 4.6% and new heart failure from 19.5 to 11.0% between 1999 and 2006. The more widespread appli- cation of evidence-based pharmacological and reperfusion therapy is closely linked with the improved outcome (with no change in the risk status of patients at presentation), highlighting the importance of 'closing the gap' between evidence from guidelines and clinical trials and application in clinical practice. International organiza- tions including the American College of Cardiology and the ESC have stressed this. Special attention needs to be drawn to the more comprehensive provision of acute resuscitation and defibrillation in the community and to the provision of early effective reperfusion. Prehospital care The priorities in prehospital care are to establish a prompt diagnosis of suspected acute infarction, to provide effective resuscitation (espe- cially for ventricular fibrillation), and to initiate prehospital thromb- olysis if primary PCI is not available. In addition, patients require effective analgesia and the management of acute complications. Where available, telemetry of the ECG can confirm the diagnosis, expedite emergency transfer for primary PCI, and prepare the car- diac team for receiving the patient in the cardiac catheter laboratory. The aim is to provide reperfusion within 90 min of symptom onset. Although this has been demonstrated to be feasible in many centres and various countries, there are major logistic challenges. 'Door-to- balloon' times

exclude the prehospital phase and, in many instances, ‘door-to-balloon’ times are longer than 90 min, just for this phase of Table 16.13.4.7 Recommendations for secondary prevention for patients with proven ACS Therapy Regime Aspirin Continue lifelong P2Y12 inhibitor Continue for 12 months (unless at high risk of bleeding) β-Blocker If LV function depressed ACE inhibitor/ARB If LV function depressed Consider for patients without depressed LV function Aldosterone antagonist/eplerenone If depressed LV function (LVEF ≤35%) and either diabetes or heart failure, without significant renal dysfunction Statin Titrate to achieve target LDL-C levels <1.8 mmol/litre (<70 mg/dl) Lifestyle Risk-factor counselling, referral to cardiac rehabilitation/secondary prevention programme ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blocker; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; LVEF, left ventricular ejection fraction.

section 16 Cardiovascular disorders 3644 treatment. In rural and other communities with prolonged transfer times to a hospital with PCI facilities, or where such facilities are not routinely available, appropriate equipment and training needs to be established to allow prehospital or timely thrombolysis to be admin- istered safely and effectively. Making a diagnosis of suspected infarction and initiating treatment A working diagnosis of suspected infarction is based upon typical severe chest discomfort of more than 15 min duration which is un- responsive to glyceryl trinitrate. Characteristically, the pain may ra- diate to the neck, lower jaw, and arms, and is often accompanied by autonomic features including sweating and pallor. Unless compli- cations are present, physical examination may reveal no significant abnormalities, other than those associated with autonomic disturb- ance, but signs can include tachycardia or bradycardia, the presence of a third or fourth heart sound, and features of heart failure. The initial ECG is seldom normal, but may not show the classical features of ST-segment elevation or evidence of Q waves (unless prior MI had occurred). Hyperacute T-wave changes can be pre- sent within minutes of the onset of ischaemia due to coronary oc- clusion, and this may be followed by the evolution of characteristic ST-segment elevation. However, minor or nonspecific ECG abnor- malities in conjunction with a characteristic history may signal the early stages of infarction. The working diagnosis relies heavily on the clinical history, and when this suggests MI, repeat ECG within 30 to 60 min (or continuous ST analysis) will frequently reveal the evolution of recognizable ECG changes. It is critically important that infarction that evolves after initial presentation should be detected promptly. In the prehospital setting, a paramedic or primary care physician may have to rely on the clinical findings to establish the working diagnosis and to initiate immediate treatment. Prompt relief of pain is important, not only for humanitarian reasons, but because pain is associated with sympathetic activation, vasoconstriction, and in- creased myocardial work. Effective analgesia is best achieved by the titration of intravenous opioids, although some paramedic crews only have access to nonopioid analgesia. Side effects of analgesia include nausea and vomiting, hypotension, and respiratory depres- sion. Antiemetics can be administered concurrently; hypotension and bradycardia will usually respond to atropine and respiratory de- pression to naloxone. Oxygen should be administered to those with reduced oxygen saturations less than 90%, those who are breathless, or those with any features of heart failure or shock (see Chapter 17.2 for information on basic and advanced life support in the manage- ment of cardiac arrest or ventricular fibrillation). The logistics of providing acute care for patients with MI de- pend upon the locally available facilities. Guidelines recommend an integrated service involving prehospital emergency care (am- bulance and paramedic personnel, primary care physicians, and so on) and hospital-based specialists, including cardiologists and emergency care physicians. Within an urban setting, with rela- tively short transfer times, the shortest delays and the most prompt initiation of reperfusion

occurs when the patient seeks an emer- gency medical ambulance and achieves direct transfer to a hos- pital with available primary PCI facilities. Studies have shown that once the diagnosis is confirmed (e.g. by telemetry of the ECG) substantial time can be saved by direct transfer of the patient to the catheterization laboratory for PCI rather than transfer via an emergency department (Fig. 16.13.4.9). Prehospital thrombolysis If a primary PCI programme is not available, or if transfer times are sufficiently prolonged that reperfusion may not be achieved within 120 min of patient call, then prehospital thrombolysis is the best op- tion. The combined analysis of primary PCI vs. thrombolysis trials clearly shows superior outcome (deaths, recurrent MI, stroke, and so on) and less bleeding complications (especially intracerebral bleeds) for primary PCI. However, whether primary PCI—with the inherent transfer delays—is superior to very early thrombolysis (adminis- tered within the first hour of symptom onset) remains untested in trials of sufficient power. A review of eight trials comparing prehospital with in-hospital administration of thrombolytic therapy showed that—depending upon the clinical setting—between 30 and 130 min are saved by prehospital thrombolysis (fibrinolytic drug plus aspirin). Overall, for the complete study population of 6607 patients, the 30-day mortality was 10.7% for those receiving in-hospital administra- tion of thrombolysis, and 9.1% for those where it was administered prior to hospital admission. This amounts to a 17% relative reduc- tion in early mortality with a p value of 0.02 (1.6% absolute reduc- tion). Complication rates were similar for community-treated and hospital-initiated thrombolysis, although ventricular fibrillation occurred more frequently with community administration and necessitated well-trained staff and the availability of defibrillators. The greatest benefit is seen when prehospital treatment is applied in remote settings where transport delays are more than 1 h. Several studies have indicated that about 20 patients with chest pain require evaluation for each patient found to be eligible for thrombolytic therapy in the community. Nevertheless, with appropriate training and facilities, prehospital care can provide a gain of approximately 20 lives per 1000 treated among eligible patients. Prehospital cardiac arrest The management of prehospital cardiac arrest requires special con- sideration. At least as many lives can be saved by prompt resuscitation and defibrillation as by reperfusion. For these reasons, emergency assessment of the patient with suspected infarction necessitates that the clinician or paramedic has access to a defibrillator and the skills to manage cardiac arrest promptly and effectively. The provision of basic or advanced life support training to paramedic ambulance crews, together with semiautomatic defibrillators, has resulted in a substantial increase in the number of patients surviving out-of- hospital cardiac arrest. Before the institution of such programmes, successful resuscitations were opportunistic and often relied on the availability of a bystander with medical or nursing training. Nationwide figures indicate that resuscitation now achieves survival in 7 to 10% of those patients found with cardiac arrest and in whom the initial rhythm is thought to be ventricular fibrillation. With effective integrated programmes, higher success rates have been achieved: for instance, in the south-eastern region of Scotland, about 14% survive to reach hospital alive, and in Seattle, with a well- established community training and resuscitation programme, the figure exceeds 20%. About one-half of those reaching hospital alive survive to be discharged home, but this is dependent on the pre- senting rhythm and duration of cardiac arrest.

16.13.4 Management of acute coronary syndrome 3645 Emergency Department triage and management Ideally, in those with typical clinical features and ST elevation on the ECG, a working diagnosis has been made in the prehospital setting (by paramedics with ECG telemetry or by a primary care physician) and early management initiated prior to hospital arrival. Where facilities are available, the patient should be transferred dir- ectly to the catheterization laboratory (with the

team alerted while the patient is in transit), or if the decision is made for thrombolysis, then this is administered before arrival in hospital. In-hospital evaluation is required in the remainder, where the symptoms are unclear, the ECG not diagnostic, or if significant comorbidity is present (e.g. bleeding risks). The priority imme- diately after arrival at the hospital is to identify those patients with ST elevation infarction for prompt reperfusion therapy (Fig. 16.13.4.10). Triage is usually performed in the emergency department, or, in some institutions, patients with a high prob- ability of infarction gain direct access to a cardiac care assessment area. An integrated strategy involving the paramedic or ambu- lance system, the emergency physicians, and the cardiologists is required. 'Fast-track' systems have been developed to minimize in-hospital delay to reperfusion: these are facilitated by specific- ally trained medical and nursing staff, with the aim of ensuring clinical assessment and ECG within 15 min of arrival and rapid transfer for PCI or the institution of thrombolytic therapy within 30 min. Audit programmes and continuous training are necessary for centres to achieve this 30-min median 'door-to-needle' time. Definite vs. suspected infarction Rapid triage systems allow the identification of patients with clearly defined clinical and ECG features of infarction, i.e. characteristic symptoms of infarction which persist at rest and are not relieved by Fig. 16.13.4.9 Prehospital and in-hospital management and reperfusion strategies for STEMI within 24 h of first medical contact. Cath, catheterization laboratory; EMS, emergency medical system; FMC, first medical contact; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation mycocardial infarction. Adapted from Wijns W, et al. (2010). Guidelines on myocardial revascularization. Eur Heart J, 31, 2501–55, by permission of Oxford University Press. Acute ST elevation or BBB myocardial infarction Thrombolysis : aspirin and fibrinolytic (if primary PCI unavailable) Emergency Reperfusion Primary PCI: +/– IIb/IIIa inhibitor Evidence of reperfusion (ST resolution) No evidence of reperfusion: Rescue PCI Risk stratification Routine predischarge coronary angiography Secondary prevention Rehabilitation Fig. 16.13.4.10 Management of ST elevation MI. BBB, bundle branch block; PCI, percutaneous coronary intervention.

 glyceryl trinitrate, in the presence of at least 1 mm ST-segment eleva- tion in two or more contiguous leads, or the development of bundle branch block. Clinical trials have employed ECG criteria of 1 mm ST elevation for limb leads and 2 mm for chest leads, a definition that improves specificity, but is associated with reduced sensitivity. Among those without diagnostic ECG changes, a working diag- nosis of suspected MI or non-ST-elevation ACS can be established. Such patients require repeat clinical and ECG assessments or con- tinuous ST analysis to detect those with evolving infarction and separate them from those with unstable angina or non-ST-elevation infarction. The rationale for minimizing delays to reperfusion Experimental and clinical data demonstrate that the duration of is- chaemia prior to reperfusion is a critical determinant of the eventual extent of myocardial damage. These data are supported by the im- proved outcome seen with prehospital vs. in-hospital thrombolysis, also observational data from large clinical trials in which survival gain diminishes with each additional hour of ischaemia. The Fibrinolytic Trials Overview suggests about 1.6 additional deaths per hour of delay per 1000 treated, and a more recent meta-analysis suggests that early time delay is especially important. The relationship between the duration of ischaemia and the extent of infarction is nonlinear: the greatest potential for salvage occurs when reperfusion is initiated within 60 min of the onset of infarc- tion. Under such circumstances, some patients (5–7%) will have the infarction aborted and will not develop Q waves or significant enzyme elevation despite characteristic ST elevation on the initial ECG. Minimizing the time delay is, therefore, critical in salvaging myocardium. Based on data from individual trials, and from the Fibrinolytic Trials Overview, most benefit occurs within the first

3 h of the onset of infarction, and highly significant benefits still occur at up to 6 h. Statistically significant gains are still present at 12 h, but beyond 12 h the benefits are marginal. However, some patients present with a stuttering pattern and in the presence of persistent or intermittent ST-segment elevation and continuing symptoms of is- chaemia, reperfusion beyond 12 h may salvage significant ischaemic myocardium. Differential diagnosis Critically, thrombolytic therapy or angiography for anticipated primary angioplasty will be of no benefit to those who do not have MI and may convey significant hazards. Such patients suffer the dual hazards of thrombolysis or angiography in the acute phase of their illness and the delay in initiating appropriate treatment. Furthermore, those treated inappropriately with thrombolysis will experience the bleeding hazards of the drug (a net increase in intracerebral haemorrhage of c.0.5%) and the disrupted coagu- lation system will render other emergency surgery (e.g. for per- forated peptic ulceration) more hazardous. Alternative cardiac diagnoses include non-ST-segment-elevation ACS, myocarditis, pericarditis, and aortic dissection. Noncardiac diagnoses include gastrointestinal pain of oesophageal, peptic, or biliary origin; pancreatitis; pulmonary embolism; and respiratory and muscu- loskeletal disorders. When angiography has been performed in a patient with a suspected ACS and found to be normal, a careful review and investigation of alternative causes is essential prior to discharge. Aortic dissection presents a particular problem when it extends proximally to the origin of the right coronary artery and produces inferior infarction. CT or transoesophageal echocardiography may be required to establish the diagnosis (see Chapter 16.14.1). Transthoracic echocardiography can be valuable when infarction is suspected but characteristic ECG features are absent: normal left ventricular function excludes significant infarction, and conversely a regional contraction abnormality helps to confirm the diagnosis of ischaemia or possible infarction. However, in those with prior myo- cardial damage, the differentiation of new from old mechanical dys- function is complex and requires specialist assistance. Cardiac enzymes are helpful when abnormal, but most patients present within 3 h of the onset of symptoms and insufficient time has elapsed to produce a diagnostic release of biomarkers of necrosis— troponins, creatine kinase (CK), or CK-MB. Patients with suspected infarction but normal ECGs require further clinical ECG and bio- marker estimations 4 to 6 h after the suspected event. Among elderly and very elderly patients (>90 years of age), the presentation of infarction is often atypical. They may not experience a typical pattern of symptoms and concomitant multisystem dis- orders may obscure the diagnosis. MI must be considered in the dif- ferential diagnosis of abrupt collapse, haemodynamic disturbance of sudden onset, or severe nonspecific symptoms in elderly patients. Continuing management in the Cardiac Department Administration of analgesia, management of rhythm and haemo- dynamic compromise, and initiation of pharmacological therapy (heparin, LMWH, aspirin, P2Y12 receptor inhibitors, and so on) should have been initiated shortly after the diagnosis of ST-elevation MI is made (in the emergency department or cardiac assessment area or prehospital). The first priority is for emergency reperfusion (primary PCI, or if unavailable thrombolysis). Patients may require management of heart failure and arrhythmias and pain relief while in transit to reperfusion therapy, but every effort should be made to avoid delays to reperfusion. Percutaneous coronary intervention Primary PCI Primary angioplasty is defined as PCI without concomitant fi- brinolytic therapy. It requires prompt availability of a highly skilled interventional cardiology team with substantial experience of the procedure. Randomized clinical trials of primary PCI vs. thrombolysis have shown consistent findings: primary PCI has superior outcomes. In experienced centres it is more effective in restoring patency, achieves better ventricular function, and improves important clin- ical outcomes, with lower rates of death, reinfarction, stroke, major bleeding, and recurrent ischaemia (Table 16.13.4.8). Particular gains are seen in haemodynamically compromised patients

and those with cardiogenic shock. In consequence, primary PCI is the preferred therapeutic option in national and international guide- lines (SIGN, ESC PCI Guidelines, American College of Cardiology, and AHA). Patients are transferred as an emergency to the cardiac catheter- ization laboratory and angiography undertaken (radial artery access preferred to femoral) to establish coronary anatomy and the nature of the vessel occlusion. A flexible guide wire is then passed across the

16.13.4 Management of acute coronary syndrome 3647 occluded lesion and balloon angioplasty (usually accompanied by stent implantation, with drug-eluting stent preferred to bare metal stent) performed (‘primary PCI’), thereby restoring patency to the previously occluded coronary artery. • Primary percutaneous coronary angioplasty (PCI) is the treat- ment of choice in patients with STEMI. • Primary PCI requires a highly experienced interventional team with 24-h availability and an integrated approach to management to achieve reperfusion with the minimum of delay—ideally within 120 min of symptom onset. • Where primary PCI is unavailable, the patient should undergo prompt thrombolytic therapy, provided no contraindications are present. • The limit in treating all potentially eligible patients with reperfusion therapy has not been reached. Internationally, at least one-third of all MIs (without a major bleeding risk) receive neither thrombolysis nor primary PCI. Rescue PCI Thrombolytic therapy may fail to achieve effective reperfusion in 30% or more of those in whom it is administered for STEMI. Patients experience continuing symptoms of ischaemia and failure of resolution of ST elevation on the ECG (<50% resolution of the ST elevation within 1 h of administration). Rescue PCI is more effective than repeat thrombolysis or conservative treatment in improving outcome (REACT trial). Thus, in centres where primary PCI is not available, logistics need to be established for prompt transfer for rescue percutaneous coronary intervention of patients in whom thrombolysis does not result in signs of reperfusion. Facilitated PCI The combination of full-dose or reduced-dose fibrinolysis fol- lowed by emergency PCI has been tested in large-scale trials and shown worse outcomes and greater bleeding risks (ASSENT 4 trial). Hence, planned emergency PCI after thrombolysis is not re- commended, although later PCI—after the impact of thrombolysis has resolved—may be of benefit (GRACIA 2 study). The latter ap- proach should also be considered as part of the strategy to deal with residual stenoses after PCI (prior to hospital discharge), ra- ther than as ‘facilitated’ PCI. Thrombolytic treatment Thrombolytic treatment refers to the combination of antiplatelet therapy (aspirin and clopidogrel) with fibrinolytic treatment. The fibrinolytic agent, directly or indirectly, converts plasminogen to plasmin and plasmin lyses fibrin in the clot. Cross-linked fibrin is more resistant to fibrinolytic drugs than a newly formed fibrin clot. The combination of aspirin and a fibrinolytic agent has under- gone extensive clinical testing in trials involving more than 100 000 patients. Additional trials have been conducted comparing one fi- brinolytic agent with another. For patients presenting within 6 h of symptom onset, and with ST elevation or bundle branch block, ap- proximately 30 deaths are prevented per 1000 patients treated. For those presenting between 7 and 12 h, approximately 20 deaths are prevented per 1000 patients treated, and beyond 12 h the benefits are inconclusive. Thrombolysis is a very cost-effective treatment for acute MI. A sustained benefit on survival has been demonstrated 14 years after thrombolysis. The ISIS-2 trial demonstrated that the benefits of aspirin treatment were additional to those of fibrinolytic treatment, each achieving about 25 lives saved per 1000 patients treated (for the whole of the study population). Thus, in combination, about 50 lives are saved per 1000 patients treated, but the benefits are larger than this among those presenting within 3 h of infarction with ST-segment elevation or bundle branch block. Overall, the largest absolute benefit is seen in patients at highest risk, although the proportional benefit may be similar for all. High- risk patients include

those over 65 years of age, those with a systolic blood pressure below 100 mm Hg, and those with anterior infarction or more extensive ischaemia. The absolute benefit in lives saved per 1000 treated is 11 ± 3 for those under 55 years of age; 18 ± 4 for those between 55 and 64; 27 ± 5 for those 65 to 74; and 10 ± 13 for those over 75. However, for ST depression there is a net hazard of 14 lives lost per 1000 treated, and for those with a normal ECG seven lives lost per 1000 treated (Fibrinolytic Trials Overview). Thus, evidence supports thrombolysis treatment only for those patients with ST ele- vation or bundle branch block. Hazards of thrombolysis Thrombolytic therapy is associated with a significant excess of haemorrhagic complications, including cerebral haemorrhage. Overall, about two nonfatal strokes occur per 1000 patients treated, Table 16.13.4.8 Advantages of primary percutaneous coronary intervention over thrombolysis Clinical indices Event rate (%) Absolute risk benefit of PCI (%) Relative risk benefit of PCI (%) NNT Thrombolysis PCI Short-term mortality (4–6 weeks) 8 5 3 36 33 Long-term mortality (6–18 months) 8 5 3 38 33 Stroke 2 <1 2 64 50 Reinfarction 8 3 5 59 20 Recurrent ischaemia 18 7 11 59 9 Death or nonfatal reinfarction 12 7 5 44 20 Need for CABG 13 8 5 36 20 CABG, coronary artery bypass graft; NNT, number needed to treat; PCI, percutaneous coronary intervention. Data from Hartwell D, et al. (2005). Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation. Health Technol Assess, 9(17).

section 16 Cardiovascular disorders 3648 and of these, half are moderately or severely disabling. An add- itional two strokes per 1000 patients are fatal, and the net impact on mortality includes such patients. The risk of stroke increases with age, especially for those over 75 years of age, and for those with systolic hypertension. There is also an excess of noncerebral bleeds of about 7 per 1000 treated. Bleeding occurs at arterial and venous puncture sites; hence blood sampling or cannulation of vessels should be limited to sites where external compression can achieve haemostasis. Streptokinase and other streptokinase-containing agents can produce hypotension and, rarely, allergic reactions. Routine ad- ministration of hydrocortisone is not indicated. When hypotension occurs, it can be managed by interrupting the streptokinase infu- sion, lying the patient flat or head down, and by the administration of atropine or intravascular volume expansion. Comparison of thrombolytic agents The most widely used thrombolytic agents are streptokinase, alteplase (tissue plasminogen activator, tPA), tenecteplase (TNK), and reteplase (rPA). The GISSI International Trial and ISIS-3 international trial both failed to find a difference in outcome between streptokinase and tPA. However, the GUSTO trial (Global Utilization of Streptokinase and Tissue plasminogen active for Occluded coronary arteries) employed an accelerated administration of alteplase over 90 min and intra- venous heparin adjusted using the activated partial thromboplastin time, finding 10 fewer deaths per 1000 patients treated with alteplase compared with the streptokinase group. Meta-analysis confirms the superiority of clot-specific agents (e.g. alteplase, tenecteplase) over streptokinase. The current reference standard for the comparison of fibrino- lytic agents is the accelerated infusion regimen of alteplase (tPA), or for simplicity the single-bolus administration of tenecteplase (TNK). Tenecteplase does not require an infusion pump or re- frigeration and hence is particularly suited for prehospital ad- ministration, but internationally streptokinase remains the most widely used fibrinolytic agent, principally because it is relatively inexpensive. Invasive assessment after fibrinolysis Following lytic therapy, a strategy of routine early angiography (3–24 h) is recommended. This approach reduces the risk of recur- rent infarction and ischaemia, without an increased risk of stroke or bleeding. Patients should have DAPT and antithrombin therapy as indicated in PPCI. Revascularization by PCI or CABG depends upon the extent and location of underlying coronary disease. Coronary artery bypass

surgery (CABG) In the acute phase of MI, the role of CABG is limited to those pa- tients with acute mechanical complications, such as ventricular septal defect or mitral regurgitation due to papillary muscle rupture. Unless such mechanical complications are present, the hazards of acute bypass surgery are significantly increased compared to delayed revascularization in a stabilized patient. The Danish DANAMI study investigated the role of revascularization in those with ischaemia during the recovery phase of MI. It suggested that, following in- farction, individuals with symptomatic or electrocardiographic is- chaemia on stress testing experience significant long-term benefit from surgical revascularization. Further in-hospital management The period of hospitalization for reperfused and uncomplicated pa- tients following STEMI has progressively shortened, and is now in the range of 2 to 5 days. The main aims of further in-hospital man- agement are the identification and treatment of acute complications of infarction, identification of patients at increased risk for subse- quent cardiac events, and initiation of secondary prevention and rehabilitation. There is time pressure to address these issues before hospital discharge in view of the risk that they will not be pursued afterwards. Major complications may be apparent at the time of presentation and haemodynamic, arrhythmic, or ischaemic complications may be evident shortly thereafter. Nevertheless, in the period beyond the first 12 to 24 h, it is appropriate to focus attention on the points just listed. Identification and treatment of complications of infarction Failure of reperfusion Electrocardiographic markers of failed thrombolysis reperfusion are the persistence of ST-segment elevation together with clinical and haemodynamic features of continuing ischaemia. Continuous computed ST analysis allows the most accurate definition of ECG changes, but an approximation can be obtained with repeated 12- lead ECGs and measurement of ST-segment elevation. In those with successful reperfusion, ST segments decrease to less than 50% of peak elevation within 60 min. In addition, some patients exhibit reperfusion arrhythmias (ventricular tachycardia, idioventricular rhythm, and—rarely— ventricular fibrillation). Such arrhythmias are more common in the presence of marked ischaemia and prompt reperfusion within 60 to 90 min of occlusion. Rescue angioplasty is the appropriate management for failed reperfusion, and consists of mechanical recanalization of the oc- cluded vessel with percutaneous intervention, including stent im- plantation. This strategy achieves an ‘open artery’, and randomized trial data (REACT trial) shows superior outcome compared with re- peat thrombolysis or conservative management. Cardiogenic shock In cardiogenic shock, mechanical contractile abnormalities of the left ventricle or acute haemodynamic complications (papillary muscle rupture or ventricular septal defect) lead to reduced blood pressure and impaired tissue perfusion. Clinically, the condition is recognized by a systolic blood pressure of less than 90 mm Hg to- gether with impaired tissue flow, as reflected impaired cerebral func- tion, peripheral vasoconstriction and oliguria. Echocardiography is very helpful to help define the mechanism of cardiogenic shock and direct treatment. Between 5 and 20% of those patients admitted to hospital with acute MI demonstrate cardiogenic shock, although the frequency has been reduced by thrombolytic therapy and pri- mary PCI. The mortality rate when cardiogenic shock complicates an acute coronary event is in excess of 70% if acute revascularization is not possible. Time delay is critically important in the management of cardiogenic shock: mortality rises progressively if more than 2 h have elapsed since its onset. Treatment aims to improve the recovery of acutely is- chaemic myocardium (mechanical and surgical revascularization),

 treat mechanical complications, and to support the circulation with a combination of inotropes, vasodilators, and loop diuretics. Evidence suggests that the most important treatment may be to reopen the infarct-related artery. In addition

to achieving reperfusion, management of the patient with cardiogenic shock after MI may require inotropic support. Dopamine is commonly used, initially at a low ‘renal dose’ (1–5 micrograms/kg per min) that activates dopaminergic receptors (but also has an effect on the circulation), but if necessary at higher doses of 5 to 20 micrograms/kg per min that have positive inotropic and chronotropic effects. In doses above 20 micrograms/kg per min, there is activation of α-adrenoceptors with undesirable peripheral vasoconstriction and a decline in renal perfusion. Dobutamine acts mainly as a β1-adrenoceptor agonist and is used in the range of 2 to 40 micrograms/kg per min. Phosphodiesterase inhibitors have both inotropic and vasodilator effects and, although they have produced favourable haemodynamic responses, the studies conducted have not shown an improvement in outcome. The management of pulmonary oedema consists of opiates (to relieve distress and to reduce vascular resistance), oxygen, vasodilators, and diuretics. If it is severe, patients may require positive end-expiratory ventilation or even full mechanical venti- lation. Vasodilators (including nitrates, salbutamol, and sodium nitroprusside) reduce venous and pulmonary arterial pressure, but tachycardia may be a limiting feature and their use is limited in those who are profoundly hypotensive. Loop diuretics are employed in bolus intravenous doses or by infusion. In all instances, decisions to proceed to mechanical external support of the circulation or mechanical ventilation need to take account of the extent to which the cardiac dysfunction may be re- versible, the presence of comorbidity, and the wishes of the patient and their family. Left ventricular dysfunction and heart failure Large-scale trials of angiotensin-converting-enzyme (ACE) in- hibitors and angiotensin receptor blockers (ARBs) have been con- ducted in patients with left ventricular dysfunction and those with clinical and radiological features of heart failure. Clear evidence demonstrates improved short-and long-term outcome with ACE in- hibitors/ARBs in patients with heart failure and those with asymp- tomatic left ventricular dysfunction. Caution must be exercised with the introduction of ACE inhibi- tors in patients with intravascular volume depletion, when they can cause hypotension, and in patients with low arterial pressure or renal impairment. ACE inhibition should commence with a very small dose (e.g. 6.25 mg of captopril), with dosages increased progressively in conjunction with clinical monitoring. They can provoke deteri- oration in renal function in patients with renal artery stenosis and in those with significant pre-existing renal impairment, hence it is important to check serum electrolytes and creatinine during early treatment and follow-up. Arrhythmias Many arrhythmias can be seen in the context of acute MI and its treatment. The most serious, including ventricular fibrillation, ventricular tachycardia, and heart block, can lead to cardiac ar- rest. However, routine administration of antiarrhythmic agents is not indicated. They are almost invariably negatively inotropic, and they may also be proarrhythmic in the context of acute cor- onary ischaemia. An overview of randomized trials into the use of prophylactic lidocaine (lignocaine) showed that it increased mortality. Ventricular fibrillation should be treated with direct current (DC) cardioversion, and recurrent ventricular arrhyth- mias require antiarrhythmics (e.g. amiodarone). Importantly, at- tention should be paid to electrolyte imbalance and the correction of reversible ischaemia or other factors provoking arrhythmias. (see Chapter 16.4 for details of the diagnosis and treatment of arrhythmias). Heart block of any degree can occur after acute MI. It is more common with inferior than anterior infarction because the right coronary artery supplies the atrioventricular node, and also be- cause vagal reflexes are more likely from this area. It is often transient, and does not necessarily imply a large infarct, except when it occurs with anterior infarction, in which case the prog- nosis is grave. Temporary transvenous pacing is justified when bradycardia compromises the circulation, but is not advocated ‘prophylactically’. Ventricular septal defect, papillary muscle rupture,

and myocardial rupture Rupture of the interventricular septum occurs in up to 3% of acute infarctions and is responsible for about 5% of deaths due to MI. Rupture in the apical area may complicate anterior infarction and in the basal inferior area may complicate inferior infarction. Clinically, the condition is associated with the development of a new pansystolic murmur and clinical features of a left-to-right shunt with increased pulmonary congestion. The findings are confirmed on echocardiog- raphy or cardiac catheterization. Surgery should be undertaken as soon as possible: the outlook for those who are not operated upon is very bleak, with few surviving. However, some patients with small shunts survive the acute phase, in which case they may suffer the later consequences of the shunt. Papillary muscle rupture occurs as a result of acute ischaemic damage due to obstruction of either the left anterior descending or circumflex coronary arteries. It causes the abrupt onset of severe mi- tral regurgitation and accounts for 5% of deaths after acute MI. The complication generally occurs within the first week after infarction, and may be recognized as the abrupt onset of acute pulmonary oe- dema. It is often accompanied by a new systolic murmur, but when the left atrial pressure rises acutely the murmur may be insignifi- cant. The findings are confirmed with echocardiography. The man- agement is acute surgical repair with or without revascularization. In the patient who deteriorates haemodynamically after MI— with hypotension, pulmonary oedema, or both—it is important to consider the possibility of a ventricular septal defect or acute mi- tral regurgitation. However, it can be impossible to distinguish be- tween the two on clinical grounds. Both classically produce a new pansystolic murmur, and although differences between the mur- murs have been described, these are not robust enough to discrim- inate with certainty in the individual case. Acute mitral regurgitation is best diagnosed by echocardiography, but transthoracic echocar- diography may be unable to detect a ventricular septal defect in a reliable manner. Transoesophageal echocardiography is better, as is the use of a contrast-enhanced technique. If this is unavailable, an al- ternative approach is to pass a flow-directed pulmonary catheter and take blood samples from the pulmonary artery, right ventricle, and

 right atrium. A step-up in oxygen tension between the right atrium and the pulmonary artery indicates the presence of a left-to-right shunt and confirms the diagnosis of a ventricular septal defect. Myocardial rupture may follow acute infarction, usually involving the free wall of the left ventricle. It is responsible for approximately 10% of all deaths in acute MI. Half of the ruptures occur within the first week, and 90% within 2 weeks. The location of rupture is usually within the infarcted area, but may be at the junction with adjacent normal myocardium. In most cases, death is immediate and due to electromechanical dissociation. The patient is unresponsive to re- suscitation measures but rarely—with subacute rupture—patients can be supported until surgical repair is performed. The diagnosis is made on clinical and echocardiographic criteria with assessment for possible cardiac tamponade (see Chapter 16.8). In some patients, partial rupture of the free wall can result in the late development of a false aneurysm. Left ventricular thrombus A left ventricular thrombus can be detected using echocardiog- raphy in up to 40% of patients with acute anterior MI. The thrombus is usually located at the apex in association with a dyskinetic or aneurysmal section of myocardium with impaired contractile function. The thrombus may be large and is associated with risks of embolization (in 15–20% of cases). Anticoagulation with hep- arin followed by warfarin is advised in patients with extensive in- farction and those in whom apical aneurysms or mural thrombi are detected for up to 6 months. Both thrombolysis and surgical removal have been successfully conducted. However, there is no clear evidence that either strategy is superior (provided there is no evidence of

embolization). Combining oral anticoagulation with DAPT increases bleeding risk. The duration of therapy is unknown but should reflect the relative risk of bleeding and stent throm- bosis. Repeat imaging may help to confirm thrombus resolution and/or improvement of LV function to guide a decision about long-term therapy. Right ventricular infarction Right ventricular infarction may occur in isolation, or associated with inferior STEMI. The triad of hypotension, clear lung fields, and raised central venous pressure should prompt its diagnosis. ECG may show ST elevation in V1 and V4R. The chest radio-graph is char- acteristically clear despite the presence of shock. Echocardiography conforms right ventricular (RV) dilatation, low pulmonary artery (PA) pressure, dilated hepatic veins. Fluid loading to maintain RV filling is the key therapeutic intervention, and PA catheter inser- tion maybe necessary for accurate monitoring. Maintaining sinus rhythm and atrioventricular synchrony is important. Pericarditis Pericarditis may complicate an extensive MI, and may be manifest clinically as a pericardial friction rub accompanied by pleuritic chest pain. A small pericardial effusion may be detected using echocar- diography. Dressler's syndrome is a rare late complication and is associated with pericarditis between 2 weeks and 3 months after acute infarction. It has an autoimmune basis, often accompanied by pleural and pericardial effusions. It is managed with salicylates, paracetamol, or colchicine. The frequency of both pericarditis and Dressler's syndrome is reduced with acute reperfusion. An integrated approach to the management of STEMI Prehospital management In a patient with suspected acute infarction, the priorities are to establish whether typical clinical features and ST elevation (or left bundle branch block) are present, and if so to initiate reperfusion with the absolute minimum of delay. Where possible, the diag- nosis is confirmed and the transfer of the patient arranged by tel- emetry of the ECG. The phrase 'time is muscle' has been coined for acute STEMI. Acute resuscitation may be required for cardiac ar- rest or major arrhythmic complications, especially ventricular fib- rillation. Additional priorities are to provide analgesia and oxygen. Prehospital thrombolysis may be given by appropriately trained paramedic crews when transfer times to a PCI hospital are such that more than 120 min will elapse from diagnosis to PCI. In-hospital management Initial triage and management Initial assessment involves the identification of those with clear-cut evidence of STEMI (based on clinical and diagnostic ECG criteria). Such patients require immediate triage to reperfusion therapy (pri- mary PCI, or if unavailable thrombolysis with a fibrinolytic agent plus an antiplatelet agents). In transit to primary PCI or while preparing pharmacological reperfusion, patients may require fur- ther analgesia and management of arrhythmic and haemodynamic complications, including heart failure. Patients in whom the diagnosis of MI is suspected, but the ECG criteria are not diagnostic, should be managed in an intensive care setting (in the emergency department or cardiac care unit) with re- peat ECG evaluation at 30-min intervals (or ST-segment analysis). Cardiac biomarkers (troponins) may be elevated at presentation, if sufficient time has lapsed from onset of ischaemia (4–6 h), or they may become elevated following arrival (repeat measurement at 8–12 h). Such patients may be divided into those with evidence of non-STEMI (ECG abnormalities and troponin elevation) and those with unstable angina (T-wave inversion, ST-segment depression, or transient ST- segment elevation, without elevated cardiac troponins). Among those with minor or nonspecific ECG changes and no enzyme elevation, re-evaluation should take place for alternative diagnoses, and stress testing performed subsequently to detect underlying coronary ar- tery disease (Fig. 16.13.4.7). A key component of initial evaluation of those without ST elevation or left bundle branch block involves risk stratification (see Table 16.13.4.2). Echocardiography may be valu- able to detect signs of ischaemia/infarction or to demonstrate normal contractile function in those with an alternative diagnosis. Later in-hospital management During this phase the management of complications, initiation of secondary prevention, and early

cardiac rehabilitation should take place. In high-risk patients (those with recurrent acute ischaemia or those with failure of ST-segment resolution and continuing pain), emergency PCI or surgical revascularization can be performed in appropriately equipped centres (Fig. 16.13.4.9).

16.13.4 Management of acute coronary syndrome 3651 Regular clinical and electrocardiographic assessments are required during the recovery phase to detect acute mechanical and arrhythmic complications, and to identify impaired contractile function in pa- tients who will benefit from ACE inhibitor/ARB treatment. This treatment is indicated in those with overt heart failure in the acute phase and also indicated for secondary prevention in patients with established vascular disease (HOPE trial). Thus, ACE inhibitors or ARBs are indicated for those with vascular disease, irrespective of whether there is evidence of overt heart failure or impaired left ven- tricular function in acute phase. Patients also require lipid-lowering therapy: robust evidence demonstrates that all patients with MI or non-ST-elevation ACS will benefit (MRC/BHF Heart Protection Study). There is evidence to support management of diabetes with glu- cose and insulin during the in-hospital and early posthospital phase. All patients will benefit from smoking cessation, the management of hypertension (systolic pressure to <140 mm Hg), and dietary and lifestyle modification, including exercise. After STEMI, patients benefit from participation in a rehabilitation programme, with im- proved quality of life, symptom relief, and return to an active lifestyle or occupation. Secondary prevention measures in those with STEMI or non-STEMI ACS Following an ACS, patients require dietary and lifestyle advice including the support necessary to discontinue smoking with the introduction of nicotine replacement therapy. (SIGN Guideline 2007). Lipids should be measured within the first 24 h of admis- sion, with evidence supporting the use of lipid-lowering therapy. Individuals with documented coronary artery disease, and espe- cially those with left ventricular contractile dysfunction or heart failure, have reduced long-term risks of death and MI if main- tained on an ACE inhibitor or ARB. In addition, patients may re- quire antianginal therapy if revascularization is incomplete, and all should receive long-term, low-dose aspirin. DAPT should be given for at least 1 month in STEMI (the limits of the evidence) and a year for non-ST-elevation ACS (or as determined by the type of stents implanted). Nonpharmacological interventions Evidence supports the following nonpharmacological interven- tions in secondary prevention: cessation of smoking (including the avoidance of passive smoking), dietary modification, exer- cise, rehabilitation, and management of obesity. Patients with impaired LV function and or later symptomatic heart failure may need to be considered for defibrillator or resynchronization therapy. Pharmacological interventions Trial evidence supports therapeutic interventions to modify the fol- lowing conditions: hyperlipidaemia, left ventricular dysfunction, and heart failure, diabetes mellitus, and hypertension. Reduction of cardiovascular risk Evidence (summarized in Tables 16.13.4.9 and 16.13.4.10) supports the following therapies to reduce the risk of subsequent cardiovas- cular events: antiplatelet therapy (aspirin in a dose of 75 mg/day, clopidogrel 75 mg day); β-blockers in those without contraindica- tions; lipid lowering with 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins); ACE inhibitor or ARB, especially in those with left ventricular dysfunction and heart failure, although benefit is also possible in other patients with vas- cular disease (Table 16.13.4.10). Anticoagulants These are indicated in those with high risks of embolism due to left ventricular or atrial thrombus. There is evidence to support the use of anticoagulants in post-MI patients but no definitive evidence that such treatment is superior to aspirin therapy. Current trials are evaluating the role or oral antithrombins and oral anti-Xa inhibitors following ACS. Table 16.13.4.9 Estimated benefits of long-term secondary prophylactic treatment/intervention after MI Treatment/intervention Problems prevented per 1000 patient-

years of treatment All post-MI patients (unless specific contraindications exist) Aspirin (meta-analysis) 7 vascular deaths 9 nonfatal reinfarctions 3 nonfatal strokes Oral β-blocker 21 deaths 21 reinfarctions Statin (hyperlipidaemia, post-MI) 7 deaths 11 revascularizations 12 nonfatal MIs 3 strokes 4 congestive heart failure 13 angina Statin (average cholesterol, post-MI) 2 deaths 9 re-vascularizations 4 nonfatal MIs 2 strokes 4 unstable angina Smoking cessation (observational studies) 15 deaths 46 reinfarctions Post-MI patients with LVD or heart failure (additional treatment unless specific contraindications exist) ACE inhibitor (left ventricular ejection fraction ≤ 40%) 12 deaths 9 MIs 10 congestive heart failure (requiring hospital admission) ACE inhibitor (heart failure) 45 deaths 26 congestive heart failure (severe) LVD, left ventricular dysfunction. Sivers, F (1999). Evidence-based strategies for secondary prevention of coronary heart disease, 2nd edn. A&M Publishing, Guildford, Surrey.

section 16 Cardiovascular disorders 3652 Hormone replacement therapy (HRT) HRT is not indicated for risk reduction after ACS. When used to relieve menopausal symptoms, HRT is associated with a small increased risk of thrombotic events. Calcium channel blockers An overview of data from 19 000 patients, based on all randomized trials of acute infarction and unstable angina, suggests that calcium channel blockers are unlikely to reduce the rate of subsequent in- farct development, infarct size, or subsequent infarction. They may, however, have indications for the relief of angina (especially heart- rate-lowering calcium antagonists). Antiarrhythmic agents A review of the effects of antiarrhythmic agents (with the excep- tion of β-blockers) does not demonstrate a beneficial impact on mortality. Many have significant proarrhythmic complications and negative inotropic effects. FURTHER READING Antithrombotic Trialists Collaboration (2002). Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, mycocardial infarction, and stroke in high risk patients. BMJ, 324, 71–86. Antman EM, et al. (1996). Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med, 335, 1342–9. Antman EM, et al. (1999). Abciximab facilitates the rate and extent of thrombolysis: results of the thrombolysis in mycocardial infarction (TIMI) 14 trial. Circulation, 99, 2720–32. Antman EM, et al. (1999). Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave mycocardial in- farction. TIMI IIB–ESSENCE meta-analysis. Circulation, 100, 1602–8. Antman EM, et al. (2006). Enoxaparin versus unfractionated heparin with fibrinolysis for ST elevation mycocardial infarction. N Engl J Med, 354, 1477–88. Armstrong PW, et al. (1998). Acute coronary syndromes in the GUSTO-IIb trial: prognostic insights and impact of recurrent is- chemia. Circulation, 98, 1860–8. ASSENT-2 Investigators (1999). Single-bolus tenecteplase com- pared with front-loaded alteplase in acute mycocardial infarc- tion: the ASSENT-2 double-blind randomised trial. Lancet, 354, 716–22. ASSENT-3 Investigators (2001). Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated hep- arin: the ASSENT-3 randomised trial in acute mycocardial infarc- tion. Lancet, 358, 605–13. Bassand J-P, et al. (2007). Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J, 28, 1598–660. Bhatt DL, et al. (2004). Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. JAMA, 292, 2096–104. Bhatt DL, et al. (2006). Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med, 354, 1706–17. Table 16.13.4.10 Comparison of the treatment benefits from interventions to prevent cardiovascular events Problems/therapy Events prevented NNT* Severe hypertension (DBP 115–129 mm Hg) Death or stroke or MI 3 Coronary artery bypass surgery for left main stem stenosis Death 6 Aspirin for transient ischaemic attack Death or stroke 6 Statin for hyperlipidaemia,

post-MI/angina Death or nonfatal MI or CABG/PTCA or
cerebrovascular event 6 Warfarin for atrial fibrillation Stroke 7 ACE inhibitor for LV dysfunction post-MI CV death or hospitalization for CHF 10 Statin for average cholesterol post-MI (CARE trial) or stroke Death or nonfatal MI or CABG/PTCA 11 Aspirin post-MI CV death or stroke or MI 12 Statin for average/elevated cholesterol, post-MI/unstable angina (LIPID trial) Death or nonfatal MI or CABG/PTCA or stroke 15 B-blocker post-MI Death 20 ACE inhibitor for LV dysfunction CV death or hospitalization for CHF 21 ACE inhibitor for vascular disease (HOPE trial) Deaths 50 MI 42 Stroke 67 Statin for hypercholesterolaemia in primary prevention Death or nonfatal MI or CABG/PTCA or stroke 26 Mild hypertension (DBP 90–109 mm Hg) Death or stroke or MI 141 ACE, angiotensin-converting-enzyme; CABG, coronary artery bypass grafting; CARE, Cholesterol and Recurrent Events Trial; CHF, congestive heart failure; CV, cardiovascular; DBP, diastolic blood pressure; HOPE, Heart Outcomes Prevention Evaluation Trial; LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease Trial; LV, left ventricle; MI, myocardial infarction; NNT, estimated number of patients that need to be treated for 5 years to prevent one event; PTCA, percutaneous transluminal coronary angioplasty. Sivers, F (1999). Evidence-based strategies for secondary prevention of coronary heart disease, 2nd edn. A&M Publishing, Guildford, Surrey.

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