Chapter 2
Acute Coronary Syndromes

Definition

Acute coronary syndromes (ACS) describe the spectrum of disease in patients who present with clinical symptoms compatible with acute myocardial ischemia. ACS are a family of disorders that share similar pathogenic mechanisms and represent different points along a common continuum. These syndromes are caused by recent thrombus formation on preexisting coronary artery plaque leading to impaired myocardial oxygen supply. In this sense they differ from stable angina, which is usually precipitated by increased myocardial oxygen demand (e.g. exertion, fever, tachycardia) with background coronary artery narrowing (limitation of oxygen supply).

ACS have traditionally been classified into Q-wave myocardial infarction, non-Q wave myocardial infarction (NQMI), and unstable angina. More recently, classification has shifted and has become based on the initial electrocardiogram (ECG): patients are divided into three groups: those with ST-elevation (ST elevation myocardial infarction, STEMI), without ST elevation but with enzymatic evidence of myocardial damage (non-ST elevation MI, or NSTEMI), and those with unstable angina. Classification according to presenting ECG coincides with current treatment strategies, since patients presenting with ST elevation benefit from immediate reperfusion and should be treated with urgent revascularization or fibrinolytic therapy. Fibrinolytic agents have been shown to be ineffective in other patients with ACS. The discussion in this chapter will follow this schematization.

Pathophysiology

Myocardial ischemia results from an imbalance between oxygen supply and demand, and usually develops in the setting of obstructive atherosclerotic coronary artery disease, which limits blood supply. The pathophysiology of unstable coronary syndromes and myocardial infarction (MI) usually involves dynamic, partial or complete

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occlusion of an epicardial coronary artery because of acute intracoronary thrombus formation.

The common link between the various ACS is the rupture of a vulnerable, but previously quiescent, coronary atherosclerotic plaque [1].

Atherosclerotic plaques are composed of a lipid core, which includes cholesterol, oxidized low-density lipoproteins (LDL), macrophages, and smooth muscle cells, covered by a fibrous cap. Plaque rupture occurs when external mechanical forces exceed the tensile strength of the fibrous cap. After plaque rupture, the clinical consequences depend largely on the balance between prothrombotic and antithrombotic forces [2]. The lipid core contains tissue factor and other thrombogenic materials that lead to platelet activation and aggregation. Fibrinolytic factors such as tissue-plasminogen activator (t-PA), prostacyclin, and nitric oxide act to counteract the potential for thrombosis. Possible sequelae of plaque rupture include thrombus formation with total occlusion, with likely development of STEMI, dissolution of thrombus and healing of the fissure, with clinical stabilization, and subtotal occlusion, which can lead to either non-STEMI or unstable angina. A major factor in the outcome of plaque rupture is blood flow. With subtotal occlusion, high-grade stenosis, or vasospasm, thrombus begins to propagate downstream in the arterial lumen. In contrast to the initial thrombi, which are platelet rich, these thrombi contain large numbers of red cells enmeshed in a web of fibrin. The relative fibrin and platelet content of these lesions vary, with unstable angina/NSTEMI more often associated with platelet-rich lesions and STEMI associated with fibrin-rich clot, although it should be noted that all lesions contain some degree of both components [2]. The former would be expected to respond best to antiplatelet therapy, the latter to antithrombotic and fibrinolytic therapy.

Diagnosis

Signs and Symptoms

Patients with myocardial ischemia can present with chest pain or pressure, shortness of breath, palpitations, syncope, or sudden death. The pain of myocardial infarction is typically severe, constant, and retrosternal. The pain commonly spreads across the chest and may radiate to the throat or jaw, or down the arms. Its duration is most often more than 20 min. Diaphoresis, nausea, pallor, and anxiety are often present. Prodromal symptoms of myocardial ischemia occur in 20–60% of patients in the days preceding the infarct. The pain of unstable angina may be similar, although it is often milder.

Although these are the classic signs of infarction, it is important to recognize that the pain of myocardial infarction may sometimes be atypical in terms of location or perception. It may be epigastric, confined to the jaw, arms, wrists, or interscapular region, or perceived as burning or pressure.

The physical examination can be insensitive and nonspecific, but is useful in diagnosing specific complications and in excluding alternative diagnoses, both cardiovascular (such as aortic dissection or pericarditis) and non-cardiac. Distended jugular veins signal right ventricular diastolic pressure elevation, and the appearance of pulmonary crackles (in the absence of pulmonary disease) indicates elevated left ventricular filling pressures. Left ventricular failure is suggested by the presence of basal crackles, tachycardia, and tachypnea, and an S3 gallop, which usually indicates a large infarction with extensive muscle damage. A systolic murmur of mitral regurgitation may be present due to papillary muscle dysfunction or LV dilation. A pansystolic murmur may also result from an acute ventricular septal defect due to septal rupture.

The Electrocardiogram

The ECG abnormalities in myocardial ischemia depend on the extent and nature of coronary stenosis and the presence of collateral flow, but the pattern of ECG changes generally gives a guide to the area and extent of infarction (see Table 2.1). The number of leads involved broadly reflects the extent of myocardium involved.

Table 2.1 Localization of myocardial infarction by electrocardiography

Area of infarction	ECG leads	Infarct-related artery
Inferior	II, III, aVF	RCA or posterolateral branch of Cx
Anterior	V2–V4	LAD or diagonal branch of LAD
Lateral	I, aVL, V5, V6	Cx
True posterior	Tall R wave in V1	Posterolateral branch of Cx or posterior descending branch of RCA
Septal	V1–V3	LAD or diagonal branch of LAD
Anterolateral	I, aVL, V2–V6	Proximal LAD
Inferolateral	II, III, aVF, I, aVL, V5, V6	Proximal Cx or large RCA in right dominant system
Right ventricular	V3R, V4R	RCA

RCA right coronary artery; *LAD* left anterior descending coronary artery; *Cx* circumflex coronary artery

With acute total acute occlusion of a coronary artery, the first demonstrable ECG changes are peaked T waves changes in the leads reflecting the anatomic area of myocardium in jeopardy. As total occlusion continues, there is elevation of the ST segments in the same leads. With continued occlusion, there is an evolution of ECG abnormalities, with biphasic and then inverted T waves. If enough myocardium is infarcted, Q waves may appear. These represent unopposed initial depolarization forces away from the mass of infarcted myocardium, which has lost electrical activity and no longer contributes to the mean QRS voltage vector. The formation of Q waves is accompanied by a decrease in the magnitude of the R waves in the same leads, representing diminution of voltage in the mass of infarcted myocardium.

Indeed, loss of R wave voltage, revealed by comparison with previous ECG tracings, may be the only ECG evidence for the presence of permanent myocardial damage.

Extension of an inferior MI to the posterior segment can be detected by enhancement of R waves in the anterior chest leads, since these forces are now less balanced by opposite posterior forces. True posterior infarction can be subtle, since the only signs may be prominent R waves, tall upright T waves and depressed ST segments in leads V_1 and V_2. Involvement of the right ventricle in inferior MI is also not readily detected on the standard 12-lead ECG because of the small mass of the right ventricle relative to the left ventricle and because of the positioning of the standard precordial leads away from the right ventricle. RV infarction may be detected by ST elevation in recordings from right precordial leads, particularly V_{4R} [3].

A number of potential pitfalls can contribute to misinterpretation of the ECG. Many conditions can mimic STEMI and lead to false positives. Early repolarization pattern with up to 3 mm ST elevation in leads V1–V3 can be seen in healthy individuals, usually young men. Pre-excitation, bundle branch block, pericarditis, pulmonary embolism, subarachnoid hemorrhage, metabolic disturbances such as hyperkalemia, hypothermia, and LV aneurysm can be associated with ST elevation in the absence of acute myocardial ischemia. In pericarditis, ST segments may be elevated, but the elevation is diffuse and the morphology of the ST segments in pericarditis tends to be concave upward, while that of ischemia is convex. Pericarditis may also be distinguished from infarction by the presence of PR segment depression in the inferior leads (and also by PR segment in lead aVR) [4]. On the other hand, some conditions can lead to false negatives, including prior myocardial infarction, paced rhythm, and left bundle branch block (LBBB) when acute ischemia is not recognized. These pitfalls are common in the real world and in large clinical trials; when ECG from the GUSTO-IIB trial were reviewed by expert readers at a core lab, 15% of patients with STEMI were found to have been misclassified as NSTEMI, and these patients had a 21% higher mortality [5].

Cardiac Biomarkers

Measurement of enzymes released into the serum from necrotic myocardial cells after infarction can aid in the diagnosis of myocardial infarction [6]. The classic biochemical marker of acute myocardial infarction is elevation of the CPK MB isoenzyme. CPK MB begins to appear in the plasma 4–8 h after onset of infarction, peaks at 12–24 h and returns to baseline at 2–4 days. To be diagnostic for MI, the total plasma CPK value must exceed the upper limit of normal, and the MB fraction must exceed a certain value (usually >5%, but depends on the assay used).

These biomarkers have now been superseded by troponin T and I, parts of the troponin-tropomyosin complex in cardiac myocytes [7, 8]. Troponin elevations are highly specific for myocardial cellular injury. Troponin is also much more sensitive than CK-MB as a result of its higher concentration in cardiac muscle, and can detect even minor cardiac injury [8]. Even minor increases in circulating troponin values correlate with adverse outcomes in the short and long term [7]. In non-ST elevation

ACS elevated troponins not only predict increased risk, but also identify the patients most likely to benefit from more aggressive therapeutic strategies [9]. Troponins may not be elevated until 4–6 h after an acute event, and so critical therapeutic interventions should not be delayed pending assay results. Once elevated, troponin levels can remain high for days to weeks, limiting their utility to detect late reinfarction.

ST Elevation Myocardial Infarction

Symptoms suggestive of MI are usually similar to those of ordinary angina but are greater in intensity and duration. Nausea, vomiting, and diaphoresis may be prominent features, and stupor and malaise attributable to low cardiac output may occur. Compromised left ventricular function may result in pulmonary edema with development of pulmonary bibasilar crackles and jugular venous distention; a fourth heart sound can be present with small infarcts or even mild ischemia, but a third heart sound is usually indicative of more extensive damage.

Patients presenting with suspected myocardial ischemia should undergo a rapid evaluation, and should be treated with oxygen, sublingual nitroglycerin (unless systolic pressure is less than 90 mmHg), adequate analgesia, and aspirin, 160–325 mg orally [9, 10]. Opiates relieve pain, and also reduce anxiety, the salutary effects of which have been known for decades and should not be underestimated. A 12-lead ECG should be performed and interpreted expeditiously.

ST-segment elevation of at least 1 mV in 2 or more contiguous leads provides strong evidence of thrombotic coronary occlusion, the patient should be considered for immediate reperfusion therapy. The diagnosis of STEMI can be limited in the presence of preexisting LBBB or permanent pacemaker. Nonetheless, new LBBB with a compatible clinical presentation should be treated as acute myocardial infarction and treated accordingly. Indeed, recent data suggest that patients with STEMI and new LBBB may stand to gain greater benefit from reperfusion strategies than those with ST elevation and preserved ventricular conduction.

One possible treatment algorithm for treating patients with ST-elevation, MI is shown in Fig. 2.1.

Thrombolytic Therapy

Early reperfusion of an occluded coronary artery is indicated for all eligible candidates. Overwhelming evidence from multiple clinical trials demonstrates the ability of thrombolytic agents administered early in the course of an acute MI to reduce infarct size, preserve left ventricular function, and reduce short-term and long-term mortality [11, 12]. Patients treated early derive the most benefit, but it is reasonable to administer fibrinolytics to patients who have continued clinical or ECG evidence of ischemia. Indications and contraindications for thrombolytic therapy are listed in Table 2.2.

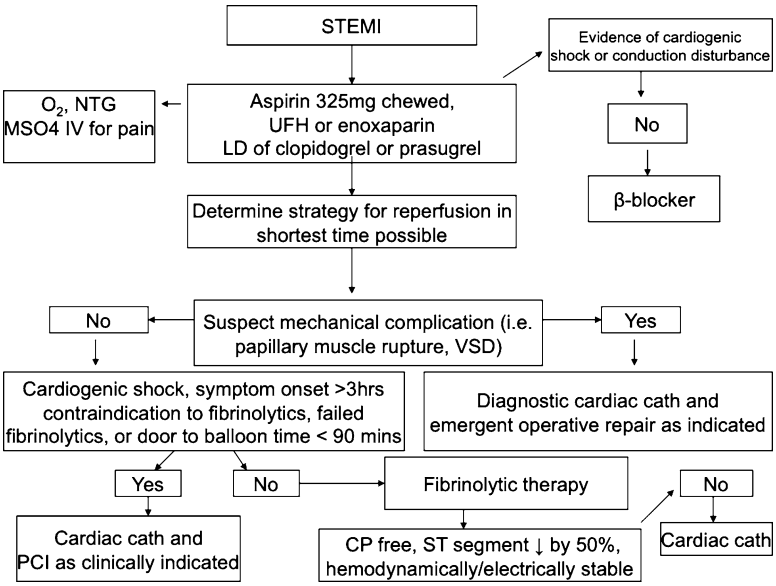

Fig. 2.1 Treatment algorithm for ST-elevation myocardial infarction. *CP* chest pain; *LD* loading dose; MSO_4 morphine; *NTG* nitroglycerin; O_2 oxygen; *UFH* unfractionated heparin; *VSD* ventricular septal defect

Table 2.2 Indications for and contraindications to thrombolytic therapy in acute myocardial infarction

Indications
Symptoms consistent with acute myocardial infarction
ECG showing 1-mm (0.1 mV) ST elevation in at least two contiguous leads, or new left bundle-branch block
Presentation within 12 h of symptom onset
Absence of contraindications
Contraindications
Absolute
Active internal bleeding
Intracranial neoplasm, aneurysm, or A–V malformation
Stroke or neurosurgery within 6 weeks
Trauma or major surgery within 2 weeks which could be a potential source of serious rebleeding
Aortic dissection
Relative
Prolonged (>10 min) or clearly traumatic cardiopulmonary resuscitation[a]
Noncompressible vascular punctures
Severe uncontrolled hypertension (>200/110 mmHg)[a]
Trauma or major surgery within 6 weeks (but more than 2 weeks)
Pre-existing coagulopathy or current use of anticoagulants with INR >2–3
Active peptic ulcer
Infective endocarditis
Pregnancy
Chronic severe hypertension

[a]Could be an absolute contraindication in low-risk patients with myocardial infarction

Because of the small, but nonetheless significant, risk of a bleeding complication, most notably intracranial hemorrhage, selection of patients with acute MI for administration of a thrombolytic agent should be undertaken with prudence and caution. High-risk patients are usually better treated with emergent coronary angiography with percutaneous coronary intervention (PCI).

Thrombolytic Agents

Streptokinase was the original fibrinolytic agent used in STEMI, but has not been superseded by t-PA, a recombinant protein that is more fibrin-selective than streptokinase and produces a higher early coronary patency rate (70–80%) [13, 14]. t-PA is given in an accelerated regimen consisting of a 15 mg bolus, 0.75 mg/kg (up to 50 mg) IV over the initial 30 min, and 0.5 mg/kg (up to 35 mg) over the next 60 min.

Reteplase (r-PA) is a deletion mutant of t-PA with an extended half-life, and is given as two 10 mg boluses 30 min apart. Reteplase was originally evaluated in angiographic trials that demonstrated improved coronary flow at 90 min compared to t-PA, but subsequent trials showed similar 30-day mortality rates [15].

Tenecteplase (TNK-tPA) is a genetically engineered t-PA mutant with amino acid substitutions that result in prolonged half-life, resistance to plasminogen-activator inhibitor-1, and increased fibrin specificity. TNK-tPA is given as a single bolus, adjusted for weight. A single bolus of TNK-tPA has been shown to produce coronary flow rates identical to those seen with accelerated t-PA, with equivalent 30-day mortality and bleeding rates [16].

Because these newer agents in general have equivalent efficacy and side effect profiles, at no current additional cost compared to t-PA, and because they are simpler to administer, they have gained popularity. An ideal fibrinolytic agent would have greater fibrin specificity, slower clearance from the circulation, and more resistance to plasma protease inhibitors, but has not yet been developed.

Primary Percutaneous Coronary Intervention in Acute Myocardial Infarction

The major advantages of primary PCI over thrombolytic therapy include a higher rate of normal (TIMI grade 3) flow, lower risk of intracranial hemorrhage and the ability to stratify risk based on the severity and distribution of coronary artery disease. Patients ineligible for fibrinolytic therapy should obviously be considered for primary PCI. In addition, data from several randomized trials have suggested that PCI is preferable to thrombolytic therapy for AMI patients at higher risk [17]. The largest of these trials is the GUSTO-IIB Angioplasty Substudy, which randomized 1,138 patients. At 30 days, there was a clinical benefit in the combined primary endpoints of death, nonfatal reinfarction, and nonfatal disabling stroke in the patients

treated with PTCA compared to t-PA, but no difference in the "hard" endpoints of death and myocardial infarction at 30 days [18].

Recent meta-analyses comparing direct PTCA with fibrinolytic therapy have suggested lower rates of mortality and reinfarction among those receiving direct PTCA [19, 20]. Thus, direct angioplasty, if performed in a timely manner (ideally within 60 min) by highly experienced personnel, may be the preferred method of revascularization since it offers more complete revascularization with improved restoration of normal coronary blood flow and detailed information about coronary anatomy [10]. There are certain subpopulations in which primary PCI is clearly preferred, and other populations in which the data are suggestive of benefit. These subsets are listed in Table 2.3.

Table 2.3 Situations in which primary angioplasty is preferred in acute myocardial infarction

Situations in which PTCA is clearly preferable to thrombolytics
Contraindications to thrombolytic therapy
Cardiogenic shock
Patients in whom uncertain diagnosis prompted cardiac catheterization which revealed coronary occlusion
Situations in which PTCA *may be* preferable to thrombolytics
Elderly patients (>75 years)
Hemodynamic instability
Patients with prior coronary artery bypass grafting
Large anterior infarction
Patients with a prior myocardial infarction

More important than the method of revascularization is the time to revascularization, and that this should be achieved in the most efficient and expeditious manner possible [21]. It is important to keep in mind that early, complete, and sustained reperfusion after myocardial infarction is known to decrease 30-day mortality. The preferred method for reperfusion in STEMI is PCI only, if it can be done within a timely manner. Practical considerations regarding transport to a PCI capable facility should be carefully reviewed before forgoing thrombolytics for PCI. Early recognition and diagnosis of STEMI are key to achieving the desired door-to-needle (or medical contact-to-needle) time for initiation of fibrinolytic therapy of 30 min or door-to-balloon (or medical contact-to-balloon) time for PCI under 90 min [10]. Achieving reperfusion in timely manner correlates with improvement in ultimate infarct size, left ventricular function, and survival [22, 23]. The ultimate goal is to restore adequate blood flow through the infarct-related artery to the infarct zone as well as to limit microvascular damage and reperfusion injury. The latter is accomplished with adjunctive and ancillary treatments that will be discussed below.

Coronary Stenting

Primary angioplasty for acute myocardial infarction results in a significant reduction in mortality but is limited by the possibility of abrupt vessel closure, recurrent

in-hospital ischemia, reocclusion of the infarct-related artery, and restenosis. The use of coronary stents has been shown to reduce restenosis and adverse cardiac outcomes in both routine and high-risk PCI [24]. The PAMI stent trial was designed to test the hypothesis that routine implantation of an intracoronary stent in the setting of myocardial infarction would reduce angiographic restenosis and improve clinical outcomes compared to primary balloon angioplasty alone. This large, randomized, multicenter trial involving 900 patients did not show a difference in mortality at 6 months but did show improvement in ischemia-driven target-vessel revascularization and less angina in the stented patients compared to balloon angioplasty alone [25]. Despite the lack of definite data demonstrating mortality benefit, virtually all of the trials investigating adjunctive therapy for STEMI have employed a strategy of primary stenting, and stenting has become the default strategy. Whether to use a bare metal stent (BMS) or a drug-eluting stent (DES) in acute MI is a question that has not yet been addressed definitively by clinical trials; selection is currently based on both patient and angiographic characteristics.

Adjunctive Therapies in STEMI

Aspirin

Aspirin is the best known and the most widely used of all the antiplatelet agents because of low cost and relatively low toxicity. Aspirin inhibits the production of thromboxane A2 by irreversibly acetylating the serine residue of the enzyme prostaglandin H_2 synthetase. Aspirin has been shown to reduce mortality in acute infarction to the same degree as fibrinolytic therapy, and its effects are additive to fibrinolytics [26]. In addition, aspirin reduces the risk of reinfarction [27, 28]. Unless contraindicated, all patients with a suspected ACS (STEMI, NSTEMI, unstable angina) should be given aspirin as soon as possible.

Thienopyridines

Thienopyridines are a class of oral antiplatelet agents that block the P2Y12 component of the adenosine diphosphate receptor and thus inhibit the activation and aggregation of platelets. Currently used thienopyridines include clopidogrel and prasugrel. Clopidogrel is converted in the liver to an active metabolite, and onset of inhibition of platelet aggregation (IPA) is dose-dependent, with a 300–600 mg loading dose achieving inhibition of platelet within 2 h.

Clopidogrel in combination with aspirin was shown to reduce the composite endpoint of infarct artery patency, death, or recurrent MI before angiography when given in conjunction with fibrinolytic therapy, heparin, and aspirin in the 3,491 patient CLARITY TIMI-28 trial [29]. When the 1,863 patients in CLARITY TIMI-28 that underwent PCI were examined, retreatment with clopidogrel in addition to

aspirin resulted in a significant reduction in cardiovascular death, MI, or stroke at 30 days (7.5 vs. 12.0%; $p=0.001$) without causing excess bleeding [30]. It is therefore routine practice to administer a loading dose of clopidogrel 300 or 600 mg prior to PCI.

Prasugrel is a recently approved thienopyridine that irreversibly binds to the P2Y12 component of the ADP receptor with a more rapid onset of action and more complete metabolism to the active metabolite, resulting in a higher level of IPA than clopidogrel. Prasugrel (given as a loading dose of 60 mg followed by maintenance dose of 10 mg in patients without renal insufficiency) decreased the combined endpoint of death, MI, and stroke compared to clopidogrel (300 mg load, followed by 75 mg maintenance) in the randomized, double-blind TRITON-TIMI 38 trial of 13,608 ACS patients undergoing PCI for ACS (3,534 STEMI, 10,074 UA/NSTEMI) [31]. The rate of major bleeding was higher in the prasugrel group, as was the rate of life-threatening bleeding. A post-hoc analysis of the trial showed harm with prasugrel patients with a history of TIA or stroke, and no benefit in patients older than 75 or weighing less than 60 kg, so caution is warranted in these groups [31].

Dual antiplatelet therapy with aspirin and thienopyridines is given to all patients undergoing PCI, as described above. However, data suggest that even patients not undergoing PCI benefit from the addition of clopidogrel to aspirin. In the COMMIT-CCS-2 trial, a broad population of 45,852 unselected patients with ST-elevation MI, only 54% of patients were treated with fibrinolytics, and most of the rest had no revascularization at all [32]. Clopidogrel added to aspirin decreased all-cause mortality from 8.1 to 7.5% ($p=0.03$), without increased bleeding in the clopidogrel group [32]. On the basis of these data, patients presenting with MI should be considered for a thienopyridine regardless of whether or not they underwent reperfusion therapy. The optimal duration of thienopyridine use in this population has yet to be defined.

Glycoprotein IIb/IIIa Receptor Antagonists

Glycoprotein IIb/IIIa receptor antagonists inhibit the final common pathway of platelet aggregation, blocking crosslinking of activated platelets, and are often used in percutaneous intervention [33]. Three agents are currently available. Abciximab is a chimeric murine-human monoclonal antibody Fab fragment with a short plasma half-life (10–30 min) but a long duration of biologic action. Tirofibanis is a small molecule, synthetic nonpeptide agent with a half-life of approximately 2.5 h and a lower receptor affinity than abciximab. Eptifibatide is a small molecule, cyclic heptapeptide with a 2-h half-life.

In the era of dual antiplatelet therapy using a thienopyridine and aspirin, the role of addition of a glycoprotein IIb/IIIa inhibitor in primary angioplasty for STEMI is uncertain. Studies such as the ADMIRAL and CADILLAC trials conducted prior to the use of dual antiplatelet therapy established the efficacy of abciximab in primary PCI (with or without stenting) in patients with STEMI [34, 35]. The results of recent clinical trials have raised questions about whether glycoprotein IIb/IIIa

antagonists have additional utility when added to dual antiplatelet therapy in patients with STEMI [36–38]. When either abciximab or placebo was added to 600 mg of clopidogrel randomized 800 patients undergoing primary stenting in the BRAVE-3 trial, there was no difference in either infarct size or the secondary composite endpoint of death, recurrent myocardial infarction, stroke, or urgent revascularization of the infarct-related artery [36]. Similar findings were seen in ON-TIME 2, in which tirofiban added to dual antiplatelet therapy in 984 patients with STEMI prior to transport for PCI improved resolution of ST segment elevation, but did not change the 30 day composite endpoint of death, recurrent MI, or urgent target-vessel revascularization [38]. The current guidelines suggest that when an STEMI patient is treated with a thienopyridine and aspirin plus an anticoagulant such as unfractionated heparin (UFH) or bivalirudin, the use of a glycoprotein IIb/IIIa inhibitor at the time of PCI may be beneficial, but cannot be recommended as routine [10].

Anticoagulants

Administration of full-dose heparin after thrombolytic therapy with t-PA is essential to diminish reocclusion after successful reperfusion [11, 26]. Dosing should be adjusted to weight, with a bolus of 60 U/kg up to a maximum of 4,000 U and an initial infusion rate of 12 U/kg/h up to a maximum of 1,000 U/h, with adjustment to keep the partial thromboplastin time (PTT) between 50 and 70 s. Heparin should be continued for 24–48 h. For patients undergoing PCI who have already been treated with aspirin and a thienopyridine, both UFH or bivalirudin (with or without prior heparin administration) are acceptable anticoagulant regimens [10].

Enoxaparin is a low-molecular weight heparin (LMWH) with established efficacy as an anticoagulant in patients with STEMI who have received fibrinolytics or are undergoing PCI [39, 40]. The standard dose of enoxaparin is a 30 mg intravenous bolus, followed 15 min later by subcutaneous injections of 1.0 mg/kg every 12 h. Patients with decreased creatinine clearance or those older than 75 are at higher risk of bleeding with standard dose enoxaparin. They should not receive a bolus but can receive a reduced dose of 0.75 mg/kg every 12 h. Patients undergoing PCI should have an additional bolus if the last dose was given 8–12 h prior. Maintenance dosing of enoxaparin should be given during the hospitalization (up to 8 days).

Bivalirudin is 20-amino acid peptide based on the structure of hirudin, a natural anticoagulant isolated from the saliva of the medicinal leech, *Hirudo medicinalis*; bivalirudin is a direct thrombin inhibitor that inhibits both clot-bound and circulating thrombin. It is administered as an initial bolus of 0.75 mg/kg, followed by a continuous infusion at 1.75 mg/kg/h for the duration of PCI, with adjustments for patients with renal dysfunction. Bivalirudin is probably as good as heparin plus a glycoprotein IIb/IIIa inhibitor in reducing ischemic events associated with unstable angina and/or non-ST elevation myocardial infarction (NSTEMI) with the added benefit of a reduction in bleeding [41]. The potential role of bivalirudin in

STEMI was clarified by HORIZONS-AMI trial, which randomized 3,602 patients with STEMI undergoing primary PCI to UFH plus a glycoprotein IIb/IIIa inhibitor or to bivalirudin alone (with provisional glycoprotein IIb/IIIa in the cardiac catheterization lab) [42]. Major adverse cardiac event (MACE) rates were equivalent, but use of bivalirudin alone was associated with a 40% reduction in bleeding [42]. Bivalirudin is also an excellent alternative to unfractionated or LMWH in patients with a history of heparin-induced thrombocytopenia.

Nitrates

Nitrates have a number of beneficial effects in acute myocardial infarction. They reduce myocardial oxygen demand by decreasing preload and afterload, and may also improve myocardial oxygen supply by increasing subendocardial perfusion and collateral blood flow to the ischemic region [43]. Occasional patients with ST elevation due to occlusive coronary artery spasm may have dramatic resolution of ischemia with nitrates. In addition to their hemodynamic effects, nitrates also reduce platelet aggregation. Despite these benefits, the GISSI-3 and ISIS-4 trials failed to show a significant reduction in mortality from routine acute and chronic nitrate therapies [44, 45]. Nonetheless, nitrates are still first-line agents for the symptomatic relief of angina pectoris and when myocardial infarction is complicated by congestive heart failure.

Beta Blockers

Beta blockers are beneficial both in the early management of myocardial infarction and as long-term therapy. In the pre-thrombolytic era, early intravenous atenolol was shown to significantly reduce reinfarction, cardiac arrest, cardiac rupture, and death [46]. In conjunction with thrombolytic therapy with t-PA, immediate β-blockade with metoprolol resulted in a significant reduction in recurrent ischemia and reinfarction, although mortality was not decreased [47].

The COMMIT-CCS 2 trial of 45,852 patients with acute MI had a factorial arm (the clopidogrel arm was discussed above) and randomized patients, 93% of whom had STEMI and 54% of whom were treated with lytics, to treatment with metoprolol (three intravenous injections of 5 mg each followed by oral 200 mg/day for up to 4 weeks) or placebo [48]. Surprisingly, there was no difference in the primary endpoint of death, reinfarction, or cardiac arrest by treatment group or in the co-primary endpoint of all-cause mortality by hospital discharge. Although reinfarction was lower in the metoprolol group, there was an increase in the risk of developing heart failure and cardiogenic shock, and death due to shock occurred more frequently in the metoprolol group [48]. Based on these findings, routine use of intravenous beta blockers in the absence of systemic hypertension is no longer recommended [10].

In contrast to the use of early, aggressive beta blocker therapy, the long-term use of beta blockers post-MI has favorable outcomes on mortality [46, 49]. The CArvedilol Post-infaRct survIval COntRolled evaluatioN (CAPRICORN) trial

randomized patients with systolic dysfunction already treated with angiotensin-converting enzyme (ACE) inhibitors after MI to carvedilol or placebo, and showed decreased cardiovascular mortality as well as a decrease in the composite outcome of all-cause mortality or nonfatal MI [50]. This study supports the claim that beta blocker therapy after acute MI reduces mortality irrespective of reperfusion therapy or ace inhibitor use. Relative contraindications to oral beta blockers include heart rate less than 60 bpm, systolic arterial pressure less than 100 mmHg, moderate or severe LV failure, signs of peripheral hypoperfusion, shock, PR interval greater than 0.24 s, second or third-degree AV block, active asthma, or reactive airway disease [10]. Diabetes mellitus is not a contraindication.

Lipid-Lowering Agents

Extensive epidemiologic, laboratory, and clinical evidence provide a convincing relationship linking cholesterol and coronary artery disease. Total cholesterol level has been linked to the development of CAD events with a continuous and graded relation, with a close association with LDL cholesterol [51]. Most of this risk is due to LDL cholesterol. Numerous large primary and secondary prevention trials have shown that LDL cholesterol lowering is associated with a reduced risk of coronary disease events. Earlier lipid-lowering trials used bile-acid sequestrants (cholestyramine), fibric acid derivatives (gemfibrozil and clofibrate), or niacin, in addition to diet, achieving a reduction in total cholesterol of 6–15%, accompanied by a consistent trend toward a reduction in fatal and nonfatal coronary events [52].

HMG-CoA reductase inhibitors (statins) produce larger reductions in cholesterol, with more impressive clinical results. Statins have been demonstrated to decrease the rate of adverse ischemic events and mortality when used both as primary prevention in high-risk patients [53, 54], and as secondary prevention in patients with documented CAD [55–57]. The goal of treatment is an LDL cholesterol level less than 70–100 mg/dL [58], although there appears to be a linear relationship between LDL levels and events, and many clinicians recommend an LDL goal of <70 mg/dL, especially for secondary prevention [59]. Maximum benefit may require management of other lipid abnormalities (elevated triglycerides, low HDL cholesterol) and treatment of other atherogenic risk factors.

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors are clearly beneficial in patients with congestive heart failure. ACE inhibitors were shown to decrease mortality in the SAVE trial, in which patients with left ventricular dysfunction (ejection fraction <40%) after MI had a 21% improvement in survival after treatment with the ACE inhibitor captopril [60]. A smaller but still significant reduction in mortality was seen when all patients were treated with captopril in the ISIS-4 study [45]. The mechanisms responsible for the benefits of ACE inhibitors probably include limitation in the progressive

left ventricular dysfunction and enlargement (remodeling) that often occur after infarction, but a reduction in ischemic events was seen as well.

ACE inhibition should be started early, preferably within the first 24 h after infarction. Immediate intravenous ACE inhibition with enalaprilat has not been shown to be beneficial [61]. Patients should be started on low doses of oral agents (captopril 6.25 mg thrice daily) and rapidly increased to the range demonstrated beneficial in clinical trials (captopril 50 mg thrice daily, enalapril 10–20 mg twice daily, lisinopril 10–20 mg once daily, or ramipril 10 mg once daily).

Calcium Channel Blockers

Randomized clinical trials have not demonstrated that routine use of calcium channel blockers improves survival after myocardial infarction. In fact, meta-analyses suggest that high doses of the short-acting dihydropyridine nifedipine increase mortality in myocardial infarction [62]. Adverse effects of calcium channel blockers include bradycardia, atrioventricular block, and exacerbation of heart failure. The relative vasodilating, negative inotropic effects, and conduction system effects of the various agents must be considered when they are employed in this setting. Diltiazem is the only calcium channel blocker that has been proven to have tangible benefits, reducing reinfarction and recurrent ischemia in patients with non-Q-wave infarctions who do not have evidence of congestive heart failure [63].

Calcium channel blockers may be useful for patients whose postinfarction course is complicated by recurrent angina, because these agents not only reduce myocardial oxygen demand but also inhibit coronary vasoconstriction. For hemodynamically stable patients, diltiazem can be given, starting at 60–90 mg orally every 6–8 h. In patients with severe left ventricular dysfunction, long-acting dihydropyridines without prominent negative inotropic effects such as amlodipine, nicardipine, or the long-acting preparation of nifedipine may be preferable; increased mortality with these agents has not been demonstrated.

Antiarrhythmic Therapy

A major purpose for admitting MI patients to the ICU is to monitor for and prevent malignant arrhythmias. Ventricular extrasystoles are common after MI and are a manifestation of electrical instability of peri-infarct areas. The incidence of sustained ventricular tachycardia or fibrillation is highest in the first 3–4 h, but these arrhythmias may occur at any time. Malignant ventricular arrhythmias may be heralded by frequent premature ventricular contractions (PVCs), complex ectopy (couplets, multiform PVCs), and salvos of nonsustained ventricular tachycardia. However, malignant arrhythmia may occur suddenly without these preceding "warning" arrhythmias. Based on these pathophysiologic considerations, prophylactic use of intravenous lidocaine even in the absence of ectopy has been advocated, but even though lidocaine decreases the frequency of PVCs and of early ventricular fibrillation, overall

mortality is not decreased. In fact, meta-analyses of pooled data have demonstrated increased mortality from the routine use of lidocaine [64], and so its routine prophylactic administration is no longer recommended [10].

Lidocaine infusion may be used after an episode of sustained ventricular tachycardia or ventricular fibrillation, and might be considered in patients with nonsustained ventricular tachycardia. Lidocaine is administered as a bolus of 1 mg/kg (not to exceed 100 mg), followed by a second bolus of 0.5 mg/kg, 10 min later, along with an infusion at 1–3 mg/min. Lidocaine is metabolized by the liver, and so lower doses should be given in the presence of liver disease, in the elderly, and in patients who have congestive heart failure severe enough to compromise hepatic perfusion. Toxic manifestations primarily involve the central nervous system, and can include confusion, lethargy, slurred speech, and seizures. Because the risk of malignant ventricular arrhythmias decreases after 24 h, lidocaine is usually discontinued after this point. For prolonged infusions, monitoring of lidocaine levels (therapeutic between 1.5 and 5 g/mL) is occasionally useful.

Intravenous amiodarone is an alternative to lidocaine for ventricular arrhythmias. Amiodarone is given as a 150 mg IV bolus over 10 min, followed by 1 mg/min for 6 h, then 0.5 mg/min for 18 h.

Perhaps the most important point in the prevention and management of arrhythmias after acute myocardial infarction is correcting hypoxemia, and maintaining normal serum potassium and magnesium levels. Serum electrolytes should be followed closely, particularly after diuretic therapy. Magnesium depletion is also a frequently overlooked cause of persistent ectopy [65]. The serum magnesium level, even if it is within normal limits, may not reflect myocardial concentrations. Routine administration of magnesium has not been shown to reduce mortality after acute myocardial infarction [45], but empiric administration of 2 g of intravenous magnesium in patients with early ventricular ectopy is probably a good idea.

Non-ST Elevation Myocardial Infarction

The key to initial management of patients with ACS without ST elevation is risk stratification. The overall risk of a patient is related to both the severity of preexisting heart disease and the degree of plaque instability. Risk stratification is an ongoing process, which begins with hospital admission and continues through discharge.

Braunwald has proposed a classification for unstable angina based on severity of symptoms and clinical circumstances for risk stratification [66]. The risk of progression to acute MI or death in ACS increases with age. ST segment depression on the ECG identifies patients at higher risk for clinical events [66]. Conversely, a normal ECG confers an excellent short-term prognosis. Biochemical markers of cardiac injury are also predictive of outcome. Elevated levels of troponin T are associated with an increased risk of cardiac events and a higher 30-day mortality, and in fact, were more strongly correlated with 30-day survival than ECG category or CPK

MB level in an analysis of data from the GUSTO-II trial [67]. Conversely, low levels are associated with low event rates, although the absence of troponin elevation does not guarantee a good prognosis and is not a substitute for good clinical judgment.

Antiplatelet Therapy

As previously noted, aspirin is a mainstay of therapy for ACS. Both the VA Cooperative Study Group [27] and the Canadian multicenter trial [68] showed that aspirin reduces the risk of death or myocardial infarction by approximately 50% in patients with unstable angina or NQMI. Aspirin also reduces events after resolution of an ACS, and should be continued indefinitely.

As in patients with STEMI, patients with NSTEMI have been shown to benefit from the use of a thienopyridine in addition to aspirin. In the CURE trial, 12,562 patients were randomized to receive clopidogrel or placebo in addition to standard therapy with aspirin, within 24 h of unstable angina symptoms [69]. Clopidogrel significantly reduced the risk of myocardial infarction, stroke, or cardiovascular death from 11.4 to 9.3% ($p<0.001$) [69]. It should be noted that this benefit came with a 1% absolute increase in major, non-life threatening bleeds ($p=0.001$) as well as a 2.8% absolute increase in major/life-threatening bleeds associated with CABG within 5 days ($p=0.07$) [69]. Because percutaneous revascularization was performed on only 23% of patients in the CURE trial during the initial hospitalization, the study provides convincing evidence that clopidogrel is beneficial in patients who are managed medically in addition to those undergoing PCI.

The TRITON-TIMI 38 trial comparing prasugrel to clopidogrel included 10,074 UA/NSTEMI patients as well as 3,534 STEMI patients [31]. The primary endpoint – cardiovascular death, nonfatal MI, and nonfatal stroke – was significantly lower in the prasugrel group at the expense of increased bleeding in the prasugrel-treated patients [31]. The dosing regimen of prasugrel for patients with UA/NSTEMI is identical to the dose used in STEMI patients (60 mg load and 10 mg maintenance); it should not be used in patients with a history of stroke or TIA and it should be used with caution in patients over the age of 75 or with a weight less than 60 kg [31].

Ticagrelor, a non-thienopyridine platelet inhibitor that binds reversibly to the P2Y12 platelet receptor, exhibited greater efficacy than clopidogrel in the PLATO trial [70]. Major bleeding events did not differ between the groups, although bleeding not related to coronary artery bypass grafting occurred more often with ticagrelor. Both prasugrel and ticagrelor may have a quicker onset of action than clopidogrel and may prove to be very useful in patients who are clopidogrel-resistant or have recurrent cardiovascular events while on clopidogrel.

The current guidelines recommend a loading dose of 300–600 mg of clopidogrel in patients with UA/NSTEMI followed by 75 mg daily. Prasugrel should be administered as a 60 mg loading dose followed by a 10 mg a day maintenance dose [10]. The duration of clopidogrel may depend on whether or not the patient has received a stent.

Typically patients who received BMSs for at least 4 weeks, and those with DESs should remain on clopidogrel for at least 12 months [9, 10]. For DES, however, adequate long-term data have not been sufficient to formulate a definite recommendation on the duration of therapy.

Anticoagulant Therapy

Heparin is an important component of primary therapy for patients with unstable coronary syndromes without ST elevation. When added to aspirin, heparin has been shown to reduce refractory angina and the development of myocardial infarction [28], and a meta-analysis of the available data indicates that addition of heparin reduces the composite end point of death or MI [71].

Heparin, however, can be difficult to administer, because the anticoagulant effect is unpredictable in individual patients; this is due to heparin's binding to heparin-binding proteins, endothelial and other cells, and heparin inhibition by several factors released by activated platelets. Therefore, the activated partial thromboplastin time (APTT) must be monitored closely. The potential for heparin-associated thrombocytopenia is also a safety concern.

LMWHs, which are obtained by depolymerization of standard heparin and selection of fractions with lower molecular weight, have several advantages. Because they bind less avidly to heparin-binding proteins, there is less variability in the anticoagulant response and a more predictable dose–response curve, obviating the need to monitor APTT. The incidence of thrombocytopenia is lower (but not absent, and patients with heparin-induced thrombocytopenia with anti-heparin antibodies cannot be switched to LMWH). Finally, LMWHs have longer half-lives, and can be given by subcutaneous injection. These properties make treatment with LMWH at home after hospital discharge feasible. Since evidence suggests that patients with unstable coronary syndromes may remain in a hypercoagulable state for weeks or months, the longer duration of anticoagulation possible with LMWH may be desirable.

Several trials have documented beneficial effects of LMWH therapy in unstable coronary syndromes. The ESSENCE and TIMI 11B trials showed that the LMWH enoxaparin reduced the combined endpoint of death, MI, or recurrent ischemia compared to UFH [72, 73]. The SYNERGY trial found no difference in efficacy between enoxaparin and UFH in high-risk patients, with a slightly higher major bleeding rate [74]. Although LMWH are substantially easier to administer than standard heparin, and long-term administration can be contemplated, they are also more expensive. Specific considerations with the use of LMWH include decreased clearance in renal insufficiency and the lack of a commercially available test to measure the anticoagulant effect. LMWH should be given strong consideration in high-risk patients, but whether substitution of LMWH for heparin in all patients is cost-effective is uncertain.

Direct Thrombin Inhibitors

Bivalirudin is a direct thrombin inhibitor, that, unlike heparin, binds directly to both circulating and clot bound thrombin and inhibits the conversion of fibrinogen to fibrin. Direct thrombin inhibitors have several theoretical advantages over heparin, including lack of binding to plasma proteins and lack of binding to platelet factor 4, which avoids the problem of heparin-induced thrombocytopenia.

The REPLACE 2 trial compared bivalirudin plus provisional glycoprotein IIb/IIIa inhibitor to UFH plus planned glycoprotein IIb/IIIa inhibitor in 6,010 patients undergoing planned or urgent PCI, and although 6-month event rates with bivalirudin were slightly higher, bleeding was lower and the prespecified composite endpoint met statistical criteria for non-inferiority [41]. Similar findings were seen in the ACUITY trial, which compared heparin with glycoprotein IIb/IIIa inhibition to bivalirudin with glycoprotein IIb/IIIa inhibition to bivalirudin alone with provisional glycoprotein IIb/IIIa inhibition [37]. Bivalirudin alone compared with heparin plus GP IIb/IIIa inhibitors resulted in noninferior rates of composite ischemia, and reduced major bleeding, but patients who got bivalirudin alone without a thienopyridine prior to angiograpy or PCI had a higher rate of ischemic events. Bilvalirudin should not be administered alone, particularly if there is going to be a delay to angiography.

Glycoprotein IIb/IIIa Antagonists

The benefits of glycoprotein IIb/IIIa inhibitors as adjunctive treatment in patients with ACS have been shown in several trials, with a relative risk reduction of 11% in NSTEMI by meta-analysis [33]. Additional analysis suggests that glycoprotein IIb/IIIa inhibition is most effective in high-risk patients, those with either ECG changes or elevated troponin [33]. The benefits appear to be restricted to patients undergoing percutaneous intervention, which may not be entirely surprising.

These studies were conducted prior to the era of dual antiplatelet therapy. As mentioned previously, it is common practice to administer a thienopyridine and aspirin in conjunction with an anticoagulant in patients with ACS. For patients with UA/NSTEMI undergoing an initial invasive approach, the most recent data suggests that either a glycoprotein IIb/IIIa inhibitor or a thienopyridine can be given in addition to aspirin and an anticoagulant if the patient is considered low risk (troponin negative). However, if the patient is considered high-risk (troponin positive, recurrent ischemic features) both a glycoprotein IIb/IIIa inhibitor and clopidogrel can be given in addition to aspirin and an anticoagulant [9, 10].

Interventional Management

Cardiac catheterization may be undertaken in patients presenting with symptoms suggestive of unstable coronary syndromes for one of several reasons: to assist with risk

stratification, as a prelude to revascularization, and to exclude significant epicardial coronary stenosis as a cause of symptoms when the diagnosis is uncertain.

An early invasive approach has now been compared to a conservative approach in several prospective studies. Two earlier trials, the TIMI IIIb study [75] and the VANQWISH trial [76], were negative, but the difference in the number of patients who had been revascularized by the end of these trials was small. In addition, these trials were performed before widespread use of coronary stenting and platelet glycoprotein IIb/IIIa inhibitors, both of which have now been shown to improve outcomes after angioplasty.

The FRISC II, TACTICS-TIMI 18, and RITA III trials each demonstrated that the composite endpoint of death, MI, or refractory angina was less frequent among patients who were randomized to the early invasive strategy, with the greatest benefit observed in high-risk patients: those with elevated cardiac biomarkers, extensive ST segment depression, and hemodynamic features suggestive of large infarctions [77–79].

The ICTUS trial enrolled 1,200 patients with UA/NSTEMI who were initially treated with aspirin and enoxaparin before randomized assignment to one of two strategies: an early invasive strategy within 48 h that included abciximab for PCI or a selective invasive strategy [80]. Patients who were assigned the latter strategy were selected for coronary angiography only if they had refractory angina despite medical treatment, hemodynamic or rhythm instability, or predischarge exercise testing demonstrated clinically significant ischemia. The trial showed no reduction in the composite endpoints of death, nonfatal MI, or rehospitalization for angina at 1 year among patients who were assigned to the early invasive strategy. After 4 years of follow-up, the rates of death and MI among the two groups of patients remained similar [80]. It is not clear why the results of ICTUS differ from previous trials. The more recent timing of intervention in acute coronary syndromes (TIMACS) study randomized 3,031 patients with UA/NSTEMI to undergo cardiac catheterization either within 24 h of symptom onset or more than 36 h later [81]. The median time to angiography was 14 h for the early intervention group and 50 h for the delayed-intervention group. There was no difference between the groups in the composite endpoint of death, myocardial infarction, or stroke at 6 months.

Risk stratification is the key to managing patients with NSTEMI ACS. One possible algorithm for managing patients with NSTEMI is shown in Fig. 2.2. An initial strategy of medical management with attempts at stabilization is warranted in patients with lower risk, but patients at higher risk should be considered for cardiac catheterization. Pharmacologic and mechanical strategies are intertwined in the sense that selection of patients for early revascularization will influence the choice of antiplatelet and anticoagulant medication. When good clinical judgment is employed, early coronary angiography in selected patients with ACS can lead to better management and lower morbidity and mortality.

It is important to be aware that if a fibrinolytic agent was chosen as a means of reperfusion in ST-segment elevation MI, success is by no means guaranteed. Should the patient continue to show clinical signs (ongoing chest pain, hemodynamic or electrical instability) or ECG evidence (failure of resolution of ST-segment elevation by >50%) of ongoing cardiac ischemia, immediate transfer to a PCI capable site

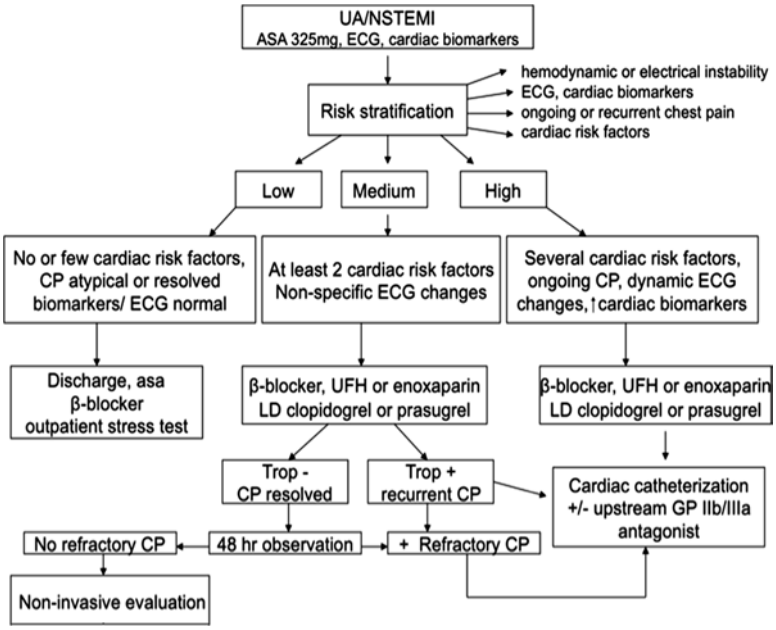

Fig. 2.2 Possible treatment algorithm for patients with non-ST elevation acute coronary syndromes. *ASA* aspirin; *CP* chest pain; *ECG* electrocardiogram; *GPIIb/IIIa* glycoprotein IIb/IIIa antagonist; *LD* loading dose; *Trop* troponin; *UFH* unfractionated heparin

should be initiated. In an effort to address the question of how to best handle the possibility of failed fibrinolysis, and when exactly to perform cardiac catheterization and PCI, the TRANSFER-AMI study randomized 1,059 high-risk patients with STEMI given fibrinolytic therapy at centers without PCI capability to immediate transfer to a PCI capable institution vs. usual care [82]. The trial demonstrated benefit with early PCI following thrombolytic therapy for ST-segment elevation MI, regardless of whether lytic therapy was effective in reperfusion. This strategy, termed "pharmacoinvasive," resulted in a decrease in the primary endpoint of death, MI, heart failure, severe recurrent ischemia, or shock by 6.2% (11.0 vs. 17.2%) as well as secondary endpoints of reinfarction and recurrent ischemia when compared to patients receiving standard treatment [82].

Complications of Acute Myocardial Infarction

Postinfarction Ischemia

Causes of ischemia after infarction include decreased myocardial oxygen supply due to coronary reocclusion or spasm, mechanical problems that increase myocardial oxygen demand, and extracardiac factors such as hypertension, anemia, hypotension,

or hypermetabolic states. Nonischemic causes of chest pain, such as postinfarction pericarditis and acute pulmonary embolism, should also be considered.

Immediate management includes aspirin, β-blockade, IV nitroglycerin, heparin, and diagnostic coronary angiography. Post-infarction angina is an indication for revascularization. PTCA can be performed if the culprit lesion is suitable. CABG should be considered for patients with left main disease, three-vessel disease, and those unsuitable for PTCA. If the angina cannot be controlled medically or is accompanied by hemodynamic instability, an intra-aortic balloon pump should be inserted.

Ventricular Free Wall Rupture

Ventricular free wall rupture typically occurs during the first week after infarction. The classic patient is elderly, female, and hypertensive. Early use of thrombolytic therapy reduces the incidence of cardiac rupture, but late use may actually increase the risk. Pseudoaneursym with leakage may be heralded by chest pain, nausea, and restlessness, but frank free wall rupture presents as a catastrophic event with shock and electromechanical dissociation. Pericardiocentesis may be necessary to relieve acute tamponade, ideally in the operating room, since the pericardial effusion may be tamponading the bleeding. Salvage is possible with prompt recognition, pericardiocentesis to relieve acute tamponade, and thoracotomy with repair [83]. A pericardial effusion may be seen by echocardiography: contrast ventriculography is not a sensitive way to detect a small rupture.

Ventricular Septal Rupture

Septal rupture presents as severe heart failure or cardiogenic shock, with a pansystolic murmur and parasternal thrill. The hallmark finding is a left-to-right intracardiac shunt ("step-up" in oxygen saturation from right atrium to right ventricle), but the diagnosis is most easily made with echocardiography.

Rapid institution of intra-aortic balloon pumping and supportive pharmacologic measures is necessary. Operative repair is the only viable option for long-term survival. The timing of surgery has been controversial, but most authorities now suggest that repair should be undertaken early, within 48 h of the rupture [84].

Acute Mitral Regurgitation

Ischemic mitral regurgitation is usually associated with inferior myocardial infarction and ischemia or infarction of the posterior papillary muscle, although anterior papillary muscle rupture can also occur. Papillary muscle rupture has a bimodal

incidence, either within 24 h or 3–7 days after acute myocardial infarction, and usually presents dramatically, with pulmonary edema, hypotension, and cardiogenic shock. When a papillary muscle ruptures, the murmur of acute mitral regurgitation may be limited to early systole because of rapid equalization of pressures in the left atrium and left ventricle. More importantly, the murmur may be soft or inaudible, especially when cardiac output is low [85].

Echocardiography is extremely useful in the differential diagnosis, which includes free wall rupture, ventricular septal rupture, and infarct extension with pump failure. Hemodynamic monitoring with pulmonary artery catheterization may also be helpful. Management includes afterload reduction with nitroprusside and intra-aortic balloon pumping as temporizing measures. Inotropic or vasopressor therapy may also be needed to support cardiac output and blood pressure. Definitive therapy, however, is surgical valve repair or replacement, which should be undertaken as soon as possible since clinical deterioration can be sudden [85–87].

Right Ventricular Infarction

Right ventricular infarction occurs in up to 30% of patients with inferior infarction and is clinically significant in 10% [88]. The combination of a clear chest X-ray with jugular venous distention in a patient with an inferior wall MI should lead to the suspicion of a coexisting right ventricular infarct. The diagnosis is substantiated by demonstration of ST segment elevation in the right precordial leads (V_{3R}–V_{5R}) or by characteristic hemodynamic findings on right heart catheterization (elevated right atrial and right ventricular end-diastolic pressures with normal to low pulmonary artery occlusion pressure and low cardiac output). Echocardiography can demonstrate depressed right ventricular contractility [89]. Patients with cardiogenic shock on the basis of right ventricular infarction have a better prognosis than those with left-sided pump failure [88]. This may be due in part to the fact that right ventricular function tends to return to normal over time with supportive therapy [90], although such therapy may need to be prolonged.

In patients with right ventricular infarction, right ventricular preload should be maintained with fluid administration. In some cases, however, fluid resuscitation may increase pulmonary capillary occlusion pressure but may not increase cardiac output, and overdilation of the right ventricle can compromise left ventricular filling and cardiac output [90]. Inotropic therapy with dobutamine may be more effective in increasing cardiac output in some patients, and monitoring with serial echocardiograms may also be useful to detect right ventricular overdistention [90]. Maintenance of atrioventricular synchrony is also important in these patients to optimize right ventricular filling [89]. For patients with continued hemodynamic instability, intra-aortic balloon pumping may be useful, particularly because elevated right ventricular pressures and volumes increase wall stress and oxygen consumption and decrease right coronary perfusion pressure, exacerbating right ventricular ischemia.

Reperfusion of the occluded coronary artery is also crucial. A study using direct angioplasty demonstrated that restoration of normal flow resulted in dramatic recovery of right ventricular function and a mortality rate of only 2%, whereas unsuccessful reperfusion was associated with persistent hemodynamic compromise and a mortality of 58% [91].

Cardiogenic Shock

Epidemiology and Pathophysiology

Cardiogenic shock, resulting either from left ventricular pump failure or from mechanical complications, represents the leading cause of in-hospital death after myocardial infarction [92]. Despite advances in management of heart failure and acute myocardial infarction, until very recently, clinical outcomes in patients with cardiogenic shock have been poor, with reported mortality rates ranging from 50 to 80% [93]. Patients may have cardiogenic shock at initial presentation, but shock often evolves over several hours [94, 95].

Cardiac dysfunction in patients with cardiogenic shock is usually initiated by myocardial infarction or ischemia. The myocardial dysfunction resulting from ischemia worsens that ischemia, creating a downward spiral (Fig. 2.3). Compensatory mechanisms that retain fluid in an attempt to maintain cardiac output may add to the vicious cycle and further increase diastolic filling pressures. The interruption of this cycle of myocardial dysfunction and ischemia forms the basis for the therapeutic regimens for cardiogenic shock.

Initial Management

Maintenance of adequate oxygenation and ventilation are critical. Many patients require intubation and mechanical ventilation, if only to reduce the work of breathing and facilitate sedation and stabilization before cardiac catheterization. Electrolyte abnormalities should be corrected, and morphine used to relieve pain and anxiety, thus reducing excessive sympathetic activity and decreasing oxygen demand, preload, and afterload. Arrhythmias and heart block may have major effects on cardiac output, and should be corrected promptly with antiarrhythmic drugs, cardioversion, or pacing.

The initial approach to the hypotensive patient should include fluid resuscitation unless frank pulmonary edema is present. Patients are commonly diaphoretic and relative hypovolemia may be present in as many as 20% of patients with cardiogenic shock. Fluid infusion is best initiated with predetermined boluses titrated to clinical endpoints of heart rate, urine output and blood pressure. Ischemia produces diastolic as well as systolic dysfunction, and thus elevated filling pressures may be necessary to maintain stroke volume in patients with cardiogenic shock. Patients who do not respond rapidly to initial fluid boluses or those with poor physiologic

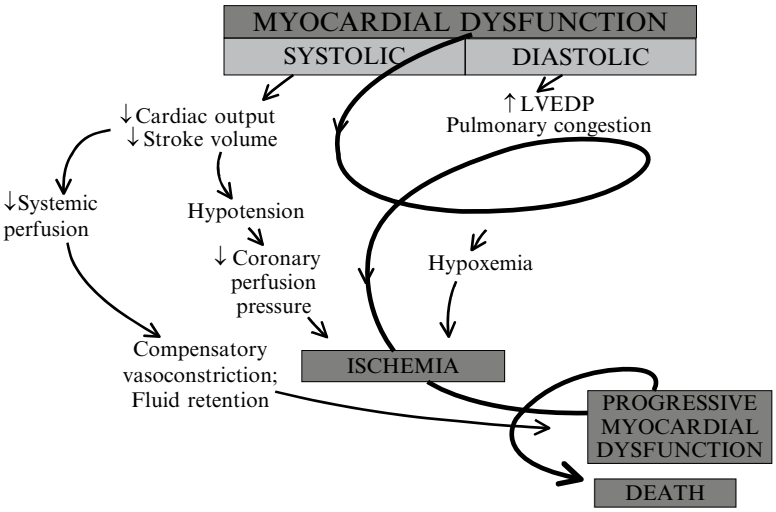

Fig. 2.3 The "downward spiral" in cardiogenic shock. Stroke volume and cardiac output fall with left ventricular (LV) dysfunction, producing hypotension and tachycardia that reduce coronary blood flow. Increasing ventricular diastolic pressure reduces coronary blood flow, and increased wall stress elevates myocardial oxygen requirements. All of these factors combine to worsen ischemia. The falling cardiac output also compromises systemic perfusion. Compensatory mechanisms include sympathetic stimulation and fluid retention to increase preload. These mechanisms can actually worsen cardiogenic shock by increasing myocardial oxygen demand and afterload. Thus, a vicious circle can be established. LVEDP, left ventricular end-diastolic pressure. Adapted with permission from Hollenberg et al. [92]

reserve should be considered for invasive hemodynamic monitoring. Optimal filling pressures vary from patient to patient; hemodynamic monitoring can be used to construct a Starling curve at the bedside, identifying the filling pressure at which cardiac output is maximized. Maintenance of adequate preload is particularly important in patients with right ventricular infarction.

When arterial pressure remains inadequate, therapy with vasopressor agents may be required to maintain coronary perfusion pressure. Maintenance of adequate blood pressure is essential to break the vicious cycle of progressive hypotension with further myocardial ischemia. Dopamine increases both blood pressure and cardiac output, but recent data suggest that norepinephrine may be a superior agent in patients with cardiogenic shock [96]. Phenylephrine, a selective alpha-1 adrenergic agonist, may be useful when tachyarrhythmias limit therapy with other vasopressors. Vasopressor infusions need to be titrated carefully in patients with cardiogenic shock to maximize coronary perfusion pressure with the least possible increase in myocardial oxygen demand. Hemodynamic monitoring, with serial measurements of cardiac output, filling pressures (and other parameters, such as mixed venous oxygen saturation) allows for titration of the dosage of vasoactive agents to the minimum dosage required to achieve the chosen therapeutic goals [97].

Following initial stabilization and restoration of adequate blood pressure, tissue perfusion should be assessed. If tissue perfusion remains inadequate, inotropic support or intra-aortic balloon pumping should be initiated. If tissue perfusion is adequate but significant pulmonary congestion remains, diuretics may be employed. Vasodilators can be considered as well, depending on the blood pressure.

In patients with inadequate tissue perfusion and adequate intravascular volume, cardiovascular support with inotropic agents should be initiated. Dobutamine, a selective β1-adrenergic receptor agonist, can improve myocardial contractility and increase cardiac output, and is the initial agent of choice in patients with systolic pressures greater than 80 mmHg. Dobutamine may exacerbate hypotension in some patients, and can precipitate tachyarrhythmias. Use of dopamine may be preferable if systolic pressure is less than 80 mmHg, although tachycardia and increased peripheral resistance may worsen myocardial ischemia. Phosphodiesterase inhibitors such as milrinone are less arrhythmogenic than catecholamines, but have the potential to cause hypotension, and should be used with caution in patients with tenuous clinical status. Levosimendan, a calcium sensitizer, has both inotropic and vasodilator properties and does not increase myocardial oxygen consumption. Several relatively small studies have shown hemodynamic benefits with levosimendan in cardiogenic shock after MI [98, 99], but survival benefits have not been shown either in cardiogenic shock or acute heart failure [100].

Intra-aortic balloon counterpulsation (IABP) reduces systolic afterload and augments diastolic perfusion pressure, increasing cardiac output and improving coronary blood flow [101]. These beneficial effects, in contrast to those of inotropic or vasopressor agents, occur without an increase in oxygen demand. IABP does not, however, produce a significant improvement in blood flow distal to a critical coronary stenosis, and has not been shown to improve mortality when used alone without reperfusion therapy or revascularization. In patients with cardiogenic shock and compromised tissue perfusion, IABP can be an essential support mechanism to stabilize patients and allow time for definitive therapeutic measures to be undertaken [101, 102]. In appropriate settings, more intensive support with mechanical assist devices may also be implemented.

Reperfusion Therapy

Although thrombolytic therapy reduces the likelihood of subsequent development of shock after initial presentation [95], its role in the management of patients who have already developed shock is less certain. The available randomized trials have not demonstrated that fibrinolytic therapy reduces mortality in patients with established cardiogenic shock. On the other hand, in the SHOCK Registry, patients treated with fibrinolytic therapy had a lower in-hospital mortality rate than those who were not (54 vs. 64%, $p = 0.005$), even after adjustment for age and revascularization status (OR 0.70, $p = 0.027$) [103].

Fibrinolytic therapy is clearly less effective in patients with cardiogenic shock than in those without. The explanation for this lack of efficacy appears to be the low reperfusion rate achieved in this subset of patients. The reasons for decreased thrombolytic efficacy in patients with cardiogenic shock probably include hemodynamic, mechanical, and metabolic factors that prevent achievement and maintenance of infarct-related artery patency [104]. Attempts to increase reperfusion rates by increasing blood pressure with aggressive inotropic and pressor therapy and IABP make theoretic sense, and two small studies support the notion that vasopressor therapy to increase aortic pressure improves thrombolytic efficacy [104, 105]. The use of intra-aortic balloon pumping to augment aortic diastolic pressure may increase the effectiveness of thrombolytics as well.

To date, emergency percutaneous revascularization is the only intervention that has been shown to consistently reduce mortality rates in patients with cardiogenic shock. An extensive body of observational and registry studies has shown consistent benefits from revascularization but could not be regarded as definitive due to their retrospective design. These data have now been supported by randomized controlled trials.

The SHOCK study was a randomized, multicenter international trial that assigned patients with cardiogenic shock to receive optimal medical management – including IABP and thrombolytic therapy – or to cardiac catheterization with revascularization using PTCA or CABG [106, 107]. The primary endpoint, all-cause mortality at 30 days, was 46.7% in the revascularization group, and 56% in the medical therapy group, a difference that did not reach statistical significance ($p = 0.11$) [107]. Planned follow-up, however, revealed a significant benefit from early revascularization at 6 months and at 1 year ($p < 0.03$) [107]. Subgroup analyses also revealed benefit in patients younger than 75 years, those with prior MI, and those randomized less than 6 h from onset of infarction [106, 107].

The SMASH trial was similarly designed, but enrolled sicker patients [108]. The trial was terminated early due to difficulties in patient recruitment, and enrolled only 55 patients, but a reduction in 30-day absolute mortality reduction similar to that in the SHOCK trial (69% mortality in the invasive group vs. 78% in the medically managed group, $p = $ NS) [108], and this benefit was also maintained at 1 year.

When the results of both the SHOCK and SMASH trials are put into perspective with results from other randomized, controlled trials of patients with acute myocardial infarction, an important point emerges: despite the moderate relative risk reduction (for the SHOCK trial: 0.72, CI 0.54–0.95; for the SMASH trial: 0.88, CI 0.60–1.20) the absolute benefit is important, with 9 lives saved for 100 patients treated at 30 days in both trials, and 13.2 lives saved for 100 patients treated at 1 year in the SHOCK trial. This latter figure corresponds to a number needed to treat (NNT) of 7.6, one of the lowest figures observed in a randomized, controlled trial of cardiovascular disease.

On the basis of these randomized trials, the presence of cardiogenic shock in the setting of acute MI is a class I indication for emergency revascularization, either by percutaneous intervention or CABG [10].

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