

## Task Force Report

# Management of acute coronary syndromes: acute coronary syndromes *without* persistent ST segment elevation

## Recommendations of the Task Force of the European Society of Cardiology

**Task Force Members: M. E. Bertrand, Chair, M. L. Simoons, K. A. A. Fox,  
L. C. Wallentin, C. W. Hamm, E. McFadden, P. J. De Feyter, G. Specchia and  
W. Ruzyllo**

### Preamble

The Task Force on Management of Acute Coronary Syndromes without persistent ST-segment elevation was created by the Committee for Scientific and Clinical Initiatives on 18 October 1998 after formal approval by the Board of the European Society of Cardiology.

The composition of the Task Force was proposed by Dr Michel E. Bertrand and was approved by the Board of the European Society of Cardiology.

The document was extensively revised and circulated to the members of the Committee for Scientific and Clinical Initiatives, to the Members of the Board and to the following reviewers: J. Adgey (U.K.), J. P. Bassand (F), G. Breithardt (D), J. L. Lopez-Sendon (E), L. Rydén (S), C. Stefanadis (GR).

After further revision, it was submitted for approval to the Committee for Scientific and Clinical Initiatives (Chairman: J. P. Bassand (F)).

The Task Force report was entirely supported financially by the European Society of Cardiology and was developed without any involvement of pharmaceutical companies.

**Key Words:** Acute coronary syndromes, unstable angina, non-Q wave myocardial infarction, percutaneous transluminal coronary angioplasty, coronary bypass surgery.

The full text of this document is available on the Website of the European Society of Cardiology: [www.escardio.org](http://www.escardio.org) in the section 'Scientific Information', Guidelines.

*Correspondence:* Dr Michel Bertrand, Department of Cardiology, Hôpital Cardiologique, Boulevard du Pr Leclercq, 59037 Lille, France.

### Introduction

The clinical presentations of ischaemic heart disease include stable angina pectoris, silent ischaemia, unstable angina, myocardial infarction, heart failure, and sudden death. For many years, unstable angina has been considered as an intermediate 'syndrome' between chronic stable angina and acute myocardial infarction. In recent years, its pathophysiology has been clarified and there have been major advances in management.

It is now apparent that the 'acute coronary syndromes', namely unstable angina and evolving myocardial infarction share a common anatomical substrate: pathological, angiographic and biological observations have demonstrated that unstable angina and myocardial infarction are different clinical presentations that result from a common underlying pathophysiological mechanism, namely, atherosclerotic plaque rupture or erosion, with differing degrees of superimposed thrombosis and distal embolization<sup>[1–3]</sup>.

Clinical criteria have been developed to allow the clinician to make timely decisions and to choose the best treatment based on risk stratification and a targeted approach to intervention.

In practice, two categories of patients may be encountered:

- (1) Patients with a presumed acute coronary syndrome with ongoing chest discomfort and persistent ST-segment elevation (or new-onset LBBB). Persistent ST-segment elevation generally reflects acute total coronary occlusion. The therapeutic objective is rapid, complete, and sustained recanalization by fibrinolytic treatment (if not contraindicated) or primary angioplasty (if technically feasible).

- (2) Patients who present with chest pain with ECG abnormalities suggesting acute ischaemic heart disease. They do not have persistent ST-segment elevation but rather persistent or transient ST-segment depression or T-wave inversion, flat T waves, pseudo-normalization of T waves, or non-specific ECG changes; they may also have a normal ECG at presentation. Patients with ischaemic ECG abnormalities but without symptoms (silent ischaemia) may be included in this category.

The strategy in these cases is to alleviate ischaemia and symptoms, to observe the patient, using serial electrocardiograms, repeat measurements of markers of myocardial necrosis (troponin and CK-MB), and to initiate appropriate therapy if the diagnosis is confirmed.

**These guidelines will only refer to the management of patients with suspected acute coronary syndromes without persistent ST-segment elevation.** The management of patients with persistent ST-segment elevation is addressed in the ESC Guidelines for management of acute myocardial infarction<sup>[4]</sup>.

Two caveats must be mentioned:

First, these guidelines are based upon evidence resulting from many clinical trials. However these trials were restricted to selected populations with different clinical characteristics which may not reflect those seen in actual clinical practice. Furthermore, it should be appreciated that this topic is a rapidly moving field; the present guidelines reflect current knowledge but will need to be revised in the light of additional data emerging after mid 2000. We are grateful to the different trialists who provided unpublished data or manuscripts in preparation for publication.

The strength of evidence related to a particular treatment depends on the available data. Accordingly, in this document, the strength of evidence will be ranked according to three levels:

Level of evidence A: Data derived from multiple randomized clinical trials or meta-analyses

Level of evidence B: Data derived from a single randomized trial or non-randomized studies.

Level of evidence C: Consensus opinion of the experts.

Acute coronary syndromes are a major health problem and represent a large number of hospitalizations annually in Europe. Studies conducted in the 1960s and 1970s showed a rate of major adverse clinical events (death/myocardial infarction) ranging from 10% at 3 months to 17% at 24 months. Even in the late 1990s the prognosis of acute coronary syndromes remains unfavourable. In recent trials concerning anti-thrombotic or antiplatelet drugs, or interventions, the risk of death or non-fatal myocardial infarction complicating unstable angina ranges from 8% to 16% at 1-month follow-up. Nevertheless, the results of recent clinical trials indicate that a clinical strategy, which incorporates careful risk stratification in conjunction with novel therapeutic agents and revascularization in

adequately selected patients, may help to improve both immediate and long-term outcome.

## Pathophysiology

During the last decades the complexity of acute coronary syndromes has been appreciated and to a great extent unravelled. Briefly, acute coronary syndromes are due to an acute or subacute primary reduction of myocardial oxygen supply, provoked by disruption of an atherosclerotic plaque associated with thrombosis, vasoconstriction and microembolization.

### *Plaque rupture and erosion*

It has been demonstrated that atherosclerosis is not a continuous, linear process but rather a disease with alternate phases of stability and instability. Sudden and unpredictable changes in symptoms appear to be related to plaque disruption. Plaques prone to rupture have a large lipid core, low smooth muscle cell density, high macrophage density, thin fibrous cap-disorganized collagen and high tissue factor concentration<sup>[5,6]</sup>. The lipid core forms a cellular mass within the collagen matrix of the plaque. After foam cell death, the lipid core may be created by active dissolution of collagen by metalloproteinases and not just by passive accumulation. The lipid core of plaques prone to rupture has a high concentration of cholesteryl esters with a high proportion of polyunsaturated fatty acids. A lower proportion of polyunsaturates is observed at the edge of disrupted plaques as compared with their centre. The relative proportion of the different fatty acids could influence local platelet and thrombus formation.

Plaque disruption may result from various combinations of the following:

*Active rupture* is probably related to secretion of proteolytic enzymes by the macrophages which may weaken the fibrous cap. *Passive plaque disruption* is related to physical forces occurring at the weakest point of the fibrous cap, which is in general the thinnest part of the fibrous cap, at the junction of the plaque and the adjacent 'normal' wall. The vulnerability of the plaque may depend on the circumferential wall stress, as well as the location, size and composition of the lipid core, and the impact of flow on the luminal surface of the plaque<sup>[6]</sup>. Besides plaque rupture, *plaque erosion* has been described as one of the underlying mechanisms in acute coronary syndromes. Plaque erosion seems to be more common in women<sup>[7]</sup>. A recent study showed a 40% prevalence of plaque erosion in sudden coronary death, and 25% in acute myocardial infarction, with a higher prevalence in women than in men. For plaque rupture these figures were 37% in women vs 18% in men<sup>[8,9]</sup>. When erosion occurs, thrombus adheres to the surface of the plaque, whereas, when the plaque ruptures, thrombus involves the deeper layers of the

plaque, down to the lipid core; when this latter situation is not accommodated by positive remodelling, it may contribute to the growth and rapid progression of the plaque.

### *Inflammation*

The fibrous cap usually has a high concentration of type I collagen and can support high tensile stress without breaking. However, it is a dynamic structure with a continuous equilibrium between collagen synthesis modulated by growth factors and degradation by metalloproteases derived from activated macrophages. In addition, apoptosis of smooth muscle cells can weaken the cap tissue<sup>[10]</sup> and favour plaque rupture. Macrophage infiltration has been demonstrated consistently in pathological studies: the proportion of macrophages is six to nine times greater in ruptured plaques than in stable plaques<sup>[11]</sup>. It has been suggested that these cells produce metalloproteases that digest the extracellular matrix. In vitro, macrophages induce breakdown of collagen obtained from human fibrous caps and metalloprotease inhibitors can block this process<sup>[10]</sup>. The presence of macrophages reflects an inflammatory process which is also characterized by the presence of activated T-lymphocytes at the site of plaque rupture. These T-lymphocytes can release various cytokines that activate macrophages and promote smooth muscle cell proliferation<sup>[10]</sup>. In addition mast cells are found at plaque edges<sup>[12,13]</sup>.

Neointimal hyperplasia has been described in 40% of pathology specimens from unstable plaque obtained by directional atherectomy<sup>[14,15]</sup>. Characterized by loose fibrous tissue with abundant extracellular matrix, this neointimal hyperplasia may be stimulated by cell-derived, thrombus-derived, or smooth muscle cell-derived inflammatory growth factors.

### *Thrombosis*

Thrombus is induced at the site of plaque rupture or erosion. It may lead to rapid changes in stenosis severity, and may result in subtotal or total vessel occlusion. It has been shown that the thrombus occurring in unstable angina is mainly platelet-rich. The lipid-rich core, which is exposed after plaque rupture, is highly thrombogenic and has a greater concentration of tissue factor than other components of the plaque<sup>[16]</sup>. Furthermore, there is a strong correlation between tissue factor activity and the presence of macrophages<sup>[11]</sup>. Systemic monocyte procoagulant activity has been found to be dramatically increased in unstable angina. Systemic hypercoagulable factors may also be involved; hypercholesterolaemia, fibrinogen, impaired fibrinolysis, and infection can contribute to thrombus generation. Spontaneous thrombolysis may explain transient episodes of thrombotic vessel occlusion/subocclusion and associated transient symptoms or ECG changes.

Thrombosis at the site of plaque rupture may fragment into small particles, which migrate downstream and may occlude arterioles and capillaries. These platelet emboli may cause small areas of necrosis (minimal myocardial damage, small infarcts) i.e. in the absence of occlusion of the epicardial coronary artery.

### *Vasoconstriction*

The platelet rich thrombus can release vasoconstrictor substances such as serotonin and thromboxane A<sub>2</sub><sup>[17]</sup> that may induce vasoconstriction at the site of plaque rupture or in the microcirculation. This vasoconstrictor effect is the dominant factor in Prinzmetal variant angina characterized by transient, abrupt constriction of a coronary segment not preceded by an increase in myocardial oxygen demand (see the chapter on Recommendations in the next section (Diagnosis)). These episodes of acute transmural ischaemia are provoked by localized coronary vasospasm, which severely constricts or occludes one or more large epicardial coronary vessels.

### *Myocardium*

Pathological studies in patients with acute coronary syndromes without persistent ST-segment elevation show a broad spectrum of findings in the myocardium supplied by the culprit vessel. In unstable angina, the myocardium may be normal or there may be varying degrees of necrosis (myocardial infarction). Some patients have focal areas of cell necrosis in the myocardium supplied by the culprit artery, which has been attributed to repeated episodes of thrombus embolization<sup>[18-20]</sup>. These limited areas of necrosis are frequently not detectable by routine CK or CK-MB measurements, which may be within or just above the upper normal limits. Cardiac troponin T or troponin I have been introduced recently as a very sensitive and specific marker for myocardial necrosis and have become the measurement of choice in patients with suspected acute coronary syndromes. Elevated levels of cardiac troponin in the absence of CK-MB elevation has been labelled minimal myocardial damage. This concept is of interest and has major practical implications as it is associated with a unfavourable clinical outcome in patients with acute coronary syndromes.

## **Diagnosis**

### *Clinical presentation*

The clinical presentation of acute coronary syndromes encompasses a wide variety of symptoms. The classic features of typical ischaemic cardiac pain are well known and will not be further described here. Traditionally,

several clinical presentations have been distinguished: prolonged (>20 min) anginal pain at rest, new onset (de novo) severe (Class III of the Canadian Cardiovascular Society Classification) angina, or recent destabilization of previously stable angina with at least CCS III angina characteristics (crescendo angina). Prolonged pain is observed in 80% of patients while de novo or accelerated angina is observed in only 20%<sup>[21]</sup>. However, atypical presentations of acute coronary syndromes are not uncommon. They are often observed in younger (25–40 years) and older (>75 years) patients, diabetic patients, and in women. Atypical presentations of unstable angina include pain that occurs predominantly at rest, epigastric pain, recent onset indigestion, stabbing chest pain, chest pain with some pleuritic features, or increasing dyspnoea. In the Multicenter Chest Pain Study, acute myocardial ischaemia was diagnosed in 22% of patients presenting to emergency departments with sharp or stabbing chest pain, in 13% of those with chest pain that had some pleuritic features, and in only 7% of those whose chest pain was fully reproduced by palpation<sup>[22]</sup>. In addition, variant angina, which forms part of the spectrum of unstable angina, may not be recognised at initial presentation (see Appendix).

### *Physical examination*

Physical examination is most often normal, including chest examination, auscultation, and measurement of heart rate and blood pressure. The purpose of the examination is to exclude non-cardiac causes of chest pain, non-ischaemic cardiac disorders (pericarditis, valvular disease), potential precipitating extra-cardiac causes, pneumothorax, and finally, to look for signs of potential haemodynamic instability and left ventricular dysfunction.

### *Electrocardiogram*

The resting electrocardiogram is a key in the assessment of patients with suspected acute coronary syndromes. It is a useful screening tool in patients with atypical presentations and it may provide evidence of an alternative diagnoses such as pericarditis, pulmonary embolism or cardiomyopathy. Ideally, a tracing should be obtained when the patient is symptomatic and compared with a tracing obtained when symptoms have resolved. Comparison with a previous electrocardiogram, if available, is extremely valuable, particularly in patients with co-existing cardiac pathology such as left ventricular hypertrophy<sup>[22,23]</sup> or a previous myocardial infarction. Significant Q waves, consistent with previous myocardial infarction, are highly suggestive of the presence of significant coronary atherosclerosis, but do not necessarily imply current instability.

ST-segment shift and T wave changes are the most reliable electrocardiographic indicators of unstable

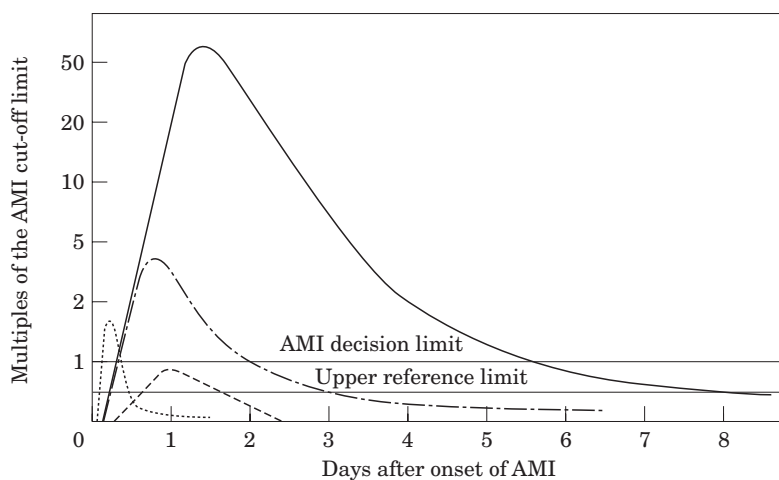
coronary disease<sup>[24]</sup>. ST-segment depression >1 mm in two or more contiguous leads, in the appropriate clinical context, is highly suggestive of unstable angina, as are inverted T waves (>1 mm) in leads with predominant R waves, although the latter finding is less specific. Deep symmetrical inversion of the T waves in the anterior chest leads is often related to significant proximal left anterior descending coronary artery stenosis. Non-specific ST-segment shift and T-wave changes (<1 mm) are less specific. Indeed, in the Multicenter Chest Pain Study, such non-specific changes were often noted in patients in whom unstable angina was ultimately ruled out<sup>[22,25]</sup>. Transient episodes of bundle branch block occasionally occur during ischaemic attacks. It should be appreciated that a completely normal electrocardiogram in patients presenting with suspicious symptoms does not exclude the possibility of an acute coronary syndrome. In several studies, around 5% of patients with normal electrocardiograms who were discharged from the emergency department were ultimately found to have either an acute myocardial infarction or unstable angina<sup>[26–28]</sup>. However, a completely normal ECG recorded during an episode of significant chest pain should direct attention to other possible causes for the patient's complaints.

ST-segment elevation indicates transmural ischaemia by coronary occlusion. Persistent ST-segment elevation characterizes evolving myocardial infarction. Transient ST-segment elevation may be observed in acute coronary syndromes and particularly in Prinzmetal's angina.

In order to detect or to rule out ST-segment changes during recurrent episodes of chest pain or in silent ischaemia, it is useful to establish multilead ST-segment monitoring.

### *Biochemical markers of myocardial damage*

Cardiac troponin T or troponin I are the preferred markers of myocardial necrosis and are more specific and more reliable than traditional cardiac enzymes such as creatine kinase (CK) or its isoenzyme MB (CK-MB) in this setting. It is now established that elevation of cardiac troponin T or I reflects myocardial cellular necrosis. In the setting of myocardial ischaemia (chest pain, ST-segment changes) this should be labelled as myocardial infarction. The old measurements of CK or CK-MB were less specific and there was an important overlap between normal and abnormal values. The myocardial isoforms of troponins have overcome these limitations of CK-MB measurements. The troponin complex is formed by three distinct structural proteins (troponin I, C, and T) and is located on the thin filament of the contractile apparatus in both skeletal and cardiac muscle tissue regulating the calcium dependent interaction of myosin and actin. Cardiac isoforms for all three troponins are encoded by different genes and thus can be distinguished by monoclonal antibodies recognising the distinct amino acid sequence<sup>[29,30]</sup>. The cardiac



**Figure 1** Time-course of the different cardiac biochemical markers. ...=early release of myoglobin or CK-MB isoforms; —=cardiac troponin after 'classical' acute myocardial infarction; - - =CK-MB after acute myocardial infarction; - - - =cardiac troponin after 'micro-infarction'.

isoforms of troponin T and I are exclusively expressed in cardiac myocytes. Accordingly, the detection of cardiac troponin T and troponin I is specific for myocardial damage, attributing to these markers the role of a new gold standard. In conditions of 'false positive' elevated CK-MB such as skeletal muscle trauma, troponins will clarify any cardiac involvement. In patients with a myocardial infarction, an initial rise in troponins in peripheral blood is seen after 3 to 4 h due to release from the cytosolic pool, with persistent elevation for up to 2 weeks caused by proteolysis of the contractile apparatus. The high proportional rise of troponins, reflecting the low plasma troponin concentrations in healthy persons, allows the detection of myocardial damage in about one third of patients presenting with unstable angina even without elevated CK-MB.

In order to demonstrate or to exclude myocardial damage repeated blood sampling and measurements are required during the first 6 to 12 h after admission and after any further episodes of severe chest pain. The current development of quantitative point-of-care tests for the rapid analysis of one or a combination of cardiac markers, e.g. troponin T, troponin I, CK-MB mass and myoglobin concentrations, will facilitate early diagnostic and prognostic evaluation.

The time course of different markers of myocardial necrosis is presented in Fig. 1. Myoglobin is a relatively early marker while elevations in CK-MB or troponin appear later. Troponin may remain elevated for 1 or 2 weeks, which may complicate the detection of recurrent necrosis in patients with recent infarction.

### Recommendations

**In patients with suspected acute ischaemic heart disease:**

- (1) An ECG should be obtained at rest and multi-lead continuous ST-segment monitoring initiated

(or frequent ECGs recorded where monitoring is unavailable).

- (2) Troponin T or I should be measured on admission and repeated 6 to 12 h later.
- (3) Myoglobin and/or CK-MB mass should be measured in patients with recent (<6 h) symptoms as an early marker of myocardial infarction and in patients with recurrent ischaemia after recent (<2 weeks) infarction to detect further infarction.

Level of evidence: C

### Risk assessment

In patients with an established diagnosis of acute coronary syndromes, the management strategy to be selected in a particular patient depends on the perceived risk of progression to myocardial infarction or death.

Acute coronary syndromes encompass a heterogeneous group of patients with different clinical presentations, who have differences in both the extent and severity of underlying coronary atherosclerosis, and who have differing degrees of acute 'thrombotic' risk (i.e. of short-term progression to infarction)<sup>[31]</sup>. In order to select the appropriate treatment for an individual patient, the risk for subsequent events should be assessed repeatedly. Such evaluation needs to be done early, at the time of initial diagnosis or admission to the hospital, based on immediately available clinical information and easily obtained laboratory data. This primary assessment needs to be modified in the light of the continuing symptoms, additional information based on ECG evidence of ischaemia, the results of laboratory tests and assessment of left ventricular function. Apart from age and a previous history of coronary artery disease, clinical examination, ECG and biological measurements provide the key elements for risk assessment.

### *Risk factors*

Age and male sex are associated with more severe coronary artery disease and consequently with an increased risk of unfavourable outcome. Previous manifestations of coronary artery disease such as severe or long-standing angina, or previous myocardial infarction are also associated with more frequent subsequent events. A history of left ventricular dysfunction or congestive heart failure are other risk factors as are diabetes mellitus and hypertension. Indeed, most of the well-known risk factors for coronary artery disease are also risk indicators for a worse prognosis in unstable coronary artery disease<sup>[32]</sup>.

### *Clinical presentation*

The clinical presentation and the time elapsed since the most recent episode of ischaemia, the presence of angina at rest and the response to medical treatment provide important prognostic information<sup>[32–34]</sup>. The classification proposed by Braunwald, based on these clinical findings, is related to clinical outcome and has been used in scientific reports to define population characteristics<sup>[33,35,36]</sup>. However, in order to select the optimal treatment, other risk indicators also need to be taken into account<sup>[32,34]</sup>.

### *Electrocardiogram*

The ECG is crucial not only for the diagnosis but also for prognostic assessment. Patients with ST-segment depression have a higher risk for subsequent cardiac events compared to those with isolated T-wave inversion, who in turn have a higher risk than those with a normal ECG on admission. Some studies have cast doubt on the prognostic value of isolated T-wave inversion<sup>[37]</sup>. The standard ECG at rest does not adequately reflect the dynamic nature of coronary thrombosis and myocardial ischaemia. Almost two-thirds of all ischaemic episodes in unstable coronary artery disease are silent and, hence, not likely to be detected by conventional ECG. Holter monitoring of the ST segment may be valuable, but is, at present, limited to 2–3 monitored leads and off-line analysis, providing the results several hours or days after the recording. On-line continuous computer-assisted 12-lead ECG monitoring is a promising technique. Continuous ST-monitoring studies have revealed that 15–30% of patients with unstable coronary artery disease have transient episodes of ST-segment changes, predominantly ST-segment depression. These patients have an increased risk of subsequent cardiac events. The ST monitoring adds independent prognostic information to the ECG at rest and other common clinical parameters<sup>[38–43]</sup>. Continuous ST monitoring is also useful for evaluation of the effects of treatment on the

ischaemic burden. For example, it has been shown that treatment with unfractionated heparin, low molecular weight heparin or glycoprotein-IIb/IIIa blockers<sup>[13]</sup> reduces episodes of ST shift<sup>[37,44–48]</sup>.

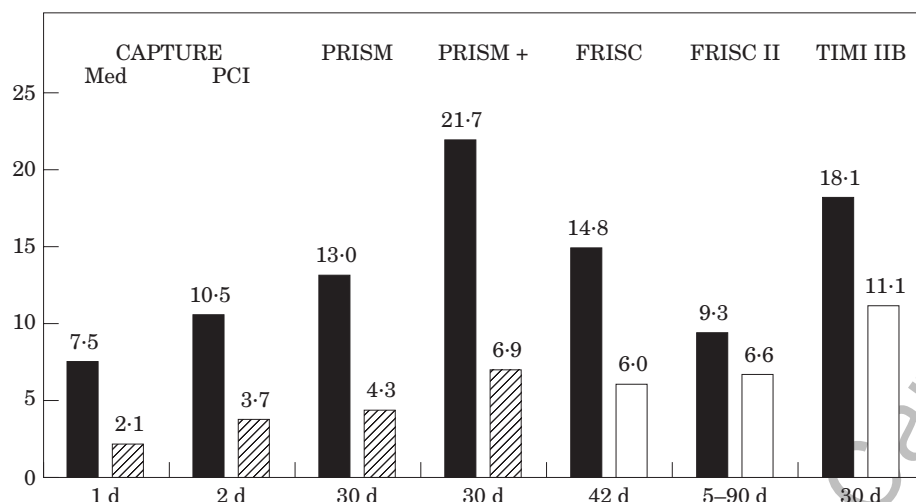
### *Markers of myocardial damage*

Unstable patients with elevated levels of troponin have an unfavourable short- and long-term clinical outcome when compared to those without troponin elevation. The appearance in the blood of markers of myocardial necrosis, in particular cardiac troponins at the index event, is related both to the risk for (re)infarction and cardiac death<sup>[49–59]</sup>. The risk of new events is correlated with the degree of troponin elevation<sup>[55,60]</sup>. The increased risk associated with elevated troponin levels is independent of other risk factors, such as ECG changes at rest or on continuous monitoring, or markers of inflammatory activity<sup>[61–63]</sup>. Furthermore, the identification of patients with elevated troponin levels is also useful for selecting appropriate treatment in patients with unstable coronary artery disease. Recent trials have shown that patients with elevated troponin specifically benefit from treatment with low-molecular weight heparin or GP IIb/IIIa blockers, while no such benefit was observed in patients without troponin elevation<sup>[60,64–66]</sup> (Figs 2 and 3).

### *Markers of inflammatory activity*

Increased fibrinogen levels and C-reactive protein have been reported as risk markers in acute coronary syndrome, although the data are not consistent<sup>[63,67,68]</sup>. For example, in the TIMI III trial, increased fibrinogen concentrations were related to more in-hospital ischaemic episodes while there was no relationship to subsequent death or myocardial infarction during the 42 days follow-up<sup>[67]</sup>. However, in the FRISC trial, an elevated fibrinogen level was associated both with the short- and the long-term risk of death and/or a subsequent myocardial infarction. The prognostic importance of fibrinogen was independent of ECG findings and troponin levels<sup>[63]</sup>. However, the prognostic value of increased C-reactive protein concentrations seems most prominent in patients with signs of myocardial damage<sup>[36,63]</sup>. In some studies, raised C-reactive protein concentrations seemed predominantly related to the risk of death at long-term follow-up, in contrast to the fibrinogen level, which was related to both subsequent myocardial infarction and mortality<sup>[63,66,69,70]</sup>.

An association between increased thrombin generation and an unfavourable outcome in unstable angina has been found in some, although not all, trials<sup>[71,72]</sup>. Protein C, protein S, resistance to APC and anti-thrombin deficiencies are defects in the anticoagulant systems associated with the development of venous thromboembolism. However, so far none of these have



**Figure 2** Death or myocardial infarction in patients with elevated troponins in contemporary trials. ■=placebo; ▨=abciximab, tirofiban; □=dalteparin, enoxaparin.

been connected to an increased risk of acute coronary syndromes. Reduced fibrinolytic capacity has been associated with an increased risk of future coronary events in community-based population studies and in unstable angina<sup>[73-76]</sup>. Increased concentrations of PAI-1 have been reported to be related to an increased risk of new coronary events in myocardial infarction survivors<sup>[77]</sup>. Increased D-dimer concentrations have been reported in unstable angina as well as in acute myocardial infarction<sup>[78]</sup>. However, there are few large-scale trials of fibrinolytic activity in unstable coronary artery disease and its relationship to acute phase proteins. Currently, haemostatic markers are not recommended for risk stratification or selection of treatment in individual patients with unstable coronary artery disease.

### Echocardiography

Left ventricular systolic function is an important prognostic variable in patients with ischaemic heart disease and can be easily and accurately assessed by echocardiography. Transient localized hypokinesia or akinesia in segments of the left ventricular wall may be detected during ischaemia, with normal wall motion on resolution of ischaemia. When identified, underlying left ventricular dysfunction or other underlying conditions such as aortic stenosis or hypertrophic cardiomyopathy are important both for prognostic assessment and management.

### Pre-discharge stress testing

After stabilization and before discharge a stress test is useful to confirm the diagnosis of coronary artery disease and to predict the medium and long-term risk for subsequent coronary events.

Exercise testing has a high negative predictive value<sup>[79-82]</sup>. Parameters reflecting cardiac performance provide at least as much prognostic information as those reflecting ischaemia, while the combination of these parameters gives additive prognostic information<sup>[79,80,82]</sup>. A significant proportion of patients cannot perform an exercise test and this in itself is associated with an adverse prognosis. Adding an imaging technique for the direct detection of ischaemia, such as perfusion scintigraphy or stress echocardiography, further increases the sensitivity and specificity for prognosis, although large long-term prognostic studies with stress echocardiography in patients after an episode of unstable coronary artery disease are still lacking<sup>[83-86]</sup>.

### Coronary angiography

This examination provides unique information on the presence and the severity of coronary artery disease. Patients with multiple vessel disease as well as those with left main stenosis are at higher risk of serious cardiac events<sup>[87]</sup>. Angiographic assessment of the characteristics and location of the culprit lesion as well as other lesions is essential if percutaneous coronary intervention is being considered. Complex, long, heavily calcified lesions, angulations and extreme tortuosity of the vessel are indicators of risk but the highest risk is associated with the occurrence of filling defects indicating intra coronary thrombus.

### Recommendations for risk stratification

**Risk assessment should be precise, reliable and, preferably, easily and rapidly available at low cost. The following methods are recommended:**

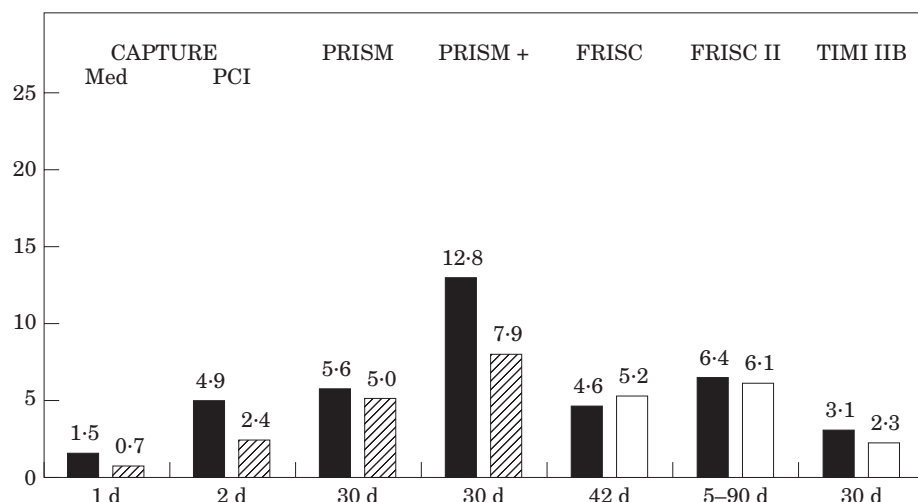


Figure 3 Death or myocardial infarction in patients with negative troponins in contemporary trials. ■=placebo; ▨=abciximab, tirofiban; □=dalteparin, enoxoparin.

Table 1 Level of evidence of the different therapeutic options

Treatment	Early benefit reduction ischaemia	Early benefit prevention, MI, death	Sustained effect of early benefit	Additional long-term reduction death, MI	References
Beta-blockers	A	B	B	A	[88–90]
Nitrates	C	—	—	—	[93–95]
Calcium antagonists	B	B	—	—	[90,101–103]
Aspirin	—	A	A	A	[109,117,118]
Iib/IIIa receptor blockers	A	A	A	A*	[129,130–132]
Unfractionated heparin	C	B	—	—	[108,109]
Low molecular weight heparin	A	A	A	C§	[31,110–114]
Specific antithrombins	—	A	A	—	[115,116]
Revascularization	C	B	B	B	[129,134–136,153]

\*No additional benefit; in contrast, indications for a negative effect  
§in selected patients.

- (A) Markers of thrombotic risk, i.e. acute risk:
- Recurrence of chest pain
  - ST-segment depression
  - Dynamic ST-segment changes
  - Elevated level of cardiac troponins
  - Thrombus on angiography
- (B) Markers of underlying disease i.e. long-term risk
- Clinical markers
    - Age
    - History of prior MI
    - History of severe angina
    - Diabetes
  - Biological markers
    - Level of C-reactive protein
  - Angiographic markers
    - LV dysfunction
    - Extent of coronary artery disease.

Level evidence for all markers: A

### Treatment options

The treatment options described in this paragraph are based on the evidence from numerous clinical trials or meta-analyses summarized in Table 1. Five categories of treatment will be discussed: antiischaemic anti-thrombin and antiplatelet agents, fibrinolytics and coronary revascularization.

### Antiischaemic agents

These drugs decrease myocardial oxygen utilization (decreasing heart rate, lowering blood pressure or depressing left ventricular contractility) or induce vasodilatation.

### Beta-blockers

Evidence for the beneficial effects of beta-blockers in unstable angina is based on limited randomized trial

data, along with pathophysiological considerations and extrapolation from experience in stable angina and acute myocardial infarction. Beta-blocking agents competitively inhibit the effects of circulating catecholamines. In unstable angina, the primary benefits of beta-blocker therapy are related to its effects on beta 1 receptors that result in a decrease in myocardial oxygen consumption.

Initial studies of beta-blocker benefits in acute ischaemic heart disease were small and uncontrolled. Three double-blind randomized trials have compared beta-blockers to placebo in unstable angina<sup>[88-90]</sup>. A meta-analysis suggested that beta-blocker treatment was associated with a 13% relative reduction in risk of progression to acute myocardial infarction<sup>[91]</sup>. Although no significant effect on mortality in unstable angina has been demonstrated in these relatively small trials, larger randomized trials of beta-blockers in patients with acute or recent myocardial infarction have shown a significant effect on mortality<sup>[92]</sup>.

Beta-blockers are recommended in acute coronary syndrome in the absence of contraindications; the intravenous route should be preferred in patients at high risk. **(Evidence level B)**. There is no evidence that any specific beta-blocking agent is more effective in producing beneficial effects in unstable angina. If there are concerns regarding patient tolerance, for example in patients with pre-existing pulmonary disease, or left ventricular dysfunction a short-acting agent should be preferred for initial therapy. Initiation of parenteral beta-blocker therapy requires frequent monitoring of vital signs, and preferably continuous ECG monitoring. Oral therapy should subsequently be instituted to achieve a target heart rate between 50 and 60 beats per minute. Patients with significantly impaired atrioventricular conduction, a history of asthma, or of acute left ventricular dysfunction should not receive beta-blockers<sup>[94]</sup>.

### Nitrates

The use of nitrates in unstable angina is largely based on pathophysiological considerations and clinical experience. There are no data from controlled trials to indicate the optimal intensity or duration of therapy. The therapeutic benefits of nitrates and similar drug classes such as sydnonimines are related to their effects on the peripheral and coronary circulation. The major therapeutic benefit is probably related to the venodilator effects that lead to a decrease in myocardial preload and left ventricular end-diastolic volume resulting in a decrease in myocardial oxygen consumption. In addition, nitrates dilate normal and atherosclerotic coronary arteries, increase coronary collateral flow, and inhibit platelet aggregation.

Trials of nitrates in unstable angina have been small and observational<sup>[93-95]</sup>. There are no randomized placebo-controlled trials to confirm the benefits of this class of drugs either in relieving symptoms or in reducing major adverse cardiac events. A randomized trial, that included only 40 patients, compared intravenous, oral,

and buccal preparations of nitrates and found no significant difference with regard to symptom relief<sup>[96]</sup>. Another small randomized trial compared intravenous nitroglycerin with buccally administered nitroglycerin and found no significant difference<sup>[97]</sup>.

In patients with acute coronary syndrome who require hospital admission, intravenous nitrates may be considered in the absence of contraindications. **(Evidence level C)**. The dose should be titrated upwards until symptoms are relieved or side effects (notably headache or hypotension) occur. A limitation of continuous nitrate therapy is the phenomenon of tolerance, which is related both to the dose administered and to the duration of treatment<sup>[98-100]</sup>.

When symptoms are controlled, intravenous nitrates should be replaced by non-parenteral alternatives with appropriate nitrate-free intervals. An alternative is to use nitrate-like drugs, such as sydnonimines or K-channel agonists.

### Calcium channel blockers

Calcium channel blockers are vasodilating drugs. In addition, some have significant direct effects on atrioventricular conduction and heart rate. There are three subclasses of calcium blockers which are chemically distinct and have differing pharmacological effects: the dihydropyridines (such as nifedipine), the benzothiazepines (such as diltiazem), and the phenylalkylamines (such as verapamil). The agents in each subclass vary in the degree to which they produce vasodilatation, decreased myocardial contractility and delayed atrioventricular conduction. Atrioventricular block may be induced by phenylalkylamines. Nifedipine and amlodipine produce the most marked peripheral arterial vasodilatation, whereas diltiazem has the least effect. All subclasses cause similar coronary vasodilatation.

There are several small randomized trials testing calcium channel blockers in unstable angina. Generally, they show efficacy in relieving symptoms that appear equivalent to beta-blockers<sup>[101,102]</sup>. The largest randomized trial, the Holland INteruniversity Trial (HINT study), tested nifedipine and metoprolol in a 2 × 2 factorial design<sup>[90]</sup>. Although no statistically significant differences were observed, there was a trend towards an increased risk of myocardial infarction or recurrent angina with nifedipine (compared to placebo) whereas treatment with metoprolol, or with a combination of both drugs, was associated with a reduction in these events. In one study, patients with unstable angina were discharged on a regimen of beta-blocker or diltiazem, and were followed for 51 months<sup>[103]</sup>. Diltiazem was associated with a non-significant increase in the adjusted death rate (33% vs 20%) and in the risk of re-hospitalization or death (hazard ratio 1.4).

A meta-analysis of the effects of calcium channel blockers on death or non-fatal infarction in unstable angina suggests that this class of drugs does not prevent

the development of acute myocardial infarction or reduce mortality<sup>[104]</sup>. In particular, several analyses that pooled data from observational studies suggest that short acting nifedipine might be associated with a dose-dependent detrimental effect on mortality in patients with coronary artery disease<sup>[105,106]</sup>. On the other hand, there is evidence for a protective role of diltiazem and verapamil in non-ST elevation myocardial infarction<sup>[106,107]</sup>.

Calcium channel blockers provide symptom relief in patients already receiving nitrates and beta-blockers; they are useful in some patients with contraindications to beta-blockade, and in the subgroup of patients with variant angina. **(Evidence level B and C)**. Nifedipine, or other dihydropyridines, should not be used without concomitant beta-blocker therapy. Calcium channel blockers should be avoided in patients with significantly impaired left ventricular function or atrioventricular conduction.

### *Antithrombin drugs*

Intracoronary thrombosis plays a major role in acute coronary syndromes. Thrombus consists of fibrin and platelets. Thrombus formation may be reduced and thrombus resolution facilitated by: drugs, which inhibit thrombin: directly (hirudin) or indirectly (unfractionated heparin or low-molecular weight heparin); antiplatelet agents (aspirin, ticlopidine, GP IIb/IIIa receptor blockers); or by fibrinolytic agents.

#### *Heparin and low-molecular-weight heparin*

Unfractionated heparin has been adopted as anti-thrombin therapy in previous guidelines for the treatment of unstable angina and non-ST elevation myocardial infarction. However, the evidence for the use of unfractionated heparin is less robust than for other treatment strategies<sup>[108]</sup>. In clinical practice, maintenance of therapeutic antithrombin control is hampered by unpredictable levels of heparin binding to plasma proteins (the latter amplified by the acute phase response). In addition, heparin has limited effectiveness against platelet-rich and clot-bound thrombin.

In the absence of aspirin, heparin treatment is associated with a lower frequency of refractory angina/myocardial infarction and death (as a combined end-point) compared to placebo (risk reduction 0.29) while the risk reduction for aspirin compared to placebo in the same study was 0.56. The combination of aspirin and heparin did not have a significantly greater protective effect than aspirin alone<sup>[109]</sup>. The initial event reduction by heparin was lost after discontinuation of the latter (rebound). Accordingly, there was no evidence of a sustained protective effect by heparin.

In a meta-analysis of the effect of heparin added to aspirin among patients with unstable angina (six randomized trials), there were 55 deaths or myocardial infarctions out of 698 in the aspirin plus heparin patients and 68 out of 655 with aspirin alone, giving a risk

reduction of 0.67 with a confidence interval of 0.44 to 1.02<sup>[108]</sup>. **(Evidence level A)**. Thus, these results do not provide conclusive evidence of benefit from adding heparin to aspirin, but it must be stressed that appropriately powered larger scale trials have not been conducted. Nevertheless, clinical guidelines recommend a strategy including administration of unfractionated heparin with aspirin as a pragmatic extrapolation of the available evidence.

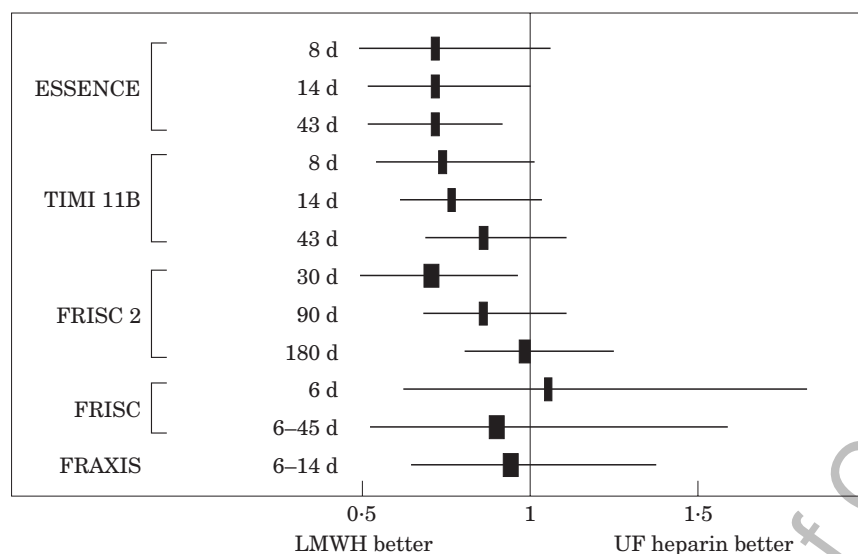
Low-molecular-weight heparins (LMWH) possess enhanced antiXa activity in relation to antiIIa (anti-thrombin) activity compared to unfractionated heparin. In addition, low molecular weight heparins exhibit decreased sensitivity to platelet Factor 4 and a more predictable anticoagulant effect, with lower rates of thrombocytopenia. These agents can be administered subcutaneously based on a weight-adjusted dose and do not require laboratory monitoring. The different low-molecular-weight-heparins available have similar activity in prevention and treatment of venous thrombosis, in spite of some differences in pharmacology. In recent years, comparison between low-molecular-weight heparin and placebo or unfractionated heparin has been performed in several clinical trials.

The FRISC trial tested dalteparin against placebo in aspirin-treated patients with unstable angina/non-ST elevation myocardial infarction<sup>[110]</sup>. One thousand five hundred and six patients were randomized to dalteparin (twice daily for the first 6 days and then once daily at a lower dose for approximately 6 weeks). The trial showed a highly significant reduction in death or new myocardial infarction at 6 days (1.8% vs 4.8% with a risk ratio of 0.37). The salutary effects were sustained at 42 days but were attenuated at 6 months. Thus, this trial clearly showed the benefit of low-molecular-weight heparin over placebo in the presence of aspirin and the feasibility of administering such treatment over a prolonged time interval.

In the FRIC trial, dalteparin was tested against unfractionated heparin in unstable angina among 1400 patients<sup>[111]</sup>. This trial had limited power to show a difference and no significant difference was seen between unfractionated heparin and dalteparin<sup>[111]</sup>.

The FRISC II trial compared long-term vs short-term treatment with the low-molecular-weight heparin<sup>[65]</sup>. After 5 days of open treatment with dalteparin, patients were randomized to placebo or weight-adjusted dalteparin for a period of 3 months. The primary end-point of death/myocardial infarction occurred in 6.7% of patients at 90 days in the dalteparin arm and 8% in the placebo arm (a non-significant difference). The risk ratio was 0.82 but 95% confidence intervals were 0.6–1.1. The secondary analysis at earlier time points (30 days) revealed a significant difference in favour of the low-molecular-weight heparin but this was diminished at 3 months follow-up.

The ESSENCE trial was a double-blind, placebo controlled comparison of enoxaparin and unfractionated heparin<sup>[31]</sup>. The treatments were given for 2 to 8 days (median 2.6 days) and the primary end-points



**Figure 4** Comparison of low-molecular weight heparins (LMWH) to unfractionated (UF) heparins in patients with acute coronary syndromes. Odds ratio and 95% confidence interval.

were death, myocardial infarction or recurrent angina. Enoxaparin reduced the primary end-point from 19.6% to 16.6% at 14 days (odds ratio 0.80, confidence intervals 0.67–0.98). At 30 days and 1 year a similar and significant benefit was maintained. At 1 year there were 3.7 fewer events/100 patients ( $P=0.022$ ). The study was not powered for death/myocardial infarction alone but demonstrated corresponding trends for these end-points.

TIMI 11b similarly tested enoxaparin vs unfractionated heparin but additionally examined 72 h of treatment vs 43 days of treatment<sup>[112]</sup>. The results up to 14 days mirrored those seen in ESSENCE<sup>[31]</sup>. At 14 days the primary end-point was 16.6% (heparin) vs 14.2% (enoxaparin), risk ratio 0.85 ( $P=0.03$ ). The curves remained separated over the succeeding treatment interval and at 43 days there were 19.6% events (heparin) vs 17.3% (enoxaparin) ( $P=0.049$ ) with no evidence of a further separation of the curves. In fact, only about 60% of the patients entered the chronic treatment phase of the study and it must be recognised that the study does not exclude a moderate effect for more prolonged treatment in selected patients. There was 1.4% absolute excess in major bleeds over the chronic phase. A combined analysis of ESSENCE and TIMI 11b reinforces the findings of ESSENCE and indicates an absolute difference of 3.1 per 100 for the combined end-point, and shows a significant risk ratio of 0.79 (CI 0.65–0.96) for death and myocardial infarction<sup>[113]</sup>. Taken together these findings indicate that short-term treatment with enoxaparin results in about 3 per 100 fewer major cardiac end-points compared to unfractionated heparin treatment and without additional major bleeding.

The FRAXIS trial tested fraxiparin, for 6 or 14 days, against unfractionated heparin. Three thousand four hundred and sixty-eight patients were randomized within 48 h of symptom onset and no difference was

seen at 6, 14 or 43 days, but once again there was a significant excess of major bleeds with longer-term outpatient treatment<sup>[114]</sup>.

There is convincing evidence in aspirin-treated patients that low-molecular-weight heparin is better than placebo<sup>[110]</sup>. **(Evidence level A)**. Two trials have provided data in favour of low-molecular-weight heparin (enoxaparin) over unfractionated heparin when administered as an acute regimen<sup>[113]</sup> (Fig. 4). The other trials have produced similar outcome results for the acute phase of treatment. Thus it can be concluded that acute treatment is at least as effective as unfractionated heparin. To date the evidence to support longer term treatment with low-molecular-weight heparin is less convincing. Low-molecular-weight heparins offer significant practical advantages with simplicity of administration, more consistent antithrombin effects, lack of the need for monitoring and a safety profile similar to that of unfractionated heparin.

#### Direct thrombin inhibitors

The GUSTO IIb study tested the direct thrombin inhibitor hirudin against heparin in patients with acute coronary syndromes but not receiving a thrombolytic agent. At 24 h the incidence of death or myocardial infarction was 0.9% with hirudin and 1.6% with unfractionated heparin. At 7 days the rate of death/myocardial infarction was about 20% lower in the hirudin arm, but by day 30 the difference was not statistically significant<sup>[115]</sup>.

The OASIS-2 trial (n=10 141) tested a higher dose of hirudin for 72 h against unfractionated heparin. The primary end-point was cardiovascular death or new myocardial infarction at 7 days, which occurred in 4.2% in the unfractionated heparin group and 3.6% in the hirudin group ( $P=0.077$ ). The treatment effect was

achieved within the first 72 h (relative risk 0.76 with confidence intervals 0.59–0.99). There was an excess of major bleeding requiring transfusion (1.2% vs 0.7%) but no excess of life-threatening bleeds or strokes.

A combined analysis of the OASIS-1 pilot studies, OASIS-2, and GUSTO IIb indicates a 22% relative risk reduction in cardiovascular death or myocardial infarction at 72 h, 17% at 7 days, and 10% at 35 days<sup>[115,116]</sup>. **(Evidence level A)**. This combined analysis is statistically significant at 72 h and 7 days and of borderline significance at 35 days ( $P=0.057$ ). Hirudin has been approved for patients with heparin-induced thrombocytopenia. None of the hirudins are currently licensed for acute coronary syndromes.

### *Management of bleeding complications related to antithrombin treatment*

Minor bleeding is usually treated by simply stopping the treatment. Major bleedings such as haematemesis, melaena or intracranial haemorrhage may require the use of heparin antagonists with the attendant risk of inducing a rebound thrombotic phenomenon. The anticoagulant and haemorrhagic effects of unfractionated heparin are reversed by an equimolar concentration of protamine sulfate, which neutralizes the antifactor IIa activity but results in only partial neutralization of the anti-factor Xa of low molecular weight heparin.

### *Antiplatelet agents*

#### *Aspirin*

Acetylsalicylic acid inhibits cyclo-oxygenase-1 and blocks the formation of thromboxane A<sub>2</sub>. Thus, platelet aggregation induced via this pathway is blocked. Three trials have consistently shown that aspirin decreases death or myocardial infarction in patients with unstable angina<sup>[109,117,118]</sup>. The doses used ranged from 75 to 325 mg per day. In addition to the early benefit established in those studies, a long-term benefit is achieved by continuation of aspirin<sup>[119,120]</sup>. Gastrointestinal side effects are relatively infrequent with these low doses. There are a few contraindications, and occasional side effects including allergy, active peptic ulcer, local bleeding or haemorrhagic diatheses. Accordingly, treatment with aspirin is recommended in *all* patients with suspected acute coronary syndromes in the absence of contraindications. **(Evidence level A)**.

#### *Adenosine diphosphate receptor antagonists: thienopyridins*

Ticlopidine and its derivative clopidogrel are inhibitors of adenosine diphosphate, resulting in inhibition of platelet aggregation. Ticlopidine has been investigated in one study<sup>[119,121,122]</sup>. Six hundred and fifty-two patients with unstable angina or non-Q wave myocardial infarction were randomized to ticlopidine (250 mg b.i.d) or

standard treatment (without aspirin or heparin). No difference was observed during the first 15 days but there was a significant reduction of death and myocardial infarction at the 6-month follow-up: 13.6% vs 7.3%. ( $P=0.01$ ). Accordingly, ticlopidin might be considered as an alternative for long-term therapy in patients who do not tolerate aspirin. However, intolerance to this drug is frequent because of gastrointestinal disorders, or allergic reactions. In addition, neutropenia or thrombocytopenia may occur and close monitoring of leukocyte and platelet counts is mandatory.

Clopidogrel, which has considerably fewer side effects than ticlopidine and, a faster mode of action, has not yet been tested in patients with acute coronary syndromes. A trial (CURE) is ongoing and the results will be available in 2001. However, in view of its effectiveness in other conditions, clopidogrel may be recommended for immediate- and long-term therapy in patients who do not tolerate aspirin (CAPRIE)<sup>[123,124]</sup> and, in combination with aspirin in the short-term, in patients receiving a stent<sup>[124–127]</sup>. **Evidence level: C**.

#### *Glycoprotein IIb/IIIa receptor blockers*

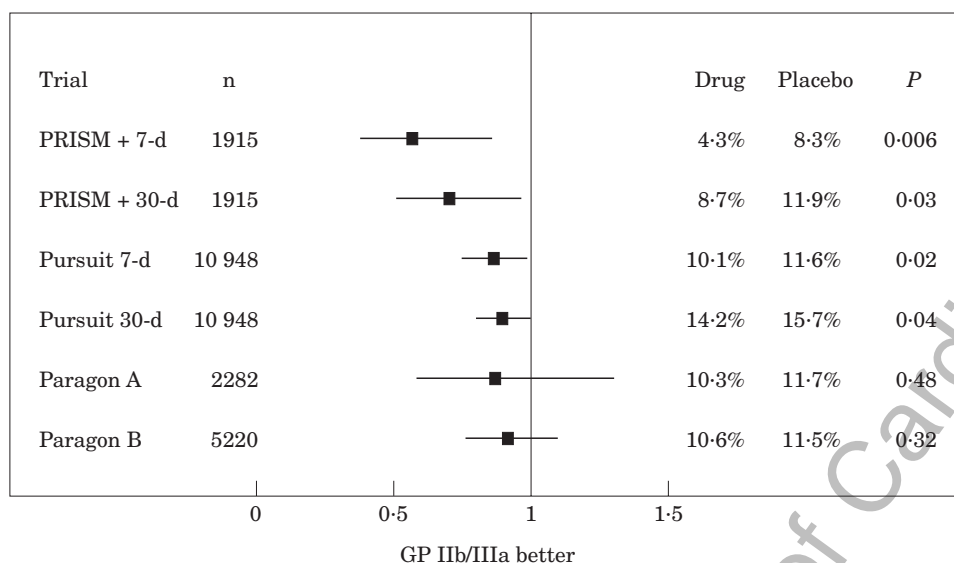
Activated GP IIb/IIIa receptors connect with fibrinogen to form bridges between activated platelets, leading to the formation of platelet thrombi. Direct inhibitors of glycoprotein IIb/IIIa receptors have been developed, and tested in various conditions where platelet activation plays a major role, in particular in patients undergoing percutaneous coronary intervention, patients admitted with acute coronary syndromes and, more recently, patients receiving thrombolytic therapy for acute myocardial infarction.

Four intravenous GP IIb/IIIa receptor blockers have been studied extensively in acute coronary syndromes. Abciximab is a monoclonal antibody. It is a non-specific blocker, with a tight receptor binding and slow reversibility of platelet inhibition after cessation of treatment. Eptifibatid is a cyclic peptide inhibiting selectively the glycoprotein IIb/IIIa receptors. It has a short half-life and platelet inhibition disappears 2 to 4 h after cessation of the treatment. Tirofiban is a small non-peptide antagonist that mimics the tripeptide sequence of fibrinogen. Blockade of the receptors is rapid (5 min), selective and rapidly reversible (4 to 6 h). Lamifiban is a synthetic, non-peptide selective receptor blocker with a half-life of 4 h approximately.

Oral GP IIb/IIIa receptor blockers have been recently studied: orbofiban, sibrafiban, ledrafiban, and others<sup>[128]</sup>.

### *GP IIb/IIIa receptor blockers in acute coronary syndromes*

In patients admitted with acute coronary syndromes, systematic use of GP IIb/IIIa receptor blockers in addition to aspirin and 'standard' unfractionated heparin was studied in a few pilot studies as well as in



**Figure 5** GP IIb/IIIa inhibitors vs conventional treatment in four trials. Odds ratio and 95% confidence interval.

six larger randomized trials: PRISM, PRISM-PLUS (PRISM+), PURSUIT, PARAGON-A, PARAGON-B and CAPTURE<sup>[129-132]</sup>. The results are very consistent and showed a significant reduction in the risk of myocardial infarction or death during the first few days. The observed benefit was sustained throughout the 30-day follow-up (Fig. 5).

The CAPTURE trial enrolled 1265 patients with refractory unstable angina scheduled for percutaneous coronary intervention<sup>[129]</sup>. The use of abciximab during approximately 24 h before intervention, significantly reduced the risk of death, myocardial infarction or target vessel revascularization from 15.9 to 11.3% at 30 days. There was a marked reduction in death or myocardial infarction from 9.0 to 4.8% ( $P=0.003$ ). Additional analysis revealed a reduction in spontaneously occurring death or myocardial infarction during the first 24 h medical treatment from 2.8% to 1.3% ( $P=0.032$ ), with an additional reduction in procedure-related events, up to 24 h after the procedure from 5.8% to 2.8% ( $P=0.009$ )<sup>[129,133]</sup>.

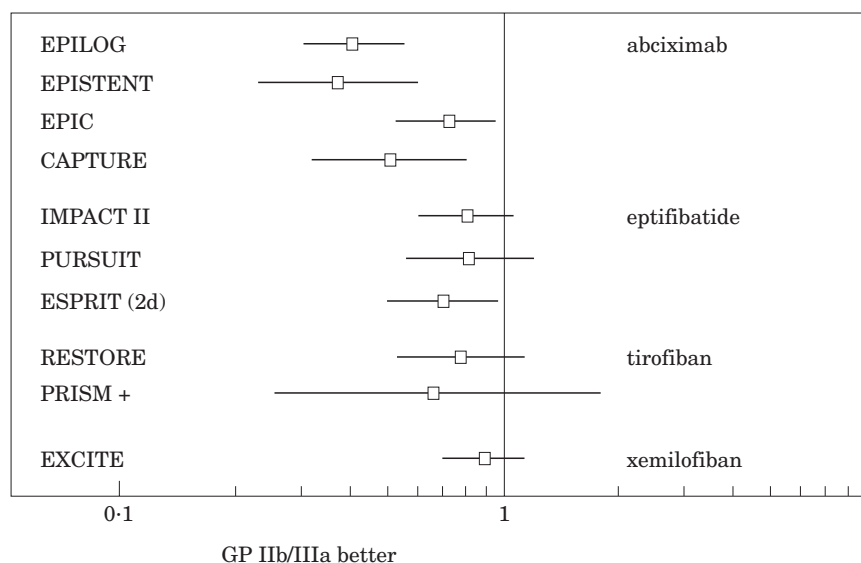
The reduction in procedure-related death and myocardial infarction with the GP IIb/IIIa receptor blockers was apparent in all subgroups of patients undergoing percutaneous coronary intervention<sup>[134-139]</sup> including patients treated with balloon angioplasty, patients receiving a stent, patients with unstable or stable angina, and patients undergoing direct PTCA for evolving myocardial infarction<sup>[136,141]</sup>.

Bleeding, particularly at the site of the introduction of arterial sheaths, was observed more frequently in patients receiving GP IIb/IIIa receptor blockers. This bleeding excess was related to the dose of heparin administered. In more recent studies with weight-adjusted low dose heparin, the rate of bleeding was reduced<sup>[134,135]</sup>.

PRISM enrolled 3232 patients with angina at rest less than 24 h before randomization, and either ECG changes indicating ischaemia or a history of coronary artery disease<sup>[130]</sup>. All patients received aspirin and either heparin or tirofiban as a continuous infusion for 48 h. At 48 h a significant reduction in death, myocardial infarction and refractory ischaemia was observed. The reduction in death and myocardial infarction remained apparent at 30 days, although no longer statistically significant, with an 18% reduction from 7.1% on placebo to 5.8% for tirofiban ( $P=0.11$ ).

The PRISM+ study enrolled patients at somewhat higher risk, with unstable angina and 'ischaemic' ECG changes in the 12 h before enrolment<sup>[131]</sup>. Three treatment arms were compared. The regimen of tirofiban in the same dose as in PRISM without heparin was discontinued because of an increased mortality rate in the first 345 patients<sup>[130]</sup>. At 7 days (primary end-point) patients receiving tirofiban with heparin had a lower rate of death, myocardial infarction and refractory ischaemia (12.9%) compared to heparin and placebo (17.9%) (relative risk reduction of 43%). At the 30 day follow-up, death and myocardial infarction were 8.7% and 11%, respectively ( $P=0.03$ ) i.e. a relative risk reduction of 30%.

In the largest trial (PURSUIT) 10 948 patients with unstable angina and symptoms within 24 h prior to enrolment with either an abnormal electrocardiogram or elevated cardiac enzymes were randomized to an eptifibatid bolus followed by an infusion up to 72 h, or to placebo<sup>[140]</sup>. All patients received aspirin and heparin. A low dose group was discontinued when at interim analysis the high dose appeared safe. The primary end-point showed a 9.6% relative risk reduction in death or myocardial infarction as assessed by the clinical event



**Figure 6** GP IIb/IIIa inhibitors vs placebo in patients with acute coronary syndromes, undergoing percutaneous coronary interventions (PCI).

committee at 30-day follow-up from 15.7% (placebo) to 14.2% (eptifibatide) ( $P=0.04$ ).

The results obtained in studies with different GP IIb/IIIa receptor blockers were remarkably consistent. However, some differences in study design should be pointed out. In particular, the proportion of patients undergoing percutaneous coronary intervention while on study drug varied. Almost all patients in CAPTURE underwent percutaneous coronary intervention at 18 to 24 h after randomization according to protocol<sup>[129]</sup>. In PRISM+ patients were scheduled to undergo coronary angiography at 48–96 h, and 35% underwent a percutaneous coronary procedure while receiving study drug<sup>[141]</sup>. Angiography and revascularization procedures were left at the discretion of the investigator in PURSUIT, which resulted in only 15% undergoing percutaneous revascularization while receiving study drug<sup>[140]</sup>. Finally, in PRISM, angiography and subsequent procedures were deferred until study drug was discontinued at 48 h<sup>[130]</sup>.

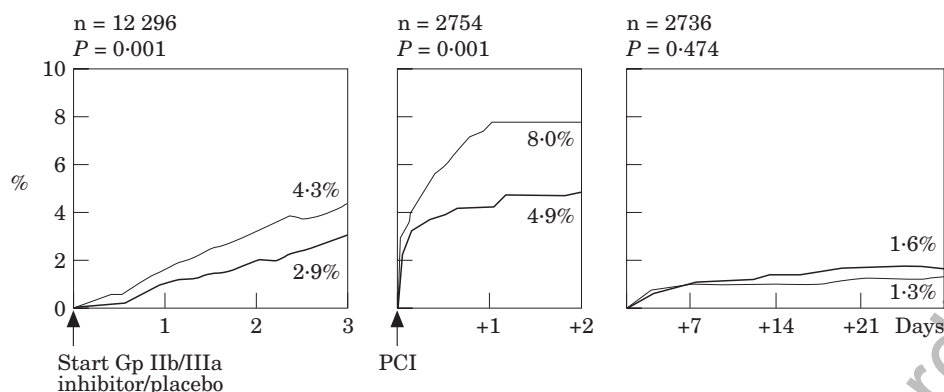
In two trials (CAPTURE, PRISM) the benefits of medical treatment with a GP IIb/IIIa receptor blocker was particularly apparent among patients admitted with elevated levels of cardiac troponin T or cardiac troponin I<sup>[64,130]</sup> (Figs 3 and 4). These results were recently confirmed by data presented from PRISM+ and PARAGON-B. This observation is in agreement with the notion that such elevated cardiac troponin levels reflects minimal myocardial damage resulting from platelet emboli. These patients seem to have active ongoing intracoronary thrombosis, which can be effectively reduced by powerful antiplatelet therapy. Therefore, treatment with a GP IIb/IIIa receptor blocker in addition to aspirin and weight-adjusted low dose heparin should be considered in all patients with acute coronary syndromes and an elevated troponin T or troponin I level.

More recently, four trials addressed prolonged treatment with oral GP IIb/IIIa receptor blockers in patients with acute coronary syndromes or after coronary intervention. Such prolonged treatment did not show evidence of benefit (OPUS-TIMI14- EXCITE, SYMPHONY 1 and 2)<sup>[128,142]</sup>. In fact, a modest increase in mortality was apparent in a meta-analysis of patients receiving oral GP IIb/IIIa receptor blockers.

#### *GP IIb/IIIa receptor blockers before and at the time of percutaneous coronary intervention*

In the larger placebo-controlled trials of GP IIb/IIIa receptor blockers in patients with acute coronary syndromes, the treatment benefit was particularly apparent in those patients who underwent early coronary revascularization<sup>[129,131,140]</sup>. This is illustrated in Fig. 5 combining data from four studies with different GP IIb/IIIa receptor blockers.

In fact, all studies with abciximab, eptifibatide, tirofiban and xemilofiban in comparison with placebo, but in addition to aspirin and heparin in patients undergoing percutaneous coronary intervention, systematically showed a reduction of death and myocardial infarction at 30 days compared with placebo (Fig. 6). The effects were most prominent and statistically significant in four large trials with abciximab. The ESPRIT study included 2064 stented patients treated with high dose of eptifibatide vs placebo. At 48 h, a reduction in death and myocardial infarction was observed from 9.2% to 6.6% ( $P=0.0013$ ) and a reduction in death and large myocardial infarction from 6.1% to 3.4% ( $P=0.053$ ). Results from longer follow-up are awaited. Patients undergoing percutaneous coronary intervention



**Figure 7** Kaplan–Meier curves showing cumulative incidence of death or non-fatal myocardial (re)infarction in patients randomly assigned to GP IIb/IIIa inhibitors or placebo.

in two trials of acute coronary syndromes (PURSUIT, PRISM+), with medium dose eptifibatide and tirofiban, had significant reductions in death and myocardial infarction at 24 h after coronary intervention<sup>[131,140]</sup>. At 30-day follow-up, the trends were still apparent, but the statistical significance was lost. Similar trends were apparent in a study with the oral GP IIb/IIIa receptor blocker xemilofiban (EXCITE).

In view of this evidence, GP IIb/IIIa receptor blockers should be considered in patients admitted with acute coronary syndromes, in addition to aspirin, and weight-adjusted low dose heparin, particularly in patients with an elevated cardiac troponin T or troponin I level<sup>[128]</sup>. **(Evidence level A).**

If a percutaneous coronary intervention is planned, treatment with the GP IIb/IIIa receptor blocker should be continued until intervention. In patients in whom a decision to perform coronary intervention is made after discontinuation of the GP IIb/IIIa receptor blocker, such treatment should be reinstated before the procedure. GP IIb/IIIa receptor blockers may be discontinued 12 h (abciximab) or 24 h (tirofiban, eptifibatide) after completion of the intervention.

Medical therapy with a GP IIb/IIIa receptor blocker during the first days after admission, followed by percutaneous coronary intervention or bypass surgery, yields a significant reduction in myocardial infarction at 72 h from 1.7% to 1.1%. In patients continuing on medical therapy in the PURSUIT and PRISM+ study, this benefit was largely sustained at 30-days follow-up<sup>[131,140]</sup> (Fig. 7). Subsequently, in patients undergoing percutaneous coronary intervention in the CAPTURE study, as well as the subgroup of patients undergoing a similar procedure in PURSUIT and PRISM+, a reduction of procedure related events was observed from 8.0 to 4.9% ( $P=0.001$ )<sup>[129,131,140]</sup>. Few events occurred more than 2 days after percutaneous coronary intervention in these patients, and no additional treatment effect was apparent up to 30-days follow-up (Fig. 7).

### *GP IIb/IIIa receptor blockers and coronary artery bypass surgery*

Inhibition of platelet aggregation may result in bleeding complications, either spontaneously or at the time of cardiac surgery. However, surgery in patients receiving such drugs has been shown to be safe when appropriate measures are taken to ensure adequate homeostasis. GP IIb/IIIa receptor blockers should be discontinued before or at the time of cardiac surgery. Eptifibatide and tirofiban have a short half-life, so that platelet function has recovered at least partly at the end of the procedure when haemostasis is necessary. Abciximab has a longer effective half-life. If excessive bleeding occurs in patients previously receiving abciximab, fresh platelet transfusions may be administered.

### *Management of complications related to administration of GP IIb/IIIa inhibitors*

With antiplatelet drugs and particularly with GP IIb/IIIa blockers the bleeding risk is clearly related to the dose of adjunctive heparin and specific dosing schedules are recommended.

In the setting of percutaneous coronary intervention, it is recommended to significantly restrict the doses of heparin to  $70 \text{ IU} \cdot \text{kg}^{-1}$  with a target activated clotting time of 200 s. When local complications such as important haematoma or continuous bleeding at the puncture site occur, surgical intervention may be required.

Thrombocytopenia may occur in a small percentage of patients during administration of parenteral GP IIb/IIIa blockers. Stopping treatment usually results in a return to normal platelet levels. Platelet infusion helps reversibility in patients receiving abciximab but this is not effective in patients receiving tirofiban or eptifibatide.

Finally, the problem of readministration exists for abciximab, due to its inherent immunogenicity. In practice, the report of the readministration registry shows similar safety and efficacy for repeat as compared with first time administration.

## Fibrinolytic treatment

Fibrinolytic treatment has been shown to decrease the amount of intracoronary thrombus and to significantly improve survival in acute coronary syndromes in patients with ST-segment elevation<sup>[143]</sup>. In contrast in several studies conducted with streptokinase, APSAC, T-PA or urokinase a deleterious effect has consistently been observed in patients with unstable angina<sup>[144-147]</sup>. The risk of death and myocardial infarction in a pooled series of 2859 patients was 9.8% in the fibrinolytic group and 6.9% in the control group. The Fibrinolytic Therapy Trialists' overview showed that in 3563 patients with suspected myocardial infarction and ST-segment depression, the mortality was 15.2% vs 13.8% for control patients<sup>[148]</sup>. Therefore, thrombolytic therapy *is not recommended* for patients with acute coronary syndromes without persistent ST-segment elevation.

## Coronary revascularization

Revascularization (either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)) for unstable coronary artery disease is performed to treat recurrent or ongoing myocardial ischaemia and to avoid progression to myocardial infarction or death. The indications for myocardial revascularization and the preferred approach depend on the extent and angiographic characteristics of the lesions identified by coronary angiography. There is a wide variation among countries in the use of coronary angiography (range 2% to as high as 60%) and subsequent revascularization (range 0.2% to as high as 36%)<sup>[149]</sup>.

In recent studies of patients with unstable coronary artery disease, intervention rates (PTCA and CABG) ranged from as low as 14% to as high as 53%. The use of PTCA was slightly higher than the use of CABG<sup>[31,37,110,111,115,130,132,150]</sup>. In a limited number of cases, special tools (angiojet, laser thrombolysis, transluminal extracting catheter, percusurge, or filters such as angioguard) have been used successfully, but properly randomized trials are needed to validate the use of these devices in these high-risk conditions. In the face of important intracoronary thrombus, in a relatively stable patient, it may be appropriate to postpone the procedure and to prepare the patient with aggressive anticoagulation and intensive antiplatelet treatment.

### Coronary angiography

Coronary angiography is the sole examination able to address the presence and extent of significant coronary

disease. Decisions to perform interventions are based on coronary angiography. The indications and timing of coronary angiography will be discussed in the chapter on management strategies in patients with acute coronary syndromes. There are no special precautions to be observed when performing coronary angiography except in haemodynamically very unstable patients (pulmonary oedema, hypotension, severe life-threatening arrhythmias) in whom it may be advisable to perform the examination with placement of an intra-aortic balloon pump, to limit the number of coronary injections and not to perform left ventricular cineangiography which might destabilize a fragile haemodynamic state. In such cases, left ventricular function may be estimated by echocardiography.

Data from TIMI IIIB and FRISC 2 show that 30% to 38% of the patients with unstable coronary syndromes have single vessel disease and 44% to 59% have multi-vessel disease. The rate of non-significant coronary disease varies from 14% up to 19%<sup>[37,151]</sup>. The incidence of left main narrowing varies from 4% to 8%<sup>[37,151]</sup>. The pattern of ECG changes, when present may help to identify the culprit lesion responsible for the instability. Description of the culprit lesion is of paramount importance to choose the appropriate intervention. Eccentricity, irregular borders, ulceration, haziness, and filling defects characteristic of intracoronary thrombus are markers of high-risk. Coronary angiography has good specificity but poor sensitivity when compared to angiography for detection of thrombi<sup>[152]</sup>. Extreme tortuosity, calcification, or location in a bend are important findings because they can preclude percutaneous coronary intervention with stent implantation.

### Percutaneous coronary interventions

In the 1980s and early 1990s, several reports demonstrated that results of percutaneous coronary intervention in patients with acute coronary syndromes were less good than those achieved in patients with stable angina. Indeed, balloon angioplasty induces plaque disruption and can enhance the thrombogenicity of the plaque. The placebo arm of CAPTURE clearly demonstrated this phenomenon. These problems have been markedly reduced by stent implantation and adjunctive treatment with GP IIb/IIIa inhibitors. Even with GP IIb/IIIa inhibitors, there are about 5% of procedure-related myocardial infarctions, albeit substantially less than about 10% observed without such treatment. The mortality rate associated with percutaneous coronary intervention is very low<sup>[129]</sup>.

Stent implantation in the setting of unstable coronary artery disease is a safe procedure, which helps to mechanically stabilize the disrupted plaque at the site of the lesion. This benefit is particularly obvious in high-risk lesions. In a prespecified subanalysis of the BENESTENT II Trial of patients with unstable angina it was shown that stent implantation was safe and associated with a lower 6-month restenosis rate than balloon dilatation<sup>[153]</sup>.

All patients undergoing percutaneous coronary intervention receive aspirin and heparin. A subanalysis of unstable angina patients from the EPIC and EPILOG trials and the CAPTURE trial convincingly demonstrated that intravenous abciximab significantly reduced the major complication rate during balloon angioplasty<sup>[129,134–136,154,155]</sup>. This initial benefit was sustained at the 6-month follow-up and beyond. Similar but smaller reductions in acute complications were achieved with eptifibatid or tirofiban but these initial beneficial effects were not sustained at 30 days<sup>[137,138]</sup>.

From subanalyses of CAPTURE and PURSUIT, it appeared that the beneficial effect of GP IIb/IIIa inhibitors was already evident 6 to 12 h before and during planned percutaneous coronary intervention. It is therefore recommended to begin adjunctive treatment with GP IIb/IIIa antagonists before percutaneous coronary intervention, and to continue abciximab for 12 h and other GP IIb/IIIa inhibitors for 24 h after the procedure<sup>[129,140]</sup>.

The EPISTENT trial demonstrated that the combination of stent implantation and abciximab was associated with a significantly lower rate of major complications, than the combination of stent and placebo and also that the combination of stent and abciximab compared to balloon and abciximab was superior<sup>[136]</sup>. These findings were consistent in the subset of patients with unstable coronary disease<sup>[136]</sup>. After stent implantation, patients can be discharged quickly on a combination of ticlopidine and aspirin for 1 month or on clopidogrel and aspirin. This latter appears to be safer and better tolerated<sup>[124–131]</sup>.

#### *Coronary artery bypass surgery*

Modern surgical techniques result in low operative mortality, of 4.7% (range 1.8% to 7.7%), and an acceptable perioperative myocardial infarction rate of 9.6% (range 1% to 16.7%)<sup>[87,156–158]</sup>. Surgery for postinfarction (<30 days) unstable angina has similar (6.8%) operative mortality rates (range 0 to 16%) and perioperative myocardial infarction (5.9%) rates (range 0 to 15%). Patients with unstable coronary artery disease undergoing bypass grafting have varying risk profiles. Perioperative mortality and morbidity is higher in patients with severe unstable angina (Braunwald Class III) and in patients with unstable angina after a recent (<7 days) myocardial infarction. However, it is noteworthy that in the most recent trials of invasive treatment (FRISC 2), CABG was associated with a low risk of mortality (2.1%), although the majority of these surgical procedures were performed in patients with left main or multivessel disease and early after infarction (<7 days)<sup>[151]</sup>.

#### *Respective indications for percutaneous coronary intervention or surgery*

Patients with single-vessel disease and indications for revascularization are usually treated by percutaneous coronary intervention with stent implantation and

adjunctive treatment with GP IIb/IIIa inhibitors. In these patients, surgical revascularization is only considered if unsuitable anatomy (extreme tortuosity of the vessel or marked angulation) precludes safe percutaneous intervention.

Patients with left main or three-vessel disease, especially those with associated left ventricular dysfunction, are usually managed with CABG. In this situation CABG is well documented to prolong survival, improve quality of life and reduce readmissions<sup>[159]</sup>. Furthermore it is a more cost-effective alternative than percutaneous coronary intervention because of better symptom relief and a decreased need for repeat intervention<sup>[159–161]</sup>.

In patients with two-vessel disease (or three-vessel disease with lesions suitable for stenting), the relative merits of surgery compared with percutaneous coronary intervention need to be evaluated on an individual patient basis. A subgroup analysis of unstable patients in the BARI and CABRI trial did not show a significant difference in the combined end-point of in-hospital mortality and myocardial infarction between the angioplasty and surgical groups<sup>[159–165]</sup>. However, there was a significant difference in the rate of repeat revascularization procedures, in both trials, which was higher for the PTCA strategy ( $\approx 40\%$  to  $60\%$ ) than for the CABG strategy ( $\approx 5\%$  to  $10\%$ ). The BARI trial followed their patients for 7 years; during that period there was no difference in the mortality rate<sup>[160]</sup>, except for patients with diabetes mellitus who had a better outcome with surgery than with PTCA.

Interventional cardiology is a continuously and rapidly evolving field and current state of the art practice of percutaneous coronary intervention is best presented in the ARTS trial. This study is a randomized trial comparing the efficacy and cost-effectiveness of stenting vs CABG in patients with multivessel coronary artery disease. A total of 1200 patients were randomized. The proportion of unstable patients was around 36% in each group. Treatment was successful in 97% of the stent group and 96% of the surgical group. The composite adverse event rate (death, myocardial infarction, stroke, and need for revascularization) at 30 days was 8.7% in the stent group and 6.8% in the surgery group ( $P=ns$ ). The composite end-point including death/myocardial infarction/stroke was 5.0% in the stent group and 6.0% in the surgery group. In these selected patients, there is no firm evidence that one strategy is superior to the other. However, in many cases with multivessel disease, some of the lesions cannot be appropriately managed with angioplasty and stenting, and therefore surgery will be the obvious first-line choice.

In a few patients with multivessel disease, who require total revascularization which is not achievable with percutaneous coronary intervention, but in whom early surgery poses an extremely high risk, one might prefer a strategy of initial percutaneous treatment of the 'culprit' lesion only. Also patients with severe comorbidity, which precludes surgery, may undergo 'staged percutaneous treatment'. In patients with left main narrowing who have severe associated

co-morbidity, angioplasty with stent implantation is acceptable in selected cases.

#### *Invasive treatment strategy vs conservative strategy*

Three randomized trials compared invasive and medical strategies: TIMI-IIIb, VANQWISH and FRISC-II<sup>[37,150,166]</sup>. The three trials had major differences in design and included different patient populations. In TIMI-IIIb, invasively and medically treated patients had similar rates of mortality and of myocardial infarction. However, a post hoc subgroup analysis showed a mortality advantage for invasive treatment in patients older than 65 years<sup>[37,150]</sup>. However, it is important to emphasize that in the TIMI-IIIb trial, an important number of patients randomized to conservative management actually underwent intervention. In VANQWISH there was an excess of death or myocardial infarction at 30 days and 1 year in the invasive arm. In particular, the in-hospital surgical mortality rate of 11% in the early invasive arm was surprisingly high whilst there were no deaths in the angioplasty group<sup>[37,150]</sup>.

The more recent FRISC-II trial enrolled 2457 high-risk unstable patients with chest pain within 48 h of admission, ST-segment depression or T-wave inversion or biochemical markers above the normal range<sup>[151]</sup>. Patients allocated to the early invasive strategy underwent a procedure at an average of 4 days (PTCA) or 8 days (CABG), and the non-invasive arm had intervention only for severe angina. Revascularization procedures were carried out within the first 10 days in 71% of the invasive and 9% of the conservative arms, and within 12 months in 78% of the invasive and 43% of the conservative arms. At 1 year, percutaneous coronary intervention was performed in 44% of patients in the invasive arm and in 21% of those in the conservative arm. Two-thirds had stent implantation while only 10% received abciximab. CABG was performed in 38% of patients in the invasive arm and in 23% of those in the conservative arm. After 1-year of follow-up there was a significant reduction in total mortality, 2.2% vs 3.9% (RR=0.57, 95% CI 0.36–0.90 as well as a significant reduction in myocardial infarction of 8.6% vs 11.6% (RR=0.74, 95% CI 0.59–0.94) in favour of the invasive strategy. Accordingly, there was a significant reduction in the composite end-point of death or myocardial infarction in the invasive compared with the non-invasive group: 10.4% vs 14.1% (RR=0.74 (95% CI 0.60–0.92). Furthermore the symptoms of angina and the need for readmissions were halved by the invasive strategy.

From FRISC 2, it appears that a modern invasive strategy, preceded by modern antiischaemic and anti-thrombotic medication, in moderate to high-risk patients with unstable coronary artery disease reduces death, myocardial infarction, symptoms and readmissions compared to a conservative strategy<sup>[151]</sup>. **(Evidence level B).** Further studies should assess whether this outcome can be further improved if the invasive procedures are performed even earlier.

## Management strategy in acute coronary syndromes

In the following paragraphs, a strategy is outlined which is applicable to most patients admitted with a suspected acute coronary syndrome. It should be appreciated, however, that specific findings in individual patients may and should result in deviation from the proposed strategy. For every patient, the physician should make an individual decision taking into account the patient's history, his presentation, findings during observation or investigation in hospital, and the available treatment facilities. 'The guidelines should be used as guidelines', which will apply to the majority of cases, while other choices may be more appropriate in individual patients or in specific local circumstances.

### *Initial assessment at presentation*

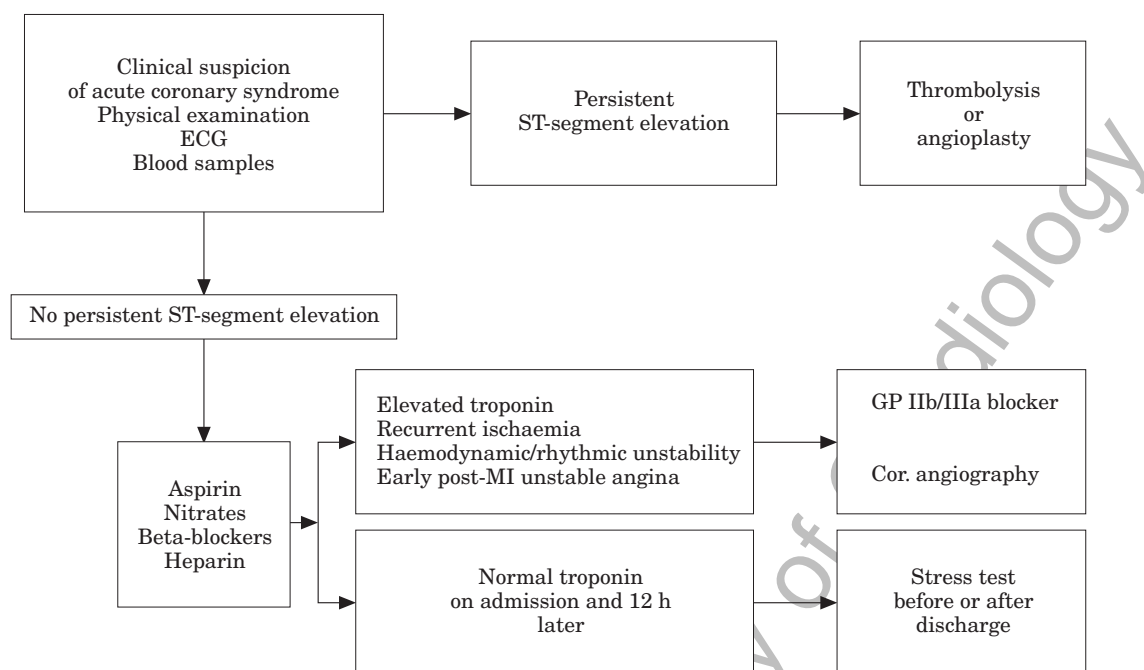
The initial assessment in patients with chest pain or other symptoms of presumed cardiac ischaemic origin should include a careful history, a physical examination with particular attention to the possible presence of valvular heart disease (aortic stenosis), hypertrophic cardiomyopathy, heart failure, and pulmonary disease. An electrocardiogram should be performed, and ECG monitoring for arrhythmias started. Multi-lead ECG ischaemia monitoring is recommended. If the patient experiences a new episode of chest pain, an ECG should be obtained and compared with a tracing obtained when symptoms have resolved spontaneously or after nitrates. Comparison with a previous ECG, if available, is very valuable, particularly in patients with co-existing cardiac pathology such as left ventricular hypertrophy. Laboratory assessments should include haemoglobin (to detect anaemia) and markers of myocardial damage; preferably cardiac troponin T or cardiac troponin I.

### *Patients with signs of recent occlusion of a major coronary artery*

Persistent ST segment elevation on the electrocardiogram or new bundle branch block are candidates for immediate reperfusion therapy. Management of these patients falls outside the scope of current guidelines. We refer to the European Society Guidelines on Acute Myocardial Infarction<sup>[4]</sup>.

### *Patients with suspected acute coronary syndromes*

Such patients (ST segment depression, negative T waves, pseudonormalization of T waves or a normal ECG) should receive initial medical treatment that may include aspirin 250 to 500 mg, heparin, beta-blocker and oral or intravenous nitrates in case of persistent or



**Figure 8** Recommended strategy in acute coronary syndromes.

recurrent chest pain. Calcium antagonists may be selected instead of beta-blockers in those patients who have contraindications to, or who are known not to tolerate a beta-blocker. In the following observation period (8–12 h) specific attention should be given to recurrence of chest pain, during which an ECG will be recorded. Signs of haemodynamic instability should be carefully noted (hypotension, pulmonary rales) and treated. Continuous multi-lead ischaemia monitoring is recommended and troponin measurements must be repeated. Based on these clinical, electrocardiographical and biochemical data, risk assessment can be performed and a further treatment strategy can be selected (Fig. 8).

*Patients judged to be at high risk for progression to myocardial infarction or death*

*High-risk patients include:*

- (a) *Patients with recurrent ischaemia (either recurrent chest pain or dynamic ST segment changes, in particular ST segment depression, or transient ST segment elevation)*
- (b) *Patients with elevated troponin levels*
- (c) *Patients who develop haemodynamic instability within the observation period*
- (d) *Patients with major arrhythmias (repetitive ventricular tachycardia, ventricular fibrillation)*
- (e) *Patients with early post-infarction unstable angina*

In these patients the following strategy is recommended:

- (1) Introduction of GP IIb/IIIa receptor blocker. While waiting and preparing for angiography, treatment with heparin should be continued. Administration of

GP IIb/IIIa receptor blocker will be started and continued for 12 (abciximab) or 24 (tirofiban, eptifibatide) h after the procedure if angioplasty is performed.

- (2) Coronary angiography should be performed during the initial hospitalization and as soon as possible in patients with major arrhythmias, haemodynamic instability, post-myocardial infarction, unstable angina, or a history of prior bypass surgery. In patients with lesions suitable for myocardial revascularization, the decision regarding the most appropriate procedure will be made after careful evaluation of the extent and characteristics of the lesions. In general, recommendations for the choice of a revascularization procedure in unstable angina are similar to those for elective revascularization procedures. If balloon angioplasty with or without a stent is the selected procedure, it may be performed immediately after angiography in the same session. In patients with single vessel disease, percutaneous intervention of the culprit lesion is the first choice. In patients with left main or triple vessel disease, CABG is the recommended procedure, particularly in patients with left ventricular dysfunction, except in cases of serious co-morbidity, which contraindicate surgery. In double-vessel and in some cases of triple-vessel coronary disease, either percutaneous intervention or coronary bypass surgery may be appropriate. In some patients, a staged procedure may be considered, with immediate balloon angioplasty and stenting of the culprit lesion and subsequent reassessment of the need for treatment of other lesions, either by a percutaneous procedure or CABG.

- (3) In patients in whom revascularization is judged **not to be feasible**, continuation of heparin (low molecular weight heparin) for second week is recommended (FRISC II).

If angiography reveals no major coronary stenosis, patients will be referred for medical therapy. The diagnosis of an acute coronary syndrome may need to be reconsidered and particular attention should be given to possible other reasons for the presenting symptoms. However, the absence of significant stenosis does not preclude the diagnosis of an acute coronary syndrome. In selected patients, an ergonovin test may detect or rule out excessive coronary vasoconstriction.

*Patients considered to be at low risk for rapid progression to myocardial infarction or death*  
*Low risk patients include:*

*Patients who have no recurrence of chest pain within the observational period*

*Patients without elevation of troponin or other biochemical markers of myocardial necrosis*

*Patients without ST-segment depression or elevation but rather negative T waves, flat T waves or normal ECG*

In these patients, oral treatment should be recommended, including aspirin, beta-blockers and possibly nitrates or calcium antagonists. Secondary preventive measures should be instituted as discussed below. Low molecular weight heparin may be discontinued when, after the observation period, **no ECG changes** are apparent and **a second troponin measurement is negative**.

A stress test is recommended. The purpose of such a test is first, to confirm or establish a diagnosis of coronary artery disease and second, to assess the risk for future events in patients with coronary artery disease.

In patients with significant ischaemia during the stress test, coronary angiography and subsequent revascularization, should be considered, particularly when this occurs at a low workload on the bicycle or treadmill. It should be appreciated that a standard exercise test may be inconclusive (no abnormalities at a relatively low workload). In such patients an additional stress echocardiogram, or stress myocardial perfusion scintigram may be appropriate. Further details are provided in the Guidelines for cardiac exercise testing of the ESC Working Group on Exercise Physiology, Physiopathology and Electrocardiography (*European Heart Journal* 1993; **14**: 969–988).

In some patients the diagnosis may remain uncertain, particularly in patients with a normal electrocardiogram throughout the observation period, without elevated markers of myocardial necrosis, and with a normal stress test and good exercise tolerance. The symptoms resulting in presentation to the hospital were probably not caused by myocardial ischaemia, and additional investigations of other organ systems may be appropriate. In any case, the risk for cardiac events in such patients is very low. Therefore, additional tests can

usually be performed at a later time, at the outpatient clinic.

## Long-term management

Aggressive and extensive risk factor modification is warranted in all patients. Observational studies show that most cardiac events occur within a few months following the initial presentation of acute coronary syndromes<sup>[21,34]</sup>. Initial stabilization of a patient's clinical condition does not imply that the underlying pathological process has stabilized. There are sparse data concerning the duration of the healing process of ruptured plaques<sup>[167]</sup>. Some studies have shown sustained potential for rapid progression of culprit lesions in acute coronary syndromes despite initial clinical stability on medical therapy. Increased thrombin generation has been observed for as long as 6 months following unstable angina or myocardial infarction<sup>[19,168,169]</sup>. In addition, trials that examined the efficacy of heparin in addition to aspirin reported an increase in clinical events after heparin withdrawal<sup>[109,117]</sup>. Continuation of low molecular weight heparin should therefore be considered in patients with recurrent ischaemia or in those at high risk for progression to myocardial infarction in whom revascularization is not possible.

Beta-blockers improve prognosis in patients after myocardial infarction and should be continued after acute coronary syndromes.

Patients should quit smoking. Lipid lowering therapy should be initiated without delay. HMG-CoA reductase inhibitors substantially decrease mortality and coronary events in patients with high or intermediate LDL cholesterol<sup>[170]</sup>. In these trials, patients were enrolled with stable coronary artery disease, and the beneficial effect of statins became apparent after 1 or 2 years therapy. There are indications, however, that such therapy may also help to improve endothelial function. Specific trials are ongoing to assess whether statins indeed provide immediate benefit in acute coronary syndromes (MIRACL, A to Z) and whether high doses are more effective than intermediate doses (TNT, SEARCH, IDEAL). Several lipid intervention angiographic trials suggest that improved clinical outcome was not necessarily related to atherosclerosis regression, but might relate to passivation of inflamed plaque, reversal of endothelial dysfunction, or a decrease in prothrombotic factors<sup>[171]</sup>.

A role for angiotensin converting enzyme (ACE) inhibitors in secondary prevention of coronary syndromes has been suggested. The SAVE (Survival and Ventricular Enlargement) and SOLVD (Studies on Left Ventricular Dysfunction) randomized trials performed in subjects with left ventricular impairment reported a reduction in cardiac events in patients with known coronary artery disease treated with ACE inhibitors<sup>[172–174]</sup>. The decrease in myocardial infarction rate became apparent after 6 months of active

treatment. These data strongly suggest that the beneficial effect of ACE inhibition goes beyond blood pressure control<sup>[175,176]</sup>. This concept is supported by experimental data indicative that the advantage may also be related to plaque stabilization<sup>[177]</sup> and by the recently published results of the HOPE (Heart Outcomes Prevention Evaluation) trial which showed a reduction of cardiovascular death (relative risk reduction for ramipril vs placebo=25%;  $P=0.0002$ ) and myocardial infarction (relative risk reduction=20%;  $P=0.005$ ) among patients without heart failure or low ejection fraction observed over 4–6 years<sup>[178]</sup>. Other trials are ongoing to confirm these findings: EUROPA (European Trial of Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease) and PEACE (Prevention of Events with ACE Inhibitors Study), which may establish new strategies to prevent occurrence of coronary syndromes<sup>[179]</sup>.

Since coronary atherosclerosis and its complications are multifactorial, much attention should be paid to treat all modifiable risk factors in an effort to reduce recurrence of cardiac events.

### Appendix: Prinzmetal variant angina

Prinzmetal's angina or variant angina is a syndrome characterized by episodes of transient acute myocardial ischaemia, with or without typical chest pain, associated with *transient* ST segment elevation. Chest pain and *transient* ST elevation can last several minutes and resolve either spontaneously or after nitroglycerin. Epidemiological data indicate that 0.5–1% of patients admitted to hospital with angina pectoris have vasospastic angina

Variant angina goes through waxing and waning phases of activity. Indeed, patients may have numerous daily episodes of ischaemia, over a short period of time, followed by long periods of apparent resolution of the disease, with absence of symptomatic or silent ischaemic attacks. It is thought that these waxing and waning phases are related to variability in the degree of local hypersensitivity, or in the intensity of the underlying, poorly understood stimuli, that provoke spasm.

The underlying mechanisms of spasm induction are still unclear. There is a consensus that local hyper-reactivity of coronary smooth muscle to a variety of constrictor stimuli (endothelium-derived factors, platelet-derived vasoactive substances, variation in autonomic tone), which operate through various surface receptors, may be involved.

In patients without a previous infarction, a diagnosis of variant angina may be suspected based on the occurrence of *transient* ST elevation, with or without typical chest pain, and by the prompt resolution of symptoms and ECG changes after sublingual or intravenous administration of nitroglycerin. However, transient

thrombotic occlusion on a non-obstructive plaque may produce similar findings. Holter recording allows the identification of episodes of myocardial ischaemia without significant changes in heart rate, a finding that suggests a primary reduction in oxygen supply i.e. vasoconstriction as the mechanism of ischaemia. *Exercise stress testing* in patients with variant angina may be negative or positive with either ST depression or elevation. ST elevation immediately after exercise is suggestive of coronary spasm<sup>[180]</sup> but can also occur with critical stenoses.

In patients with unstable angina and significant stenosis, transient ST segment elevation may be related to platelet aggregation, and subsequent mural thrombus formation accompanied by increased coronary tone rather than coronary spasm. This can lead to transient complete occlusion<sup>[181]</sup>.

Widespread diffuse coronary vasoconstriction is rare, but in patients with typical variant angina, a mild, diffuse vasoconstriction of non-spastic segments is often observed.

Angiography can identify near normal vessels or significant narrowing. The typical picture of variant angina is clearly seen in patients with normal or nearly normal coronary arteries at angiography.

Provocative tests such as ergonovine and hyperventilation have provided specific and reliable methods to define the clinical and angiographical conditions in which coronary spasm plays a key role in the induction of myocardial ischaemia<sup>[182–185]</sup>. A positive response to provocative tests (ergonovine) has been reported in 4% of all patients with angiographically non-significant coronary artery stenoses<sup>[182]</sup> and in up to 20% of patients with a recent myocardial infarction. Provocative tests should be considered in patients with episodes of angina at rest and negative exercise stress testing, specifically when attempts to document ST elevation during pain have failed. Sustained hyperventilation is also used but is less sensitive than ergonovine.

In the waxing phase of the disease patients with variant angina are at risk of myocardial infarction and sudden cardiac death<sup>[186]</sup>. Lethal cardiac events are more frequent in patients with complex ventricular tachyarrhythmias or atrioventricular block associated with transient myocardial ischaemia. On treatment, the long-term outcome is quite favourable but more than a third of patient remains symptomatic<sup>[186,187]</sup>. The cardiovascular death rate is 0.5% per year, and the risk of myocardial infarction: 1.2% per year.

Many factors have been considered predictive for cardiac events during follow-up, but there is a large consensus that the greater the number of diseased arteries the higher the risk of death or acute myocardial infarction during follow-up<sup>[188–190]</sup>. Treatment consists of calcium antagonists, often at high doses, in association with nitrates. It is useful to adapt the medication schedule as a function of the circadian variation in episodes of spasm. Stent implantation has been proposed for treatment of focal refractory spasm.

## References

- [1] Davies MJ, Richardson PJWN, Katz DR, Mann J. Risk of thrombosis in human atherosclerotic plaques: role of extracellular lipid, macrophage, and smooth muscle cell content. *Br Heart J* 1993; 69: 377–381.
- [2] Davies M. Acute coronary thrombosis: the role of plaque disruption and its initiation and prevention. *Eur Heart J* 1995; 16 (Suppl L): 3–7.
- [3] Davies M. The composition of coronary artery plaque. *N Engl J Med* 1997; 336: 1312–13.
- [4] Task force on the management of acute myocardial infarction of the European Society of Cardiology. Acute myocardial infarction: prehospital and in-hospital management. *Eur Heart J* 1996; 17: 43–63.
- [5] Fuster VBL, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med* 1992; 326: 242–50, 310–18.
- [6] Fuster V. Mechanisms leading to myocardial infarction: insights from studies of vascular biology. *Circulation* 1994; 90: 2126–46.
- [7] Burke APFA, Tang AL. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med* 1997; 336: 1276–82.
- [8] Farb ABA, Tang AL. Coronary plaque erosion without rupture into a lipid core: a frequent cause of coronary thrombosis in sudden coronary death. *Circulation* 1996; 93: 1354–63.
- [9] Arbustini EDBB, Morbini P, Burke AP, Bociarelli M, Specchia G, Virmani. Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. *Heart* 1999; 82: 269–72.
- [10] Libby P. Molecular basis of the acute coronary syndromes. *Circulation* 1995; 91: 2844–50.
- [11] Moreno PR, Falk E, Palacios IF, Newell JB, Fuster V, Fallon JT. Macrophage infiltration in acute coronary syndromes. Implications for plaque rupture. *Circulation* 1994; 90: 775–8.
- [12] Kaartinen A, Penttila A, Kovanen P. Accumulation of activated mast cells in the shoulder region of human coronary atheroma, the predilection site of atheromatous rupture. *Circulation* 1994; 90: 1669–78.
- [13] Kaartinen M, van der Wal A, van der Loos C. Mast cell infiltration in acute coronary syndromes: implications for plaque rupture. *J Am Coll Cardiol* 1998; 32: 606–12.
- [14] Arbustini E, De Servi S, Bramucci E *et al.* Comparison of coronary lesions obtained by directional coronary atherectomy in unstable angina, stable angina, and restenosis after either atherectomy or angioplasty. *Am J Cardiol* 1995; 75: 675–82.
- [15] Arbustini E, Morbini P, De Servi S *et al.* Histopathologic features in atherectomy samples obtained from patient with unstable angina, stable angina and restenosis. Directional Atherectomy Lombardi Group. *G Ital Cardiol* 1996; 26: 623–33.
- [16] Toschi V, Gallo R, Lettino M, Fallon J. Tissue factor predicts the thrombogenicity of human atherosclerotic components. *Circulation* 1997; 95: 594–9.
- [17] Willerson J, Golino PEJ, Campbell W, Buja M. Specific platelet mediators and unstable coronary artery lesions: experimental evidence and potential clinical implications. *Circulation* 1989; 80: 198–205.
- [18] Falk E. Morphologic features of unstable atherothrombotic plaques underlying acute coronary syndromes. *Am J Cardiol* 1989; 63: 114E–120E.
- [19] Falk E, Fuster V. Angina pectoris and disease progression [editorial; comment]. *Circulation* 1995; 92: 2033–5.
- [20] Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995; 92: 657–71.
- [21] van Domburg R, van Miltenburg-van Zijl A, Veerhoeck R, Simoons M. Unstable angina: good long-term outcome after a complicated early course. *J Am Coll Cardiol* 1998; 31: 1534–9.
- [22] Lee T, Cook F, Erb R. Acute chest pain in the emergency room. *Arch Int Med* 1985; 145: 65–9.
- [23] Fesmire FM, Percy RF, Bardoner JB, Wharton DR, Calhoun FB. Usefulness of automated serial 12-lead ECG monitoring during the initial emergency department evaluation of patients with chest pain. *Ann Emerg Med* 1998; 31: 3–11.
- [24] Fisch C. *The Clinical ECG: Sensitivity and Specificity*. Elsevier Science publishers, 1997.
- [25] Lee T, Cook E, Weisberg M. Impact of the availability of a prior ECG on the triage of the patient with acute chest pain. *J Gen Intern Med* 1990; 5: 381–8.
- [26] McCarthy B, Wong J, Selker H. Detecting acute ischemia in the emergency department. *J Gen Intern Med* 1990; 5: 365–73.
- [27] Rouan G, Lee T, Cook E. Clinical characteristics and outcome of acute myocardial infarction in patients with normal or nonspecific electrocardiograms. *Am J Cardiol* 1989; 64: 1087–92.
- [28] Pozen M, D'Agostino R, Selker H. A predictive instrument to improve CCU admission practices in acute ischemic heart disease. A prospective multicenter clinical trial. *N Engl J Med* 1984; 310: 1279–92.
- [29] Katus H, Looser S, Hallermayer K. Development and in vitro characterization of a new immunoassay of cardiac troponin T. *Clin Chem* 1992; 38: 386–93.
- [30] Davies E, Gawad Y, Takashi M. Analytical performance and clinical utility of a sensitive immunoassay for determination of human cardiac troponin I. *Clin Biochem* 1997; 30: 479–90.
- [31] Cohen M, Demers C, Gurfinkel EP *et al.* A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med* 1997; 337: 447–52.
- [32] Campbell R, Wallentin L, Verheugt F, Turpie A. Management strategies for a better outcome in unstable coronary artery disease. *Clin Cardiol* 1998; 21: 314–22.
- [33] Braunwald E, Jones RH, Mark DB *et al.* Diagnosing and managing unstable angina. Agency for Health Care Policy and Research. *Circulation* 1994; 90: 613–22.
- [34] Theroux P, Fuster V. Acute coronary syndromes: unstable angina and non-Q-wave myocardial infarction. *Circulation* 1998; 97: 1195–206.
- [35] Braunwald E. Unstable angina. A classification. *Circulation* 1989; 80: 410–4.
- [36] van Miltenburg-van Zijl AJ, Simoons ML, Veerhoeck RJ, Bossuyt PM. Incidence and follow-up of Braunwald subgroups in unstable angina pectoris. *J Am Coll Cardiol* 1995; 25: 1286–92.
- [37] TIMI IIIB investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation* 1994; 89: 1545–56.
- [38] Andersen K, Eriksson PMD. Ischaemia detected by continuous on-line vectocardiographic monitoring predicts unfavourable outcome in patients admitted with probable unstable coronary artery disease. *Coron Art Dis* 1996; 7: 753–60.
- [39] Langer A, Freeman MR, Armstrong PW. ST segment shift in unstable angina: pathophysiology and association with coronary anatomy and hospital outcome. *J Am Coll Cardiol* 1989; 13: 1495–502.
- [40] Gottlieb S, Weisfeldt M, Ouyang P. Silent myocardial ischemia as a marker for early unfavorable outcomes in patients with unstable angina. *N Engl J Med* 1986; 314: 1214–19.
- [41] Larsson H, Areskog M, Areskog NH *et al.* The diagnostic and prognostic importance of ambulatory ST recording compared to a predischARGE exercise test after an episode of unstable angina or non-Q wave myocardial infarction. *Eur Heart J* 1995; 16: 888–93.

- [42] Wilcox I, Ben Freedman S, Kelly DT, Harris PJ. Clinical significance of silent ischemia in unstable angina pectoris. *Am J Cardiol* 1990; 65: 1313-6.
- [43] Patel DJ, Holdright DR, Knight CJ *et al*. Early continuous ST segment monitoring in unstable angina: prognostic value additional to the clinical characteristics and the admission electrocardiogram. *Heart* 1996; 75: 222-8.
- [44] Andersen K, Dellborg M. Heparin is more effective than inogatran, a low-molecular weight thrombin inhibitor in suppressing ischemia and recurrent angina in unstable coronary disease. Thrombin Inhibition in Myocardial Ischemia (TRIM) Study Group. *Am J Cardiol* 1998; 81: 939-44.
- [45] Frostfeldt GAG, Gustafsson G, Helmius G *et al*. Low molecular weight heparin (Dalteparin) as adjuvant treatment to thrombolysis in acute myocardial infarction — a pilot study: Biochemical markers in Acute Coronary Syndromes (BIOMACSII). *J Am Coll Cardiol* 1999; 33: 627-33.
- [46] Klootwijk P, Meij S, von Es GA *et al*. Comparison of usefulness of computer assisted continuous 48-h 3-lead with 12-lead ECG ischaemia monitoring for detection and quantitation of ischaemia in patients with unstable angina. *Eur Heart J* 1997; 18: 931-40.
- [47] Klootwijk P, Meij S, Melkert R, Lenderink T, Simoons ML. Reduction of recurrent ischemia with abciximab during continuous ECG-ischemia monitoring in patients with unstable angina refractory to standard treatment (CAPTURE). *Circulation* 1998; 98: 1358-64.
- [48] Klootwijk P, Lenderink T, Meij S *et al*. Anticoagulant properties, clinical efficacy and safety of efigatran, a direct thrombin inhibitor, in patients with unstable angina. *Eur Heart J* 1999; 20: 1101-11.
- [49] Hamm CW, Ravkilde J, Gerhardt W *et al*. The prognostic value of serum troponin T in unstable angina. *N Engl J Med* 1992; 327: 146-50.
- [50] Pettersson T, Ohlsson O, Tryding N. Increased CKMB (mass concentration) in patients without traditional evidence of acute myocardial infarction. A risk indicator of coronary death. *Eur Heart J* 1992; 13: 1387-92.
- [51] Ravkilde J, Hansen AB, Horder M, Jorgensen PJ, Thygesen K. Risk stratification in suspected acute myocardial infarction based on a sensitive immunoassay for serum creatine kinase isoenzyme MB. A 2.5-year follow-up study in 156 consecutive patients. *Cardiology* 1992; 80: 143-51.
- [52] Stubbs P, Collinson P, Moseley D, Greenwood T, Noble M. Prospective study of the role of cardiac troponin T in patients admitted with unstable angina. *Br Med J* 1996; 313: 262-4.
- [53] Wu AH, Abbas SA, Green S *et al*. Prognostic value of cardiac troponin T in unstable angina pectoris. *Am J Cardiol* 1995; 76: 970-2.
- [54] Lindahl B. Biochemical markers of myocardial damage for early diagnosis and prognosis in patients with acute coronary syndromes. Minireview based on a doctoral thesis. *Ups J Med Sci* 1996; 101: 193-232.
- [55] Lindahl B, Venge P, Wallentin L. Relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease. The FRISC study group. *Circulation* 1996; 93: 1651-7.
- [56] Lindahl B, Venge P, Wallentin L. Troponin T identifies patients with unstable coronary artery disease who benefit from long-term antithrombotic protection. Fragmin in Unstable Coronary Artery Disease (FRISC) Study Group. *J Am Coll Cardiol* 1997; 29: 43-8.
- [57] Antman EM, Tanasijevic MJ, Thompson B *et al*. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996; 335: 1342-9.
- [58] Lüscher MS, Thygesen K, Ravkilde J, Heickendorff L. Applicability of cardiac troponin T and I for early risk stratification in unstable coronary artery disease. TRIM Study Group. Thrombin Inhibition in Myocardial ischemia. *Circulation* 1997; 96: 2578-85.
- [59] Galvani M, Ottani F, Ferrini D *et al*. Prognostic influence of elevated values of cardiac troponin I in patients with unstable angina. *Circulation* 1997; 95: 2053-9.
- [60] Lindahl B, Andren B, Ohlsson J, Venge P, Wallentin L. Risk stratification in unstable coronary artery disease. Additive value of troponin T determinations and pre-discharge exercise tests. FRISK Study Group. *Eur Heart J* 1997; 18: 762-70.
- [61] Holmvang L, Andersen K *et al*. Relative contributions of a single-admission 12-lead electrocardiogram and early 24-hour continuous electrocardiographic monitoring for early risk stratification in patients with unstable coronary artery disease. *Am J Cardiol* 1999; 83: 667-74.
- [62] Dellborg M, Andersen K. Key factors in the identification of the high-risk patient with unstable coronary artery disease: clinical findings, resting 12-lead electrocardiogram, and continuous electrocardiographic monitoring. *Am J Cardiol* 1997; 80: 35E-39E.
- [63] Toss H, Lindahl B, Siegbahn A, Wallentin L. Prognostic influence of increased fibrinogen and C-reactive protein levels in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. *Circulation* 1997; 96: 4204-10.
- [64] Hamm C, Heeschen C, Goldmann B *et al*. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin level. *N Engl J Med* 1999; 340: 1623-9.
- [65] FRISC II Investigators. Long-term low-molecular-weight heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999; 354: 701-7.
- [66] Heeschen C, Hamm C, Goldmann B, Deu A, Langenbrink L, White H. Troponin concentrations for stratification of patients with acute syndromes in relation to therapeutic efficacy of tirofiban. *Lancet* 1999; 354: 1757-62.
- [67] Becker R, Cannon C, Bovill E *et al*. Prognostic value of plasma fibrinogen concentration in patients with unstable angina and non-Q-wave myocardial infarction (TIMI IIIB trial). *Am J Cardiol* 1996; 78: 142-7.
- [68] Pollak H, Fischer M, Fritsch S, Enekel W. Are admission plasma fibrinogen levels useful in the characterization of risk groups after myocardial infarction treated with fibrinolysis? *Thromb Haemost* 1991; 66: 406-9.
- [69] Morrow D, Rifai N, Antman E. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes. *J Am Coll Cardiol* 1998; 31: 1460-5.
- [70] Kuller L, Tracy R, Shaten J. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. *Am J Epidemiol* 1996; 144: 537-47.
- [71] Ardissone D, Merlini P, Gamba G. Thrombin activity and early outcome in unstable angina. *Circulation* 1996; 93: 1634-9.
- [72] Ernfors M, Strekerud F, Toss H, Abildgaard U, Wallentin L, Siegbahn A. Low-molecular weight heparin reduces the generation and activity of thrombin in unstable coronary artery disease. *Thromb Haemost* 1998; 79: 491-4.
- [73] Meade TW, Ruddock V, Stirling Y, Chakrabarti R, Miller GJ. Fibrinolytic activity, clotting factors, and long-term incidence of ischaemic heart disease in the Northwick Park Heart Study. *Lancet* 1993; 342: 1076-9.
- [74] Meade TW. Routine measurement of fibrinogen concentration. Clinically feasible [letter; comment]. *Br Med J* 1993; 307: 1562.
- [75] Meade TW. Fibrinogen in ischaemic heart disease. *Eur Heart J* 1995; 16 (Suppl A): 31-5.
- [76] Munkvad S, Gram J, Jespersen J. A depression of active tissue plasminogen activator in plasma characterizes patients with unstable angina pectoris who develop myocardial infarction. *Eur Heart J* 1990; 11: 525-8.
- [77] Hamsten A, Walldius G, Szamosi A. Plasminogen activator in plasma: risk factor for recurrent myocardial infarction. *Lancet* 1987; 3-8.

- [78] Kruskal JCP, Franks J, Kirsch R. Fibrin and fibrinogen-related antigens in patients with stable and unstable coronary artery disease. *N Engl J Med* 1987; 22: 1361-5.
- [79] Wilcox I, Freedman SB, Allman KC *et al.* Prognostic significance of a predischARGE exercise test in risk stratification after unstable angina pectoris. *J Am Coll Cardiol* 1991; 18: 677-83.
- [80] Wilcox I, Freedman SB, Li JN, Harris PJ, Kelly DT. Comparison of exercise stress testing with ambulatory electrocardiographic monitoring in the detection of myocardial ischemia after unstable angina pectoris. *Am J Cardiol* 1991; 67: 89-91.
- [81] Launbjerg J, Fruergaard P, Jacobsen HL, Madsen JK. Long-term risk factors from non-invasive evaluation of patients with acute chest pain, but without myocardial infarction. *Eur Heart J* 1995; 16: 30-7.
- [82] Nyman I, Wallentin L, Areskog M, Areskog NH, Swahn E. Risk stratification by early exercise testing after an episode of unstable coronary artery disease. The RISC Study Group. *Int J Cardiol* 1993; 39: 131-42.
- [83] Amanullah AM, Lindvall K, Bevegard S. Exercise echocardiography after stabilization of unstable angina: correlation with exercise thallium-201 single photon emission computed tomography. *Clin Cardiol* 1992; 15: 585-9.
- [84] Amanullah AM, Lindvall K. PredischARGE exercise echocardiography in patients with unstable angina who respond to medical treatment. *Clin Cardiol* 1992; 15: 417-23.
- [85] Amanullah AM, Lindvall K, Bevegard S. Prognostic significance of exercise thallium-201 myocardial perfusion imaging compared to stress echocardiography and clinical variables in patients with unstable angina who respond to medical treatment. *Int J Cardiol* 1993; 39: 71-8.
- [86] Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging in patients with unstable angina who respond to medical treatment. *J Am Coll Cardiol* 1991; 17: 1053-7.
- [87] Luchi R, Scott, Deupree. Comparison of medical and surgical treatment for unstable angina pectoris. *N Engl J Med* 1987; 316: 977-84.
- [88] Gottlieb S, Weisfeldt ML, Ouyang P *et al.* Effect of the addition of propranolol to therapy with nifedipine for unstable angina pectoris: a randomized, double-blind, placebo-controlled trial. *Circulation* 1986; 73: 331-7.
- [89] Telford A, Wilson C. Trial of heparin versus atenolol in prevention of myocardial infarction in intermediate coronary syndrome. *Lancet* 1981; 1 (8232): 1225-8.
- [90] Lubsen JTT. Efficacy of nifedipine and metoprolol in the early treatment of unstable angina in the coronary care unit: findings from the Holland Interuniversity Nifedipine/metoprolol Trial (HINT). *Am J Cardiol* 1987; 60: 18A-25A.
- [91] Yusuf S, Witte J, Friedman L. Overview of results of randomized trials in heart disease: unstable angina, heart failure, primary prevention with aspirin and risk factor modifications. *JAMA* 1988; 260: 2259-63.
- [92] Miami Trial Research Group. Metoprolol in acute myocardial infarction. *Eur Heart J* 1985; 6: 199-226.
- [93] DePace N, Herling IM, Kotler MN, Hakki AH, Spielman SR, Segal BL. Intravenous nitroglycerin for rest angina. Potential pathophysiologic mechanisms of action. *Arch Intern Med* 1982; 142: 1806-9.
- [94] Kaplan K, Davison R, Parker M, Przybyl J, Teagarden JRML. Intravenous nitroglycerin for the treatment of angina at rest unresponsive to standard nitrate therapy. *Am J Cardiol* 1983; 51: 694-8.
- [95] Roubin G, Harris PJ, Eckhardt I. Intravenous nitroglycerin in refractory unstable angina pectoris. *Aust NZ J Med* 1982; 12: 598-602.
- [96] Curfman G, Heinsimr JA, Lozner EC, Fung HL. Intravenous nitroglycerin in the treatment of spontaneous angina pectoris: a prospective randomized trial. *Circulation* 1983; 67: 276-82.
- [97] Dellborg M, Gustafsson G, Swedberg K. Buccal versus intravenous nitroglycerin in unstable angina pectoris. *Eur J Clin Pharmacol* 1991; 41: 5-9.
- [98] May DCPJ, Black WH *et al.* In vivo induction and reversal of nitroglycerin tolerance in human coronary arteries. *N Engl J Med* 1987; 317: 805-9.
- [99] Reichek N, Priest C, Zimrin D, Chandler T, Sutton MS. Antianginal effects of nitroglycerin patches. *Am J Cardiol* 1984; 54: 1-7.
- [100] Thadani U, Hamilton SF, Olsen E *et al.* Transdermal nitroglycerin patches in angina pectoris. Dose titration, duration of effect, and rapid tolerance. *Ann Intern Med* 1986; 105: 485-92.
- [101] Theroux P, Taeymans Y, Morissette D *et al.* A randomized study comparing propranolol and diltiazem in the treatment of unstable angina. *J Am Coll Cardiol* 1985; 5: 717-22.
- [102] Parodi OSI, Michelassi C *et al.* Comparison of verapamil and propranolol therapy for angina pectoris at rest. A randomized, multiple crossover, controlled trial in the coronary care unit. *Am J Cardiol* 1986; 57: 899-906.
- [103] Smith NLRG, Psaty BM *et al.* Health outcomes associated with beta-blocker and diltiazem treatment of unstable angina. *J Am Coll Cardiol* 1998; 32: 1305-11.
- [104] Held PYS, Furberg CD. Calcium channel blockers in acute myocardial infarction and unstable angina: an overview. *Br Med J* 1989; 299: 1187-92.
- [105] Psaty BM, Heckbert SR, Koepsell TD *et al.* The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 1995; 274: 620-5.
- [106] Yusuf S, Held P, Furberg C. Update of effects of calcium antagonists in myocardial infarction or angina in light of the second Danish Verapamil Infarction Trial (DAVIT-II) and other recent studies. *Am J Cardiol* 1991; 67: 1295-7.
- [107] Boden W, Van Gilst W, Scheldewaert R *et al.* Secondary prevention with diltiazem once daily versus placebo in patients with acute myocardial infarction treated with thrombolysis. *Lancet* 2000; in press.
- [108] Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *JAMA* 1996; 276: 811-5.
- [109] Theroux P, Ouimet H, McCans J *et al.* Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988; 319: 1105-11.
- [110] FRISC study group. Low-molecular-weight heparin during instability in coronary artery disease, Fragmin during Instability in Coronary Artery Disease (FRISC) study group. *Lancet* 1996; 347: 561-8.
- [111] Klein W, Buchwald A, Hillis SE *et al.* Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC). *Circulation* 1997; 96: 61-8.
- [112] Antman EM. TIMI 11B. Enoxaparin versus unfractionated heparin for unstable angina or non-Q-wave myocardial infarction: a double-blind, placebo-controlled, parallel-group, multicenter trial. Rationale, study design, and methods. *Thrombolysis in Myocardial Infarction (TIMI) 11B Trial Investigators. Am Heart J* 1998; 135: S353-60.
- [113] Antman EM, Cohen M, Radley D *et al.* Assessment of the treatment effect of enoxaparin for unstable Angina/Non-Q-wave myocardial infarction: TIMI 11B-ESSENCE meta-analysis. *Circulation* 1999; 100: 1602-8.
- [114] FRAXIS study group. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q wave myocardial infarction: FRAXIS (FRAXiparin in Ischaemic Syndrome). *Eur Heart J* 1999; 20: 1553-62.
- [115] Gusto IIB investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary

- syndromes. The Global Use of Strategies to Open Occluded Coronary Arteries. *N Engl J Med* 1996; 335: 775–82.
- [116] Fox KA. Implications of the Organization to Assess Strategies for Ischemic Syndromes-2 (OASIS-2) study and the results in the context of other trials. *Am J Cardiol* 1999; 84: 26M–31M.
- [117] RISC Group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. The RISC Group. *Lancet* 1990; 336: 827–30.
- [118] Theroux P, Waters D, Qiu S, McCans J, de Guise P, Juneau M. Aspirin versus heparin to prevent myocardial infarction during the acute phase of unstable angina. *Circulation* 1993; 88: 2045–8.
- [119] Cairns JA, Singer J, Gent M *et al.* One year mortality outcomes of all coronary and intensive care unit patients with acute myocardial infarction, unstable angina or other chest pain in Hamilton, Ontario, a city of 375,000 people. *Can J Cardiol* 1989; 5: 239–46.
- [120] Wallentin LC. Aspirin (75 mg/day) after an episode of unstable coronary artery disease: long-term effects on the risk for myocardial infarction, occurrence of severe angina and the need for revascularization. Research Group on Instability in Coronary Artery Disease in Southeast Sweden [comment]. *J Am Coll Cardiol* 1991; 18: 1587–93.
- [121] Balsano F, Violi F, Cimminiello C. Ticlopidine in unstable angina. *Circulation* 1990; 82: 2282–3.
- [122] Balsano F, Rizzon P, Violi F *et al.* Antiplatelet treatment with ticlopidine in unstable angina. A controlled multicenter clinical trial. The Studio della Ticlopidina nell'Angina Instabile Group. *Circulation* 1990; 82: 17–26.
- [123] CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events. *Lancet* 1996; 348: 1329–39.
- [124] Bertrand M, Legrand V, Boland J *et al.* Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting. The full anticoagulation versus aspirin and ticlopidine (Fantastic) study. *Circulation* 1998; 98: 1597–1603.
- [125] Schömig A, Neumann FJ, Kastrati A *et al.* A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery. *N Engl J Med* 1996; 334: 1084–9.
- [126] Leon M, Baim DS, Popma JJ *et al.* A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med* 1998; 339: 1665–71.
- [127] Bertrand M, Rupprecht H, Urban P, Gershlick A. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin combined with ticlopidine in combination with aspirin after coronary stenting. *Circulation* 2000; in press.
- [128] Alexander JH, Al-Khatib S, Cantor W *et al.* Highlights from the American College of Cardiology 48th Annual Scientific Sessions: March 7 to 10, 1999. *Am Heart J* 1999; 138: 175–90.
- [129] CAPTURE. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. *Lancet* 1997; 349: 1429–35.
- [130] PRISM. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM). *N Engl J Med* 1998; 338: 1498–505.
- [131] PRISM-PLUS. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. *N Engl J Med* 1998; 338: 1488–97.
- [132] PARAGON investigators. International, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. The PARAGON Investigators. Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network. *Circulation* 1998; 97: 2386–95.
- [133] Boersma E, Akkerhuis KM, Theroux P, Califf RM, Topol EJ, Simoons ML. Platelet glycoprotein IIb/IIIa receptor inhibition in non-ST-elevation acute coronary syndromes: early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. *Circulation* 1999; 100: 2045–8.
- [134] EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigators. *N Engl J Med* 1994; 330: 956–61.
- [135] EPILOG investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. The EPILOG Investigators. *N Engl J Med* 1997; 336: 1689–96.
- [136] EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. The EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet* 1998; 352: 87–92.
- [137] IMPACT II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II. *Lancet* 1997; 349: 1422–8.
- [138] RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. The RESTORE Investigators. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation* 1997; 96: 1445–53.
- [139] Brener SJ, Barr LA, Burchenal JE, Wolski KE, Effron MB, Topol EJ. Effect of abciximab on the pattern of reperfusion in patients with acute myocardial infarction treated with primary angioplasty. RAPPORT investigators. ReoPro And Primary PTCA Organization and Randomized Trial. *Am J Cardiol* 1999; 84: 728–30.
- [140] PURSUIT investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med* 1998; 339: 436–43.
- [141] PRISM-PLUS Study investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. *N Engl J Med* 1998; 338: 1488–97.
- [142] SYMPHONY Investigators. Comparison of Sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial. *Lancet* 2000; 355: 337–45.
- [143] TIMI IIIA investigators. Early effects of tissue-type plasminogen activator added to conventional therapy on the culprit coronary lesion in patients presenting with ischemic cardiac pain at rest. Results of the Thrombolysis in Myocardial Ischemia (TIMI IIIA) Trial. *Circulation* 1993; 87: 38–52.
- [144] Karlsson JE, Berglund U, Bjorkholm A, Ohlsson J, Swahn E, Wallentin L. Thrombolysis with recombinant human tissue-type plasminogen activator during instability in coronary artery disease: effect on myocardial ischemia and need for coronary revascularization. TRIC Study Group. *Am Heart J* 1992; 124: 1419–26.
- [145] Schreiber TL, Macina G, McNulty A *et al.* Urokinase plus heparin versus aspirin in unstable angina and non-Q-wave myocardial infarction. *Am J Cardiol* 1989; 64: 840–4.

- [146] Schreiber TL, Macina G, Bunnell P *et al.* Unstable angina or non-Q wave infarction despite long-term aspirin: response to thrombolytic therapy with implications on mechanisms. *Am Heart J* 1990; 120: 248–55.
- [147] Schreiber TL, Rizik D, White C *et al.* Randomized trial of thrombolysis versus heparin in unstable angina. *Circulation* 1992; 86: 1407–14.
- [148] FTT trialists. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet* 1994; 343: 311–22.
- [149] Yusuf S, Flather M, Pogue J *et al.* Variations between countries in invasive and cardiac procedures and outcomes in patients with suspected unstable angina or myocardial infarction without initial ST elevation. *Lancet* 1998; 352: 507–14.
- [150] Boden WE, O'Rourke RA, Crawford MH *et al.* Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med* 1998; 338: 1785–92.
- [151] FRISC II investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. *Lancet* 1999; 354: 708–15.
- [152] Van Belle E, Lablanche JM, Bauters C, Renaud N, McFadden EP, Bertrand ME. Coronary angiographic findings in the infarct-related vessel within 1 month of acute myocardial infarction: natural history and the effect of thrombolysis. *Circulation* 1998; 97: 26–33.
- [153] Serruys PW, van Hout B, Bonnier H *et al.* Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* 1998; 352: 673–81.
- [154] Lincoff AM. Trials of platelet glycoprotein IIb/IIIa receptor antagonists during percutaneous coronary revascularization. *Am J Cardiol* 1998; 82: 36P–42P.
- [155] Lincoff AM, Califf RM, Anderson KM *et al.* Evidence for prevention of death and myocardial infarction with platelet membrane glycoprotein IIb/IIIa receptor blockade by abciximab (c7E3 Fab) among patients with unstable angina undergoing percutaneous coronary revascularization. EPIC Investigators. Evaluation of 7E3 in Preventing Ischemic Complications. *J Am Coll Cardiol* 1997; 30: 149–56.
- [156] Ahmed WH, Bittl JA, Braunwald E. Relation between clinical presentation and angiographic findings in unstable angina pectoris, and comparison with that in stable angina. *Am J Cardiol* 1993; 72: 544–50.
- [157] Rahimtoola SH, Fessler CL, Grunkemeier GL, Starr A. Survival 15 to 20 years after coronary bypass surgery for angina. *J Am Coll Cardiol* 1993; 21: 151–7.
- [158] Naunheim KS, Fiore AC, Arango DC *et al.* Coronary artery bypass grafting for unstable angina pectoris: risk analysis. *Ann Thorac Surg* 1989; 47: 569–74.
- [159] Yusuf S, Zucker D, Peduzzi P. Effects of CABG on survival: overview of 10-year results from randomised trials. *Lancet* 1994; 344: 563–7.
- [160] BARI investigators. Five-year clinical and functional outcome comparing bypass surgery and angioplasty in patients with multivessel coronary disease. A multicenter randomized trial. Writing Group for the Bypass Angioplasty Revascularization Investigation (BARI) Investigators. *JAMA* 1997; 277: 715–21.
- [161] CABRI Investigators. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularization Investigation). *Circulation* 1996; 93: 847.
- [162] RITA investigators. Coronary angioplasty versus coronary artery bypass surgery: the Randomized Intervention Treatment of Angina (RITA) trial. *Lancet* 1993; 341: 573–80.
- [163] King SB 3rd, Lembo NJ, Weintraub WS *et al.* A randomized trial comparing coronary angioplasty with coronary bypass surgery. Emory Angioplasty versus Surgery Trial (EAST). *N Engl J Med* 1994; 331: 1044–50.
- [164] Hamm CW, Reimers J, Ischinger T, Rupprecht HJ, Berger J, Bleifeld W. A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. German Angioplasty Bypass Surgery Investigation (GABI). *N Engl J Med* 1994; 331: 1037–43.
- [165] Rodriguez A, Bouillon F, Perez-Balino N, Paviotti C, Liprandi MI, Palacios IF. Argentine randomized trial of percutaneous transluminal coronary angioplasty versus coronary artery bypass surgery in multivessel disease (ERACI): in-hospital results and 1-year follow-up. ERACI Group. *J Am Coll Cardiol* 1993; 22: 1060–7.
- [166] FRISC II. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. *Lancet* 1999; 354: 708–15.
- [167] Kontny F. Reactivation of the coagulation system: rationale for long-term antithrombotic treatment. *Am J Cardiol* 1997; 80: 55E–60E.
- [168] Chen L, Chester MR, Redwood S, Huang J, Leatham E, Kaski JC. Angiographic stenosis progression and coronary events in patients with 'stabilized' unstable angina. *Circulation* 1995; 91: 2319–24.
- [169] Merlini PA, Bauer KA, Oltrona L *et al.* Persistent activation of coagulation mechanism in unstable angina and myocardial infarction. *Circulation* 1994; 90: 61–8.
- [170] 4S investigators. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344: 1383–9.
- [171] Rossouw JE. Lipid-lowering interventions in angiographic trials. *Am J Cardiol* 1995; 76: 86C–92C.
- [172] Pfeffer MA, Braunwald E, Moya LA *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992; 327: 669–77.
- [173] SOLVD investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med* 1991; 325: 293–302.
- [174] SOLVD investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. *N Engl J Med* 1992; 327: 685–91.
- [175] Collins R, Peto R, MacMahon S *et al.* Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990; 335: 827–38.
- [176] Rabbani RTE. Strategies to achieve coronary arterial plaque stabilization. *Cardiovasc Res* 1999; 41: 402–17.
- [177] Yusuf S, Kostis JB, Pitt B. ACE inhibitors for myocardial infarction and unstable angina [letter; comment]. *Lancet* 1993; 341: 829.
- [178] HOPE Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients: The Heart outcomes Prevention Evaluation study Investigators. *N Engl J Med* 2000; 342: 145–53.
- [179] Yusuf S, Lonn E. Anti-ischemic effects of ACE inhibitors: review of current clinical evidence and ongoing trials. *Eur Heart J* 1998; 19 (Suppl J): 36–44.
- [180] Specchia GDSS, Falcone C, Bramucci E *et al.* Coronary arterial spasm as a cause of exercise-induced ST segment elevation in patients with variant angina. *Circulation* 1979; 59: 948–54.
- [181] De Servi SAE, Marsico F, Bramucci E *et al.* Correlation between clinical and morphologic findings in unstable angina. *Am J Cardiol* 1996; 77: 128–132.

- [182] Bertrand M, Lablanche J, Tilmant P. Frequency of provoked coronary arterial spasm in 1,089 consecutive patients undergoing coronary arteriography. *Circulation* 1982; 65: 1299–1306.
- [183] Previtali MAD, Barberis P, Panciroli C, Chimienti M, Salerno JA. Hyperventilation and ergonovine Tests in Prinzmetal's Variant Angina Pectoris in Men. *Am J Cardiol* 1989; 63: 17–20.
- [184] Previtali MPC, De Ponti R, Chimienti M, Montemartini C, Salerno JA. Time-related decrease in sensitivity to ergonovine in patients with variant angina. *Am Heart J* 1989; 117: 92–9.
- [185] Yasue HWM, Omote S, Takizawa K, Tanaka S. Coronary arterial spasm and Prinzmetal's variant angina reduced by hyperventilation and Tris-Buffer infusion. *Circulation* 1978; 58: 56–62.
- [186] Severi S, Davies G, Maseri AMP, L'Abbate, A. Long-term prognosis of 'variant' angina with medical treatment. *Am J Cardiol* 1980; 46: 226–32.
- [187] Bory M, Pierron F, Panagides D, Bonnet J. Coronary artery spasm in patients with normal or near normal coronary arteries. *Eur Heart J* 1996; 17: 1015–21.
- [188] Rovai DB, Baratto M. Organic coronary stenosis in Prinzmetal's variant angina. *J Cardiol* 1997; 30: 299–305.
- [189] Scholl JMVP, Benacerraf A, Brau J, Henriet G, Achard F. Long-term prognosis of medically treated patients with vasospastic angina and no fixed significant coronary atherosclerosis. *Am Heart J* 1988; 115: 559–64.
- [190] Hannebicque G, Lablanche J, Gommeaux A, Fourrier J, Bertrand M. Pronostic à long terme du spasme artériel coronaire. *Arch Mal Coeur* 1990; 83: 461–7.

© 2000 The European Society of Cardiology