CHAPTER 119  ■  NON ST ELEVATION ACUTE CORONARY SYNDROME: CONTEMPORARY MANAGEMENT STRATEGIES

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OVERVIEW

Definition of Terms

The term, acute coronary syndrome (ACS), describes a spectrum of clinical conditions ranging from ST-segment elevation myocardial infarction (STEMI) to non-ST-segment elevation MI (N–STEMI) and unstable angina (UA) (Fig. 119.1). These manifestations of acute myocardial ischemia may revert to the presymptomatic state or evolve into a non-Q wave (also termed nontransmural) MI or to Q wave (or transmural) MI (Fig. 119.1).

The boundaries between UA, N-STEMI, and STEMI are not always well defined. Indeed, the three entities should be considered as different and dynamic clinical manifestations of a continuous pathogenetic spectrum; N-STE-ACS are represented by UA and N-STEMI.

Unstable Angina (UA)

Anginal pain is the pivotal symptom for the diagnosis of UA, and its intensity, duration, and exercise-related threshold are usually graded according to the Canadian Cardiovascular Society (CCS) classification (Table 119.1) (2). UA may have three clinical presentations (Table 119.2) (3): (1) de novo or new-onset angina of at least CCS III-IV severity in patients without previously diagnosed angina; (2) crescendo, or increasing angina in patients with previously diagnosed angina that has become significantly more frequent, more severe in duration, and with a markedly reduced threshold (CCS Class III-IV); (3) postinfarction angina in patients with an MI within 2 weeks in whom biomarkers of myocardial necrosis have returned within normal range.

In all three clinical presentations of UA, pain may occur at rest and, typically, the low threshold for angina (CCS III and IV) represents an essential clinical feature for the diagnosis of UA. In all three clinical manifestations of UA, the presence of angina at rest is associated with a worse prognosis and a higher rate of events (4). In all cases, of course, it is crucial to exclude extracardiac conditions that can intensify or precipitate myocardial ischemia (secondary UA) such as anemia, fever, infection, hypotension, uncontrolled hypertension, hypoxemia, and thyrotoxicosis. The resting ECG may show ST-segment depression and/or T-wave inversion or transient ST-segment elevation or, rarely, may remain normal. The serum markers (troponin I, troponin T, and CK-MB) may remain within their normal biological ranges or fall between the normal range and the level diagnostic of myocardial infarction, the latter being, according to ACC/AHA recommendations, more than twice the upper normal limit (1). In the absence of release of myocardial markers of necrosis, the diagnosis of UA may be made, whereas if markers of myocardial necrosis have been released, the patient with ACS can be considered to have experienced N-STEMI. In the latter condition, ECG ST-segment or T-wave changes may be persistent, whereas in UA, they may or may not occur and, if they are seen, are usually transient.

A peculiar clinical manifestation of UA was described in 1959 by Prinzmetal and associates detailing an atypical ischemic coronary syndrome characterized by sudden onset angina occurring almost exclusively at rest, particularly in the first hours of the day, associated with ST segment elevation on the ECG (1). Because of its peculiar clinical pattern, this acute coronary syndrome was defined as a variant form of angina. Prinzmetal and colleagues hypothesized that variant angina is caused by a focal spasm of a coronary artery (5); this initial hypothesis has been convincingly demonstrated by coronary angiography. Variant angina may be associated with acute myocardial infarction, severe cardiac arrhythmias—including ventricular tachycardia and fibrillation, and sudden death. Despite these potentially devastating consequences, long term follow-up of patients with documented coronary vasospasm is not well documented. In a large population of patients with variant angina—i.e. normal or near normal coronary arteries—and treated with calcium channel blockers, the 7.5-year incidence of sudden death and myocardial infarction were 3.6% and 6.5%, respectively (6). Although the clinical presentation of this variant form of angina is also characterized by instability, with evidence of subendocardial and/or transmural myocardial ischemia, the specific pathogenetic mechanisms—i.e. coronary spasm—is completely different from those leading to N-STE-ACS.

Non-ST-Segment Elevation Myocardial Infarction

N-STEMI may have symptoms and a clinical pattern indistinguishable from UA. While the resting ECG more frequently shows ST-segment depression or T-wave inversion (Fig. 119.2), ST-segment elevation, while sometimes observed, is, by definition, never sustained. There will always be a clear-cut rise in the serum biomarkers to levels that are diagnostic for myocardial infarction. Thus, the essential difference between UA and N-STEMI is mainly related to the amount of biomarkers of myocardial injury.
Epidemiology of N-STEMI. In the United States, two million patients are admitted annually to cardiac care units with ACS. The number of hospital admissions for patients with UA/N-STEMI is greater than the number with STEMI: 1.4 million and 600,000, respectively (7). The consequences of N-STE-ACS are not benign: among those who reach the hospital alive, approximately 13% of patients will die in the succeeding six months, and 8% will be left with unstable angina (8). The frequency of new stroke ranges between 1.5% and 3%, and rehospital- ization for a further episode of ACS ranges between 17% and 20% over the same time interval. Survival data indicate that the risk associated with N-STEMI is greatest during the first 15 to 30 days from symptom presentation.

The Euro Heart Survey–Acute Coronary Syndromes (EHS–ACS) (9) and the Global Registry of Acute Coronary Events (GRACE) studies (8) provided insight into the practice of cardiology in different hospital settings and in different coun- tries. EHS–ACS recorded prospectively 14,271 patients admit- ted with chest pain, with subsequently documented ACS in 10,484 (73%) of these. GRACE identified, in a prospective or retrospective manner, 11,543 patients with a final diagnosis of myocardial infarction or unstable angina—i.e., an ACS—in 10,709 patients (93%).

In both EHS–ACS and GRACE, about half of all patients underwent diagnostic coronary angiography, and percutaneous revascularization (PCI) was performed in 40% of patients ad- mitted with ST elevation and in about a quarter of patients without initial ST elevation. Inpatient medical therapy included aspirin in over 90% of patients, appropriate use of unfraction- ated or low molecular weight heparin, but low use of glycopro- tein IIb/IIIa receptor blockers when compared to guideline rec- ommendations. Therapy at discharge included aspirin and/or ticlopidine/clopidogrel in over 90% of patients, ACE inhibitors (EHS–ACS 56%, GRACE 55%), β-blockers (EHS–ACS 73%, GRACE 71%), and statins (EHS–ACS 53%, GRACE 47%) (8,9). These findings indicate an increasing awareness of the need for preventive medication in most patients with ACS.

TABLE 119.1

<table>
<thead>
<tr>
<th>New-Onset Angina</th>
<th>New-onset angina of at least CCS Class III severity.</th>
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<tbody>
<tr>
<td>Increasing Angina</td>
<td>Previously diagnosed angina that has become distinctly more frequent, longer in duration, or lower in threshold (i.e., increased by greater than or equal to 1 CCS class to at least CCS Class III severity).</td>
</tr>
<tr>
<td>Postinfarction Angina</td>
<td>Patients with recent myocardial infarction (within 2 weeks) in whom biomarkers of myocardial necrosis have returned within normal range.</td>
</tr>
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</table>

TABLE 119.2

GRADING OF ANGINA PECTORIS ACCORDING TO THE CANADIAN CARDIOVASCULAR SOCIETY CLASSIFICATION [MODIFIED FROM REFERENCE 1]

<table>
<thead>
<tr>
<th>Type of Angina</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Ordinary physical activity does not cause angina, such as walking two blocks or climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.</td>
</tr>
<tr>
<td>II</td>
<td>“Slight limitation of ordinary activity.” Angina occurs on walking or climbing stairs rapidly, walking uphill, walking on stairs climbing after meals, in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on level ground and climbing more than 1 flight of ordinary stairs at a normal pace and under normal conditions.</td>
</tr>
<tr>
<td>III</td>
<td>“Marked limitations of ordinary physical activity.” Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs under normal conditions and at a normal pace.</td>
</tr>
<tr>
<td>IV</td>
<td>“Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest.”</td>
</tr>
</tbody>
</table>
Pathogenesis of N-STE-ACS. N-STE-ACS are usually caused by a sudden reduction of myocardial perfusion resulting from coronary artery narrowing due to a nonocclusive thrombus. The latter, in turn, is a consequence of disruption or erosion of an atherosclerotic coronary artery plaque. Distal microembolization of thrombus and disrupted plaque components may further reduce perfusion of the distal microvasculature. Recent research has focused on the characterization of coronary atherosclerotic plaques more prone to rupture—termed, vulnerable plaque (10). The vulnerable plaque is characterized by a necrotic lipid core infiltrated by inflammatory cells—macrophages and lymphocytes, with evidence of intraplaque hemorrhage and abundant generation of von Willebrand on the adventitial site, surrounded by a thin fibrous cap (10). The most convincing hypothesis to explain plaque rupture is based on the critical role of inflammatory mediators driving the expression of proteases and proteolytic inhibitors that progressively weaken the fibrous cap, leading to plaque rupture (11).

The severity of coronary arterial obstruction and the volume of affected myocardium determine the pattern of clinical presentation. Patients with complete occlusion may manifest with a STEMI if the lesion occludes an artery supplying a substantial volume of myocardium, although the same occlusion in the presence of extensive collateralization may manifest as a N-STEMI or UA.

EARLY EVALUATION AND RISK STRATIFICATION

Immediate Concerns

ACS constitutes a clinical emergency. Therefore, early recognition and initiation of treatment is mandatory. Every patient with chest pain should be comprehensively evaluated, including a history and clinical examination of the cardiovascular system, the immediate recording of a resting ECG, and urgent evaluation of the serum markers of myocardial injury. Particular attention must be paid to the factors that influence the patient’s risk stratification. These factors are found among the clinical features, the magnitude of ECG change, and the elevation of serum markers of myocardial necrosis. Among those without ST elevation on the ECG, an ACS is diagnosed by the presence of a clinical syndrome of acute ischemia with either pain at rest or a crescendo pattern of ischemic pain with minimal exertion, plus electrocardiographic and/or marker evidence of acute ischemic injury. The predictive accuracy of ST elevation for a final diagnosis of MI is very high, but for non-ST elevation MI, less than 50% are suspected as infarction on initial presentation.

Within the spectrum of ACS, N-STEMI represents the most difficult diagnostic challenge. Separation of N-STEMI from UA is based on the biomarker elevation in the former and the absence of detectable marker release in the latter (repeat assay at 6 to 12 hours after presentation is recommended).

Tools for Risk Stratification

Symptoms and Physical Examination

The features of cardiac ischemic chest pain are usually well recognized. The pain may vary in severity from mild compressive discomfort to sharp, severe pain. It may be located in the anterior chest, particularly substernally, or predominantly involve the mandible, neck, shoulders, either or both arms, the back, or epigastrium. It may be associated with shortness of breath, perspiration, palpitations, nausea or vomiting; however, none of these features predicts the severity of the underlying coronary involvement. The pain is generally of short duration but may last longer than 30 minutes without necessarily resulting in myocardial infarction. In ACS, the chest pain is frequently spontaneous in onset and unrelated to the usual stressors known to precipitate stable angina pectoris. It may occur with no—or less than the usual amount of—provocation, and be more severe or more prolonged. Less frequently, ACS may present with little or no chest pain but, instead, with atypical pain, or it can be accompanied by the features of an acute transient reduction in cardiac output—tachycardia, hypotension, and poor peripheral circulation, pulmonary venous congestion, breathlessness or pulmonary edema or, rarely, a potentially lethal ventricular tachyarrhythmia—a rapid heart rate with a weak or nonpalpable pulse (1).

Male gender, age above 50 years and, in women, early menopause, as well as a history of smoking, dyslipidemia, hypertension, diabetes mellitus, and/or a family history of coronary disease all increase the likelihood of ACS in a given patient with chest pain. Repeated attacks of chest pain or ongoing chest pain before admission, or pain which recurs on treatment, is associated with a worse outcome.

Physical examination often fails to contribute to the diagnosis of ACS. There may be no abnormal findings. However, a fourth heart sound, a mitral regurgitant murmur, or signs of pulmonary congestion are suggestive of transient ischemic myocardial dysfunction (1).

Heart failure (HF) is a frequent complication of ACS (12) and significantly worsens the prognosis of patients with ischemic heart disease (13). In a recent subanalysis of the GRACE Registry, HF on hospital admission was associated with an approximately 3- to 4-fold increase in hospital and 6-month death rates (14). HF was also associated with longer hospital stay and
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higher readmission rates. As in previous studies, the development of HF during hospital stay—as opposed to HF at admission—was associated with an even worse outcome (13,15). Importantly, there was a reduced frequency of PCI and lower β-blocker usage among patients with HF on admission. Notably, given the high mortality rate of patients with HF and ACS, this group would be expected to derive an even greater benefit from revascularization and, indeed, patients with HF who underwent revascularization had lower cumulative 6-month mortality rates than those who did not, even after adjustment for baseline differences (14).

Electrocardiogram

The presence of ECG changes, especially when occurring at rest and associated with angina, are a powerful indicator of higher risk. ST elevation and ST depression are well recognized electrocardiographic markers of risk. It has been demonstrated that when the other elements of baseline risk have been under control, ST deviation conveys the same risk for death whether this deviation is upwards or downwards (16) (Fig. 119.3). New onset T-wave changes—especially T-wave inversion, although less specific—are also important markers of subendocardial ischemia. Clinically, the normalization of ECG alterations and anginal relief are very important within minutes after sublingual nitrate administration; persistence of pain and ECG alterations for more than 20 minutes despite repeated nitrate administration is a marker of increased risk for myocardial infarction (1).

Biochemical Markers

Not all patients presenting with N-STE-ACS have elevated serum markers; at the time of the initial assessment, these markers may be within normal ranges, especially when they have been obtained very shortly after the onset of chest pain. All patients who have normal serum marker results on presentation must have a second assessment 4 to 6 hours later, or 8 to 12 hours after the onset of symptoms, whichever is longer. Elevated levels of creatine kinase (CK), creatine kinase MB iso-enzyme (CK-MB), troponin T or I, and myoglobin are indicators of myocardial injury (Table 119.3).

Myoglobin is the earliest marker of an infarct event to appear in the serum. Although myoglobin is a very sensitive indicator of infarction, its clinical usefulness as the sole marker of myocardial injury/infarction is limited by the high incidence of false-positive results. CK in conjunction with CK-MB, CK-MB alone (17), and the troponins (18) are all sensitive and specific markers of myocardial injury/infarction that appear within the

<table>
<thead>
<tr>
<th>Marker</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>CK-MB</td>
<td>1. Rapid, cost-efficient, accurate assays</td>
<td>1. Loss of specificity in setting of skeletal muscle disease or injury, including surgery</td>
</tr>
<tr>
<td></td>
<td>2. Ability to detect early reinfarction</td>
<td>2. Low sensitivity during very early MI (less than 6 h after symptom onset) or later after symptom onset (more than 36 h) and for minor myocardial damage (detectable with troponins)</td>
</tr>
<tr>
<td>CK-MB Isoforms</td>
<td>1. Early detection of MI</td>
<td>1. Specificity profile similar to that of CK-MB</td>
</tr>
<tr>
<td></td>
<td>2. Useful in early detection of MI</td>
<td>2. Current assays require special expertise</td>
</tr>
<tr>
<td></td>
<td>3. Detection of reperfusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Most useful in ruling out MI</td>
<td></td>
</tr>
<tr>
<td>Myoglobin</td>
<td>1. High sensitivity</td>
<td>1. Very low specificity in setting of skeletal muscle injury or disease</td>
</tr>
<tr>
<td></td>
<td>2. Useful in early detection of MI</td>
<td>2. Rapid return to normal range limits sensitivity for later presentations</td>
</tr>
<tr>
<td></td>
<td>3. Most useful in ruling out MI</td>
<td></td>
</tr>
<tr>
<td>Cardiac Troponins</td>
<td>1. Powerful tool for risk stratification</td>
<td>1. Low sensitivity in very early phase of MI (less than 6 h after symptom onset) and requires repeat measurement at 8 to 12 h, if negative</td>
</tr>
<tr>
<td></td>
<td>2. Greater sensitivity and specificity than CK-MB</td>
<td>2. Limited ability to detect late minor reinfarction</td>
</tr>
<tr>
<td></td>
<td>3. Detection of recent MI up to 2 weeks after onset</td>
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</tr>
<tr>
<td></td>
<td>4. Useful for selection of therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Detection of reperfusion</td>
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</table>
serum in raised amounts from about 4 hours after the onset of the ischemic event. Whereas CK and CK-MB are cleared from the serum within 2 to 3 days, an elevation of the troponin level may persist for up to 14 days after an event, making the troponins poor markers of early reinfarction.

The bedside use of a “multi-marker strategy” that evaluated CK-MB, troponin I or T, and myoglobin in combination improved much superior to any “single-marker” strategy, and was also better than CK-MB and troponin without myoglobin in reaching an earlier diagnosis and identifying those at higher risk of death or MI by 30 days (19). Elevated levels of troponin T or I (20–22) or CK-MB (17) on admission indicate a poorer outcome (Fig. 119.4). The later appearance of an elevated troponin level, suggesting ongoing ischemia, is also associated with higher risk (23).

Extensive evidence supports the powerful and independent prediction of thrombotic complications, including MI and death, associated with troponin elevation (21). Furthermore, the evidence from trials of PCI revascularization suggests that troponins can be used as one part of the measures to identify higher risk—although it is not the sole arbiter of risk—and the extent of this risk is also better than CK-MB and troponin without myoglobin in reaching an earlier diagnosis and identifying those at higher risk of death or MI by 30 days (19). Elevated levels of troponin T or I (20–22) or CK-MB (17) on admission indicate a poorer outcome (Fig. 119.4). The later appearance of an elevated troponin level, suggesting ongoing ischemia, is also associated with higher risk (23).

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of other analgesic treatments such as tramadol, a synthetic
analogue of codeine, which may have been administered by
paramedical staff during transport to the hospital. Adverse in-
teractions might arise if a narcotic analgesic were adminis-
tered inadvertently shortly thereafter. Intravenous injection of anal-
gesics and other drugs should be preferred, because intramus-
cular injection may perturb certain serum markers of cardiac
injury/infarction (1), have variable absorption, and are, in gen-
eral, more painful and less humane than IV injections.

Anti-ischemic Drugs

Nitrates, β-adrenergic blockade, and calcium channel blockade
have been used to treat patients with ACS. These therapies aim
to control symptoms, reduce myocardial ischemia, and prevent
the dire complications of this syndrome. The randomized trials
that have evaluated the effects of an antianginal agent against
placebo therapy or compared one class of antianginal agent
with another in ACS are relatively few and fairly small.

Nitrates. Nitrates act by reducing preload and afterload, pro-
moting coronary vasodilation, relieving coronary vasospasm
or vasoconstriction, and by putative effects upon platelet ag-
ggregability. These effects combine to improve myocardial blood
flow and relieve ischemia. Although nitrates effectively relieve
cardiac ischemic pain, they have not been found to improve the
outcome in ACS (39). They may be administered sublingually,
orally, or intravenously in standard doses (Table 119.6).

Beta-blockers. Beta-blockade reduces myocardial oxygen de-
mand and diminishes ischemia. Although there are large trials
that have demonstrated the benefit of β-blockade following
acute myocardial infarction, there are limited evaluations of this
treatment in N-STE-ACS. The effects of β-blockade upon sub-
sequent myocardial infarction and survival are uncertain. The
drugs that have been scrutinized in small trials or retrospec-
tive subgroup analyses are metoprolol (40), propranolol (41),
and esmolol (42). Whichever β-blocker is selected, the dose
should be titrated to obtain a resting heart rate of 50 to 60
beats per minute, while maintaining an adequate blood pres-
sure and satisfactory peripheral perfusion.

Calcium Channel Blockers. Calcium channel blockers are a
diverse group of compounds that cause smooth muscle relax-
ation by blocking cellular calcium entry. Their action results
in coronary vasodilation, relieving coronary vasospasm
and thereby tend to diminish myocardial oxygen demand. The Hol-
land Interuniversity Nifedipine/Metoprolol Trial (40) showed
that the short-acting dihydropyridine, nifedipine, was detri-
mental in comparison with placebo in unstable angina. Cal-
cium channel blockers should be reserved for the control of in-
tractable chest pain or hypotension that cannot be alleviated
by other means. Diltiazem is a nondihydropyridine calcium
channel blocker that is superior to placebo treatment in reduc-
ing reinfarction and postinfarction angina in non-Q wave my-
cardial infarction (43). Mortality was unaffected in the trial.
A trial comparing diltiazem treatment to propranolol found
no differences in outcome in groups of patients with unstable
angina or Prinzmetal angina (44). In a trial that compared intra-
venous glyceryl trinitrate with intravenous diltiazem, the com-
bined endpoint of refractory angina and myocardial infarction

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**TABLE 119.4**

<table>
<thead>
<tr>
<th>RISK INDICATORS OF A POOR OUTCOME IN ACS</th>
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<tbody>
<tr>
<td>Event-Related:</td>
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<tr>
<td>Ongoing or recurring chest pain</td>
</tr>
<tr>
<td>ST-segment depression/new ischemia on ECG</td>
</tr>
<tr>
<td>Elevated serum biomarkers of cardiac injury/infarction</td>
</tr>
<tr>
<td>Hemodynamic instability</td>
</tr>
<tr>
<td>Preexisting:</td>
</tr>
<tr>
<td>Age over 65 years</td>
</tr>
<tr>
<td>Three or more risk factors for CAD, especially diabetes mellitus</td>
</tr>
<tr>
<td>Aspirin use within 7 days</td>
</tr>
<tr>
<td>Known CAD</td>
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<tr>
<td>Prior left ventricular dysfunction</td>
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</tbody>
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**HOSPITAL CARE AND MANAGEMENT STRATEGIES**

**Early Pharmacologic Treatment**

**Control of Pain**

While analgesics have no influence on the pathophysiological
process, narcotic analgesia with IV morphine sulphate and/or
sedation with oral benzodiazepines in standard doses may as-
sist in alleviating the patient’s pain and anxiety. As morphine
may induce nausea and vomiting, it is advisable to premedici-
cate the patient with IV metoclopramide prior to commenc-
ing the IV morphine titration. It is important to be aware of other
analgesic treatments such as tramadol, a synthetic
Chapter 119: Non ST Elevation Acute Coronary Syndrome: Contemporary Management Strategies

Immediate angiography

Follow up

Early invasive strategy

Early conservative strategy

12–24 h angiography


was less with diltiazem than with the nitrate (45). Although verapamil has similar effects to diltiazem, its effects in ACS have not been evaluated in any large trial. Dihydropyridines should be used only in combination with β-blockade, as the combination avoids induction of tachycardia. Short-acting dihydropyridine calcium channel blockers should not be used at all. The nondihydropyridine calcium channel blocker, diltiazem, may be used alone as an alternative therapy if it is not possible to use β-blockade. However, β-blockers are preferred in all other patients, as they have marked benefits in those who go on to develop MI. Furthermore, the use of any calcium channel blocker is contraindicated when there is left ventricular dysfunction.

Antiplatelet Therapy (see Table 119.7)

Aspirin. Aspirin irreversibly inhibits cyclooxygenase-1, thus reducing the generation of thromboxane A2, a potent mediator of platelet aggregation. The most recent update of the Antiplatelet Trialists’ Collaboration, based upon 287 studies in
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High/Intermediate Risk

Left Main Coronary Dis., 3-Vessel Dis+severe LV dysfunction and/or DM
1- or 2-Vessel disease, suitable for PCI

Consider CABG

Clopidogrel IIb/IIIa Inhibitors

Consider PCI

Normal

Consider Alternative Diagnosis

Discharge on ASA, Clopidogrel, Statin, ACE-I

13,500 patients, demonstrates a highly significant reduction in the risk of MI/stroke/vascular death as a result of antiplatelet treatment versus control (46). Overall, the event rates were 13.2% in control patients and 10.7% in those treated with antiplatelet therapy, a 22% relative risk reduction (46). In acute MI, and in other high risk patients, the absolute and relative risk reductions were greater: 23 per 1,000 fewer vascular deaths and 13 per 1,000 fewer MIs. Thus, abundant evidence supports the use of aspirin in patients with ACS.

13. Additional antiplatelet treatment requires evidence of benefit on top of aspirin, rather than as an alternative to aspirin. Recent data suggest that the bleeding risk doubles for aspirin doses above versus below 160 mg daily, with no improved efficacy (1). Unless there are specific contraindications—intolerance or allergy; active bleeding; hemophilia; severe hypertension; renal, genitourinary, or gastrointestinal bleeding; active peptic ulcer—aspirin should be given to all patients with N-STE-ACS as soon as possible and continued indefinitely.

Thienopyridines. Thienopyridines (ticlopidine and clopidogrel) inhibit adenosine diphosphate (ADP) mediated platelet aggregation and, although initial studies were conducted with ticlopidine, this has been superseded by clopidogrel due to a much superior safety and more rapid onset of action. The blockade of ADP receptors by thienopyridines is irreversible but relatively slow to become manifest—several days for ticlopidine. Furthermore, recent evidence indicates that a substantial number of individuals appear to be resistant to the antiplatelet action of thienopyridines. For this reason, a high loading dose of 300 to 600 mg of clopidogrel or 500 mg of ticlopidine can be used to obtain a rapid onset of action. As the antaggregation effects of aspirin and thienopyridines are mediated by different mechanisms, an additive benefit by using both drugs may exist. In N-STE-ACS, the AHA/ACC guidelines recommend approximately nine months treatment with clopidogrel (1). Longer term treatment in higher risk vascular patients awaits the results of the large scale CHARISMA trial. The association of aspirin and clopidogrel increases the risk of bleeding during major surgery and coronary surgery (CABG), thus clopidogrel should be interrupted 5 to 7 days before elective surgery. If early diagnostic catheterization is scheduled within 24 to 36 hours, clopidogrel administration can be

**FIGURE 119.6.** Algorithm for the management of NSTE-ACS patients at high-intermediate risk undergoing coronary angiography.

**FIGURE 119.7.** Algorithm for the treatment of high risk patients with unstable angina/non-ST-segment elevation myocardial infarction.
Table 119.5: Risk Scores for N-STE-ACS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>TIMI (0-7)</th>
<th>Age 65 years or greater</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or more risk factors for CAD</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Use of ASA (last 7 days)</td>
<td>1</td>
<td>1</td>
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</tr>
<tr>
<td>Known CAD (stenosis 50% or more)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>More than 1 episode rest angina in less than 24 h</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ST-segment deviation</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Elevated cardiac markers</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest at admission</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Killip class II</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>43</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest at admission</td>
<td>43</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Elevated cardiac markers</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>ST-segment deviation</td>
<td>30</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Risk scores for N-STE-ACS

Initiated after coronary angiography when it is clear that CABG will not be undertaken; in the case of immediate percutaneous revascularization, the therapy can be initiated with a loading dose immediately.

Thienopyridines reduce the risk of stent thrombotic occlusion and are now part of standard treatment for at least four weeks in all patients undergoing elective PCI. With drug eluting stents, at least six months and perhaps 12 months of clopidogrel and aspirin are required (1). The CURE trial tested clopidogrel in 12,562 N-STE-ACS patients on top of background treatment and aspirin (47). A 2.1% absolute risk reduction (20% relative risk reduction, p = 0.0001) occurred in the frequency of nonfatal MI, stroke, or cardiovascular death (47). The treatment effect was evident within the first 24 hours of starting therapy and, although the absolute benefits were greatest in the first three months of treatment, the relative risk reduction was the same beyond three months. Approximately 1% more patients experienced major bleeding, but there was no significant excess of life-threatening bleeding or hemorrhagic strokes (47). Nevertheless, in view of the irreversible nature of the ADP antagonist, current guidelines suggest that clopidogrel should be withheld for five days before CABG surgery. In candidates for very urgent CABG, a small molecule Gp IIb/IIIa inhibitor—epibatidine or tirofiban—can be used before surgery.

Three new antiplatelet drugs are in phase III clinical trials, including a potent, fast-acting thienopyridine (prasugrel [48]), a reversible oral P2Y12 inhibitor (AZD6140, a cyclopyrrolone [49]), and a potent, short-acting intravenous P2Y12 inhibitor (cangrelor [50]). In patients with N-STE-ACS, preliminary data from the DISPERSE 2 (Safety, Tolerability and Preliminary Efficacy of AZD6140, the First Oral Reversible ADP Receptor Antagonist, Compared with Clopidogrel in Patients with Non-ST-Stage Elevation Acute Coronary Syndrome) trial comparing AZD6140 with placebo demonstrated that AZD6140, 180 mg twice daily, achieved greater and more consistent platelet inhibition, and showed favorable effects on clinical outcomes without an increase in major bleeding (51).

Glycoprotein IIb/IIIa Receptor Antagonists. Platelet aggregation involves the GP IIb/IIIa receptor linked to fibronogen or von Willebrand factor. Intravenous GP IIb/IIIa receptor antagonists have been extensively tested in patients with ACS and, in a meta-analysis of all the major randomized trials, the absolute risk reduction for death or MI at 30 days was 1% (11.8% control vs. 10.8% with GP IIb/IIIa) (52). The absolute treatment benefit was largest in high risk patients—in particular, those with evidence of troponin release or those undergoing acute PCI (52). Among those without troponin elevation or PCI, no significant benefits were observed with Gp IIb/IIIa administration.

The CREDO (Clopidogrel for the Reduction of Events During Observation) trial has helped to resolve the question of whether clopidogrel plus GP IIb/IIIa receptor antagonists may be required in patients undergoing PCI (53). Approximately half of the patients received GP IIb/IIIa antagonists (a non-randomized subset) and two thirds had presented with an ACS. The frequency of MI, stroke, or death at one year was reduced from 11.5% to 8.5% (p = 0.02), with similar risk ratios in the presence or absence of GP IIb/IIIa inhibitors (53). In the ISAR-REACT 2 (Abciximab in Patients with Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention After Clopidogrel Pre-treatment) trial, abciximab...
### TABLE 119.6

**DOSAGES OF NTG AND NITRATES IN ANGINA [MODIFIED FROM BRAUNWALD ET AL. (1)].**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTG</td>
<td>Sublingual tablets</td>
<td>0.3 to 0.6 mg up to 1.5 mg</td>
</tr>
<tr>
<td></td>
<td>Spray</td>
<td>0.4 mg as needed</td>
</tr>
<tr>
<td></td>
<td>Transdermal</td>
<td>0.2 to 0.8 mg/h every 12 h</td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>3 to 200 mcg/min</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Oral</td>
<td>5 to 80 mg, 2 or 3 times daily</td>
</tr>
<tr>
<td></td>
<td>Oral, slow release</td>
<td>40 mg 1 or 2 times daily</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>Oral</td>
<td>20 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>Oral, slow release</td>
<td>60 to 240 mg once daily</td>
</tr>
<tr>
<td>Pentaerythritol tetranitrate</td>
<td>Sublingual</td>
<td>10 mg as needed</td>
</tr>
<tr>
<td>Erythritol tetranitrate</td>
<td>Sublingual</td>
<td>5 to 10 mg as needed</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>10 to 30 mg 3 times daily</td>
</tr>
</tbody>
</table>

### TABLE 119.7

**COMMONLY USED ANTIPLATELET AND ANTICOAGULANT AGENTS IN UNSTABLE ANGINA AND N-STEMI—DRUG DOSES AND SPECIAL PRECAUTIONS**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral antiplatelet</td>
<td></td>
<td>Gastrointestinal bleeding</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Initially 300 mg p.o.; then 75 to 150 mg daily</td>
<td>Peptic ulceration</td>
</tr>
<tr>
<td>Clopidogrel (Plavix/Iscover)</td>
<td>Initial loading dose of 300 mg (or 600 mg); then 75 mg daily</td>
<td>Aspirin allergy</td>
</tr>
<tr>
<td>Heparins</td>
<td></td>
<td>Increased bleeding risk</td>
</tr>
<tr>
<td>Unfractionated</td>
<td>60 U/kg IV bolus to a maximum of 4,000 units; then 12 units/kg/h infusion to a maximum of 1,000 units/h</td>
<td>Antiplatelet therapy contraindicated</td>
</tr>
<tr>
<td>Low-molecular-weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dalteparin (Fragmin)</td>
<td>120 IU/kg subcutaneously every 12 h</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin (Clexane)</td>
<td>1 mg/kg subcutaneously every 12 h</td>
<td></td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitors</td>
<td>180 μg/kg IV over 1 to 2 min; then 2 μg/kg/min infusion over 72 h or until hospital discharge, whichever occurs first</td>
<td>Bleeding disorder, Thrombocytopenia, Surgery &lt;6 weeks, Abnormal bleeding &lt;30 d, Active GI ulceration, Puncture of a non-compressible vessel, Prior stroke, organic CNS pathology, Any systolic BP &gt;180 mm Hg during the acute event, As above, 1/2 dose in renal insufficiency, As above</td>
</tr>
<tr>
<td>Eptifibatide (Integrel)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tirofiban (Aggrastat)</td>
<td>0.4 μg/kg/mm IV over 30 min; then 0.1 μg/kg/min infusion for 48 to 108 h</td>
<td></td>
</tr>
<tr>
<td>Abciximab (ReoPro)</td>
<td>0.25 mg/kg IV bolus 10 to 60 min before PCI, then 10 μg/min IV infusion for 12 h</td>
<td></td>
</tr>
</tbody>
</table>
reduced the composite of death, MI, or urgent target vessel revascularization within 30 days compared with placebo by 23% among 2,022 patients with N-STE-ACS, all of whom received clopidogrel, 600 mg, at least 2 h before PCI (54). However, the benefit of abciximab was observed only in patients with N-STEMI (54).

The EVEREST (Randomized Comparison of Upstream Tirofiban versus Downstream High Bolus Dose Tirofiban or Abciximab on Tissue-Level Perfusion and Tropinin Release in High-Risk Acute Coronary Syndromes Treated with Percutaneous Coronary Interventions) trial of 93 patients with high risk N-STE-ACS compared upstream tirofiban given in the CCU several hours before coronary angiography to downstream (immediately after coronary angiography) high bolus-dose tirofiban and downstream abciximab given 10 min before PCI (55). Upstream tirofiban improved TIMI myocardial perfusion before and after PCI, achieved a higher myocardial contrast echocardiographic score, and resulted in lower rates of postprocedure troponin elevation (55). Results from the open-label ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) timing trial in 9,207 patients randomized to upstream GPI Ib/IIa inhibitors administered, on average, 6 hours before PCI compared with downstream use begun in the catheterization laboratory demonstrated that a downstream strategy was noninferior for a quaternary net clinical benefit end point—death, myocardial infarction, unplanned revascularization for ischemia, major bleeding—but did not satisfy the noninferiority criterion for the triple ischemic end point (56). A cost-effective analysis using data from the TACTICS-TIMI-18 (Prognostic Implications of Elevated Troponin in Patients with Suspected Acute Coronary Syndrome but No Critical Epicardial Coronary Disease—Thrombolysis In Myocardial Infarction-18) trial concluded that the upstream use of tirofiban was superior to selective use and was cost-effective in moderate to high risk patients (57). Taken together, these studies suggest that upstream GPI therapy may be more effective than downstream use in moderate to high risk patients managed with an invasive strategy in whom immediate catheterization is not planned. The EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome) study (58) is an ongoing randomized, double-blind, clinical trial comparing upstream double-bolus eptifibatide to downstream selective use in high risk patients with N-STE-ACS who are not undergoing PCI in the first 12 hours, and should help shed further light on this issue.

**Anticoagulation Therapy**

Thrombin (Factor IIa) is a highly potent stimulus not only of the generation of fibrin, but also platelet activation. In addition, it leads to monocyte chemotaxis, mitogenesis, increased permeability of the vascular wall, and secretion of cytokines and growth factors from smooth muscle cells. Effective antithrombotic treatment requires the inhibition of both platelet function and thrombin.

Unfractionated heparin has been widely used, but suffers from practical difficulties in maintaining antithrombin activity within the therapeutic range, which are influenced by acute phase proteins and binding to antithrombins. Nevertheless, there is clear evidence that a form of heparin, either unfractionated or low molecular weight heparin (LMWH), is superior to placebo in patients with ACS. The meta-analysis of trials demonstrates a reduction in absolute rates of death or MI from 7.4% to 4.5% (odds ratio 0.53, 95% CI 0.38 to 0.73) (59).

Direct antithrombins may offer significant advantages over the indirect inhibitors (unfractionated and LMWH). Combined analysis of the hirudin studies suggests a relative risk reduction compared to unfractionated heparin. At this point in time, hirudin has only been approved for patients with heparin-induced thrombocytopenia, and none of the hirudins are licensed for ACS. LMWHs partially inhibit factor X of the coagulation cascade, but newer specific inhibitors of Xa have been developed—for example, bivalirudin and fondaparinux. Such agents inhibit thrombin generation as distinct from thrombin activity. In the recently published ACUITY trial, 13,819 patients with moderate to high risk N-STE-ACS were randomized to 1 of 3 arms: (1) heparin + GP Ib/IIa inhibitors (standard), (2) bivalirudin + GP Ib/IIa inhibitors (combination), or (3) bivalirudin alone (monotherapy) (56). Combination therapy was noninferior to the standard (neither arm was superior), while monotherapy was superior to standard therapy, driven by a reduction in bleeding with bivalirudin monotherapy (56).

A common theme among the studies evaluating bivalirudin is the marked reduction in bleeding observed when GP Ib/IIa inhibitors are not routinely administered.

Direct comparisons with LMWH did not show advantages for fondaparinux. The results of a randomized, double-blind trial of fondaparinux versus enoxaparin in 20,000 patients with unstable angina or non-STEMI are pending (OASIS 5) (61).

An alternative approach involves an orally administered, direct thrombin antagonist, ximelagatran. It is converted to melagatran in the circulation and directly binds with the active site of the thrombin molecule. Ximelagatran does not require anticoagulation monitoring, and is administered as a fixed dose. In a phase II trial, it reduced the frequency of death, nonfatal MI, and severe recurrent ischemia compared to placebo treatment (hazard ratio 0.76, 95% CI 0.59 to 0.98) (62). Ximelagatran has also been used as an alternative to warfarin in the management of atrial fibrillation (SPORTIF trials), and demonstrates similar efficacy but less bleeding than warfarin. A potential hazard of ximelagatran involves alterations in liver enzymes: 6% to 10% of patients experience a rise in alanine aminotransferase to at least three times the upper limit of normal (62). This appears to resolve with or without cessation of drug treatment. Widespread application of ximelagatran as an alternative to other antithrombins in ACS requires large scale safety and efficacy studies.

**HMG-CoA Reductase Inhibitors**

In the past year, ancillary analyses from randomized trials of intensive statin therapy and mechanistic studies provided new insights into the role of lowering lipids in patients with ACS. The case for intensive statin therapy after N-STE-ACS was strengthened by a meta-analysis of 6 randomized controlled trials demonstrating that intensive, but not moderate, statin treatment reduces early recurrent ischemic events and stroke (63). A detailed comparison of two trials comparing intensive to moderate statin therapy emphasized the importance of intensive therapy beginning in the early post-ACS phase, and suggested that the early benefit may be associated with a more profound reduction in CRP achieved with earlier intensive therapy (64).
These results have been rapidly reflected in subsequent changes in the particular statin and dose prescribed. A trend-over-time analysis in Ontario, Canada, documented a greater than two-fold increase in the use of atorvastatin, 80 mg, within months after publication of the PROVE IT–TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction-22) and REVERSAL (Reversing Atherosclerosis With Aggressive Lipid Lowering) studies (65).

The benefit of atorvastatin, 80 mg, compared with pravastatin, 40 mg, occurred within 30 days in the PROVE IT–TIMI-22 trial (28% reduction in the hazard ratio of death, myocardial infarction, or rehospitalization for recurrent ACS) consistent with greater early pleotropic effects (66). A number of potential early benefits of statins independent of LDL have been postulated and include favorable effects on inflammation, endothelial function, and the coagulation cascade (67). In a secondary analysis from the PROVE IT–TIMI-22 trial, randomization to intensive statin therapy was associated with a lower CRP level, irrespective of the presence of a single or multiple uncontrolled cardiovascular risk factors (68). Endothelium-dependent, flow-mediated dilation increased between one and four months after initiating either atorvastatin, 80 mg, or pravastatin, 40 mg, in the BRAVER (Intensity of Lipid Lowering With Statins and Brachial Artery Vascular Endothelium Reactivity After Acute Coronary Syndromes) trial, independent of reductions in LDL and CRP (69).

Two important observations regarding the safety of statins were reported during the past year. An analysis of 15,693 patients from the GRACE (Global Registry of Acute Coronary Events) registry demonstrated that, in general, patients receiving the combination of clopidogrel and a statin did not have an increase in clinical events, thus suggesting no adverse interaction exists between these two therapies. Indeed, even after adjustment for differences in baseline variables and bias in treatment allocation, an analysis of patients administered aspirin with or without clopidogrel and with or without statin revealed that the group taking all 3 drugs had the lowest mortality (70). In an analysis of patients who achieved very low LDL concentrations in the PROVE IT–TIMI-22 trial, there was no adverse safety signal, while clinical efficacy improved as the LDL was lowered to less than 40 mg/dL (71), thus suggesting that downward adjustment of the statin dose is not required in patients who achieve very low LDL concentrations. Despite such favorable results with high intensity statins, only 44% of patients randomized to atorvastatin, 80 mg, with baseline total cholesterol less than 240 mg/dL (average LDL 106 mg/dL) achieved the dual goals of LDL less than 70 mg/dL and CRP less than 2 mg/L (72). Better control of traditional risk factors (68) and even more potent pharmacologic therapy are necessary to achieve these ambitious targets that have been associated with relatively lower rates of death and recurrent ischemic complications (73).

**Invasive Strategies**

**The Role of Coronary Angiography**

Presently, coronary angiography represents the only reliable tool for the assessment of coronary anatomy in patients with N-STE-ACS. Patients with high risk coronary lesions—left main disease, three vessel disease, and proximal left anterior descending coronary artery disease—represent about 50% of all patients with N-STE-ACS (74,75) and, despite the use of risk scores and biomarkers of myocardial damage, it is frequently impossible to correctly identify these high risk patients who are most likely to benefit from revascularization both in terms of survival and symptom improvement (Table 119.8). Thus, the concept of low and high risk patients suggested by the various scores derived by investigational studies and registry is rather relative. According to the TIMI risk score, about 50% of patients with N-STE-ACS are in the low risk subgroup (below score 3); nevertheless about 25% of these patients develop a major event—death, nonfatal MI, or urgent revascularization—within 14 days from hospitalization. Thus, as the predictive accuracy of these risk scores is rather low, all patients with N-STE-ACS should be regarded at risk to develop major coronary events. In this context, the early knowledge of coronary anatomy and the possibility to promptly restore myocardial perfusion appear to have important therapeutic and prognostic implications.

**Early Conservative versus Invasive Strategies**

Studies comparing head-to-head early conservative versus an early invasive strategy are flawed by the substantial rate of crossover patients originally randomized into the conservative arm who were treated invasively because of unstable symptoms. Indeed, when the difference in revascularization rate between the treatment arms is large, the benefit of revascularization strategy is evident. According to a recently published meta-analysis, managing N-STE-ACS by early invasive approach improves long-term survival and reduces late nonfatal myocardial infarction and rehospitalization for symptoms recurrence (76–78). Thus the issue is not whether but when a patient with N-STE-ACS should undergo coronary angiography and eventually revascularization. Combined data from seven large randomized trials indicate that the goal in patients with N-STE-ACS should be to perform early invasive therapy within 48 hours from hospital admission (76,77) (Fig. 119.8).

Obviously, coronary angiography should be anticipated if clinical instability occurs. This time interval is also supported by the CRUSADE (Can Rapid risk stratification of Unstable

11. Libby P. Act local, act global: inflammation and the multiplicity of “vulner-

10. vanishing is reasonable applicable in the majority of cardiology cen-


8. Fox KAA, Goodman SG, Klein W, et al; for the GRACE Investigators. Man-


5. Haywood LJ, Khan AH, de Guzman M. Prinzmetal angina. Normal arteries


2. Myler RK, Shaw RE, Stertzer SH, et al. Unstable angina and coronary an-

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logy; American Heart Association. Committee on the Management of Pa-


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7. Fox KAA, Goodman SG, Klein W, et al; for the GRACE Investigators. Man-


5. Haywood LJ, Khan AH, de Guzman M. Prinzmetal angina. Normal arteries


2. Myler RK, Shaw RE, Stertzer SH, et al. Unstable angina and coronary an-

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conservative strategies in patients with unstable coronary syndromes treated
with the glycoprotein IIb/IIIa inhibitor tirofiban. J Am Coll Cardiol.

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13. Data from Vital and Health Statistics.


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7. Fox KAA, Goodman SG, Klein W, et al; for the GRACE Investigators. Man-


5. Haywood LJ, Khan AH, de Guzman M. Prinzmetal angina. Normal arteries


2. Myler RK, Shaw RE, Stertzer SH, et al. Unstable angina and coronary an-

1. Braunwald E, Antman EM, Bailey JR, et al.; American College of Cardio-

logy; American Heart Association. Committee on the Management of Pa-


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7. Fox KAA, Goodman SG, Klein W, et al; for the GRACE Investigators. Man-


5. Haywood LJ, Khan AH, de Guzman M. Prinzmetal angina. Normal arteries


2. Myler RK, Shaw RE, Stertzer SH, et al. Unstable angina and coronary an-

1. Braunwald E, Antman EM, Bailey JR, et al.; American College of Cardio-


CHAPTER 120  ■  ST ELEVATION MYOCARDIAL INFARCTION (STEMI) CONTEMPORARY MANAGEMENT STRATEGIES

ACHILLE GASPARDONE  •  LEONARDO DE LUCA

OVERVIEW OF ST ELEVATION MYOCARDIAL INFARCTION

Definition of Terms

The definition of acute myocardial infarction (MI) may refer to different perspectives related to clinical, electrocardiographic (ECG), biochemical, and pathologic characteristics, all reflecting death of cardiac myocytes caused by prolonged ischemia (1,2). A definition for acute evolving myocardial infarction in the presence of clinically appropriate symptoms has been established as:

1. Patients with ST-segment elevation (ST elevation MI [STEMI])—that is, new ST-segment elevation at the J-point with the cutoff points greater than or equal to 0.2 mV in V1 through V3 and greater than or equal to 0.1 mV in other leads, or
2. Patients without ST-segment elevation (non–ST elevation MI [N-STEMI])—that is, ST-segment depression or T-wave abnormalities with elevated biomarkers of myocardial damage. ST-segment elevation is usually indicative of transmural MI, while ST-segment depression—whether associated or not with T-wave abnormalities—is more likely indicative of subendocardial MI.

Clinically established myocardial infarction may be defined by any Q wave in leads V1 through V3, or a Q wave greater than or equal to 0.03 s in leads I, II, II, aVL, aVF, V5, or V6. In the setting of acute MI, ECG changes are associated with elevation of the biomarkers of myocardial damage. The standard biomarker for myocardial damage is cardiac troponin I or T, which has an elevated myocardial tissue specificity as well as high sensitivity, and creatine kinase (CK)-MB mass, which is less tissue specific than cardiac troponin but more specific for irreversible injury (1,2). Recently, a Global Task Force composed of several worldwide scientific working groups redefined the ESC/ACC criteria for the diagnosis of MI from various perspectives (2A) (Table 120.1). Clinically, the various types of MI, according to this new definition, can be classified as shown in Table 120.2.

Epidemiology

Acute MI represents a significant public and social health problem in industrialized countries, and is becoming an increasing significantly issue in developing countries (3). Although the exact incidence is difficult to ascertain, using primary listed and secondary hospital discharge data, the incidence has been estimated at 500,000 STEMI events per year in the United States (3). Several registries have reported significant declines in the incidence of STEMI such that ST-elevation MIs are becoming less frequent (4). Accompanying these trends, the overall proportion of admissions for chest pain caused by STEMI is also declining, while several sources have indicated that the incidence of unstable angina and N-STEMI is increasing (4).

Pathogenesis of ST Elevation Myocardial Infarction and Its Complications

ST elevation is conventionally thought of as representing transmural ischemia in response to fissuring or rupture of an atheromatous plaque with total and prolonged occlusion of a major coronary artery. Less frequently vessel occlusion may be caused by a prolonged coronary artery spasm.

After an acute MI, mechanical problems that result from dysfunction or disruption of critical myocardial structures (e.g., loss of contracting muscle causing left ventricular dysfunction,