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Task Force Report

Management of acute coronary syndromes in patients presenting *without* persistent ST-segment elevation

The Task Force on the Management of Acute Coronary Syndromes of the European Society of Cardiology*

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

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 physiopathology has been clarified and there have been major advances in management.

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It is now apparent that the 'acute coronary syndromes', namely unstable angina and evolving myocardial infarction share a common anatomical substrate: pathological, angioscopic 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[1–3].

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 with serial electrocardiograms and repeat measurements of markers of myocardial necrosis (troponin preferred or 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[4]. The definition of myocardial infarction was reviewed and updated by a joint consensus document of the European Society of Cardiology and the American College of Cardiology[5]. The current document is the updated version of the document published in 2000 (Eur Heart J 2000; 1406–32). The revision started in October 2001 and was completed and reviewed by the members of the committee for practice guidelines at the end of July 2002.

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 is a rapidly moving field; the present guidelines reflect current knowledge and were revised in the light of additional data presented in late 2000 and during 2001; other guidelines (ACC/AHA, BCS)[6–8], were also considered in detail. A European View on the North American Fifth consensus on Antithrombotic Therapy was expressed by the ESC Working Group in June 2000[9].

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.

The strength of recommendations is presented using the following classification:

Class I: Conditions for which there is evidence that a given therapy is useful and effective.
Class II: Conditions for which there is conflicting evidence and/or divergence about the efficacy/usefulness of a given treatment.
Class III: Contra-indications.

In these guidelines, the level of evidence and the strength of recommendation are summarized in Table 1. The legal implications of medical guidelines have been discussed previously[10].

Acute coronary syndromes are a major health problem and represent a large number of hospitalizations annually in Europe. In the EuroHeart Survey conducted from September 2000 to May 2001 in 103 tertiary and community centres from 25 countries in Europe the 6-month mortality of acute coronary syndromes without ST-segment elevation was 12%[11]. This rate was similar to that observed in the GRACE registry[12–14].

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 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 inflammation, thrombosis, vasoconstriction and microembolization.

Plaque rupture and erosion

Atherosclerosis is not a continuous, linear process but rather a disease with alternate phases of stability and

Table 1

	FRIC	ESSENCE	TIMI-11B	FRAXIS
Enrolment period	March 1993–April 1995	October 1994–May 1996	August 1996–March 1998	May 1995–July 1997
No. of patients	1499	3171	3910	3468
Last episode of chest pain	<72 h	<24 h	<24 h	<48 h
Evidence of ischaemia			Yes	
ST-depression	>1 mm	>1 mm		Yes not defined
T-wave inversion	1 mm	Yes		Yes not defined
CK-MB elevation				
Troponin elevation				
Study drug	Dalteparin	Enoxaparin	Enoxaparin	Nardroparin
Bolus	120 IU . kg^{-1} SQ t.i.d. (day 1–6)	1 mg . kg^{-1} t.i.d.	30 mg i.v.	86 aXaIU . kg^{-1}
Infusion			1·0 mg . kg^{-1} t.i.d.	86 aXaIU . kg^{-1} t.i.d.
Duration	7500 IU day 6–45	48 h–8 days	8 days	G&: 6 days Gr 2: 14 days
ASA	75–165 mg . day^{-1}	100–325 mg . day^{-1}	100–325 mg . day^{-1}	100–325 mg . day^{-1}
Control group				
UFH bolus	5000 IU	5000 IU	70 IU . kg^{-1}	5000 IU
Infusion	1000 IU . h^{-1}	1000 IU	15 IU . kg^{-1} . h^{-1}	1250 IU . h^{-1}
Aspirin	75–165 mg . day^{-1}	100–325 mg . day^{-1}	100–325 mg . day^{-1}	100–325 mg . day^{-1}
Additional management				
PCI	Excluded	Discretion of invest	No <24 h	Discretion of invest
CABG	Excluded	Discretion of invest	No <24 h	Discretion of invest
Efficacy				
Primary EP	Death, MI, rec angina	Death, MI, rec ang	Death, MI, urg revasc	Death, MI, ref ang
Date	Day 6 and 45	14 days	8 and 43 days	14 days
Definition MI (CK or CK-MB)	CK >2 ULN or CK-MB >1 ULN	CK >2 ULN	CK-MB >1 ULN	CK-MB >2 ULN
MI if PCI (CK or CK-MB)		CK >3 ULN	CK-MB >3 ULN	
MI if CABG (CK or CK-MB)		C >5 ULN	CK-MB >5 ULN	

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[15–18]. 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 likely 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 widely corresponds with 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[16]. 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, diabetics and hypertensive patients; some evidence exits that it more commonly occurs on high-grade stenoses and on stenoses located in the right coronary artery[19,20]. A recent study showed a 40% prevalence of plaque erosion in sudden coronary death, and a 25% prevalence 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[21,22]. 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 might 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[23] 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[24]. 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[23]. 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[23]. In addition mast cells are found at plaque edges[25].

Neointimal hyperplasia has been described in 40% of pathology specimens from unstable plaque obtained by directional atherectomy[26,27]: 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

Thrombosis 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. 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[28]. Furthermore, there is a strong correlation between tissue factor activity and the presence of macrophages[24]. Systemic monocyte procoagulant activity has been found to be dramatically increased in unstable angina. Factors implicated in systemic hypercoagulability may also be involved, hypercholesterolemia, fibrinogen, impaired fibrinolysis, and infection may all contribute to thrombus generation. The thrombus occurring in acute coronary syndromes is mainly platelet-rich. Spontaneous thrombolysis may explain transient episodes of thrombotic vessel occlusion/subocclusion and the 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) in the absence of occlusion of the epicardial coronary artery.

Vasoconstriction

The platelet-rich thrombus can release vasoconstrictor substances such as serotonin and thromboxane A2[29] that induces vasoconstriction at the site of plaque rupture or 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. 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. The myocardium may be normal or there may be varying degrees of necrosis (myocardial infarction). In some patients focal areas of cell necrosis in the myocardium supplied by the culprit artery have been shown, which have been attributed to repeated episodes of thrombus embolization[30–32]. Cardiac troponin T or troponin I are the more sensitive and specific markers for myocardial necrosis and have become the markers of choice in patients with suspected acute coronary syndromes, while small amounts of necrosis may not be detected by CK or CK-MB measurements which remain within or just above the upper limits of normal. Elevated levels of cardiac troponins in the absence of CK-MB elevation have been labelled 'minimal myocardial damage'. This concept is of clinical importance, because it has major practical implications with respect to an unfavourable outcome and the choice of a therapeutic regimen.

Diagnosis

Clinical presentation

The clinical presentation of acute coronary syndromes encompasses a wide variety of symptoms. 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 are observed in only 20%[33]. The classic features of typical ischaemic cardiac pain are well known and will not be further described here.

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, 13% of those with chest pain that had some pleuritic features, and in 7% of those whose chest pain was fully reproduced by palpation[34]. In addition, variant angina, which forms part of the spectrum of unstable angina, may not be recognized at initial presentation.

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 search for signs of potential haemodynamic instability and LV 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 valuable, particularly in patients with co-existing cardiac pathology such as left ventricular hypertrophy[34,35] 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[36,37]. ST-segment depression >1 mm (0·1 mV) in two or more contiguous leads, in the appropriate clinical context, is highly suggestive of an acute coronary syndrome, 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 stenosis of the proximal left anterior descending coronary artery stenosis. Non-specific ST-segment shift and T-wave changes (<0·1 mV) are less specific. Indeed, in the Multicenter Chest Pain Study, such non-specific changes were often noted in patients in whom acute coronary syndromes were ultimately ruled out. Transient episodes of bundle branch block occasionally occur during ischaemic attacks. It should be appreciated that a completely normal electrocardiogram 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[38–40]. 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 institute continuous multilead ST-segment monitoring.

Biochemical markers of myocardial damage

Cardiac troponin T or troponin I are the preferred markers of myocardial necrosis, because they 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 believed that any elevation of cardiac troponin T or I reflects irreversible myocardial cellular necrosis. In the setting of myocardial ischaemia (chest pain, ST-segment changes) this should be labelled as myocardial infarction according to the recent consensus document of the ESC and ACC[5,41].

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 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 recognizing the distinct amino acid sequence[41,42]. The cardiac 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 these markers the role of a new gold standard[43]. In conditions of 'false-positive' elevated CK-MB, such as skeletal muscle trauma, troponins will clarify any cardiac involvement. In patients with 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 acute coronary syndromes without elevated CK-MB. It is important to stress that other life threatening conditions presenting with chest pain, such as dissecting aortic aneurysm or pulmonary embolism, may also result in elevated troponin and should always be considered in the differential diagnosis.

It should be appreciated that a single test for troponins on arrival of the patient in hospital is not sufficient, as in 10 to 15% of patients troponin deviations can be detected in subsequent h. In order to demonstrate or to exclude myocardial damage, repeated blood sampling and measurements are required 6 to 12 h after admission and after any further episodes of severe chest pain. If the patient's last episode of chest pain was more than 12 h prior to the initial determination of troponin, a second sample may be omitted, in the absence of any other index of suspicion.

Elevation of cardiac troponins also occurs in the setting of non-ischemic myocardial injury, e.g., myocarditis, severe congestive heart failure, pulmonary embolism, or cardio toxic chemotherapeutic agents[44–46]. This should not be labelled as false-positive test results, but rather reflect the sensitivity of the marker. True false-positive results have been documented for troponin T in the setting of skeletal myopathies or chronic renal failure and for troponin I related to interaction of the immunoassays with fibrin strands or heterophilic antibodies[47–50]. Current assays have largely overcome these deficiencies, although infrequent false-positive results may still occur.

There is no fundamental difference between troponin T and troponin I testing. Differences between study results are predominantly explained by varying inclusion criteria, differences in sampling pattern and use of assays with different diagnostic cut-offs. Only one manufacturer of troponin T assays is on the vehicle, while several manufacturers provide assays for troponin T. The consensus committee's recommendations specify a diagnostic cut-off for myocardial infarction using cardiac troponins based on the 99th percentile of levels among healthy controls rather than comparison to CK-MB. Acceptable imprecision (coefficient of variation) at the 99th percentile for each assay should be below $\leq 10\%$. Each individual laboratory should regularly assess the range of reference values in their specific setting. For troponin T, cut-off levels between 0·01 and $0{\cdot}03\ \mu g\ .\ l^{-1}$ have been shown to be associated with adverse cardiac outcomes in acute coronary syndromes[51,52]. For troponin I the decision limits must be based on carefully conducted clinical studies for individual troponin I assays and should not be generalized between different troponin I assays. Slight or moderate elevations of troponins appear to carry the highest early risk in patients with acute coronary syndromes[53].

If patients with acute coronary syndromes without ST-elevations stabilize clinically, there may be time delays before the diagnosis is confirmed and therapy is started. This may not be as critical as in ST-elevation myocardial infarction. Nevertheless, to rapidly establish the correct diagnosis relevant for prompt triage, point-of-care testing for biochemical markers may become advantageous. Point-of-care tests are assays that can be performed either directly at the bedside or at 'near patient' locations such as the emergency department, chest pain evaluation centre or intensive care unit. The rationale for point-of-care testing is the potential for such tests to provide more rapid results. Point of care tests should be implemented when a central laboratory cannot consistently provide test results within 45 to

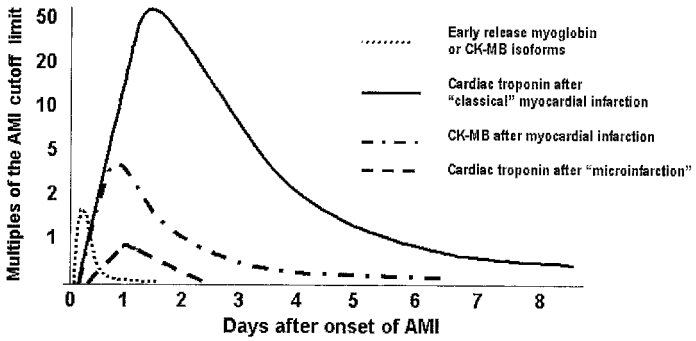

Figure 1 **Time-course of the different cardiac biochemical markers. From Wu AH *et al.* Clin Chem 1999; 45: 1104, with permission.**

60 min[54]. No special skill or prolonged training is required to read the result of these assays. Accordingly, these tests can be performed by a variety of members of the healthcare team after adequate training. However, reading of these mostly qualitative tests is performed visually and therefore is observer dependent. A potential limitation is that visual assessment only allows a binary classification of test results without definitive information regarding the concentration of the marker in the blood. Careful reading, exactly at the assay-specific indicated time, under good illumination is essential to reduce observer misinterpretation especially in cases of marginal antibody binding. Even the faintest colouring should be read as a positive test result.

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 in patients with a large infarct, which may complicate the detection of recurrent necrosis (re-infarction) in patients with recent infarction. Here repeated CK-MB or myoglobin measurements are the preferred markers to detect re-infarction.

Recommendations

In patients with suspected acute ischaemic heart disease:

(1) An ECG should be obtained at rest and multilead continuous ST-segment monitoring initiated (or frequent ECGs recorded where monitoring is unavailable).

(2) Troponin T or I should be measured on admission and, if normal, repeated 6 to 12 h later.

(3) Myoglobin and/or CK-MB mass may 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: A

Risk assessment

In patients with an established diagnosis of acute coronary syndromes (ACS), 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. risk of progression to infarction)[55]. 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 should later 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 CAD and consequently with an increased risk of unfavourable outcome. Previous manifestations of CAD such as severe or long-standing angina, or previous MI are also associated with more frequent subsequent events. A history of left ventricular dysfunction or congestive heart failure is another risk factor, as are diabetes mellitus and hypertension. Indeed, most of the well-known risk factors for CAD are also risk indicators for a worse prognosis in unstable CAD[56].

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[56–58]. The

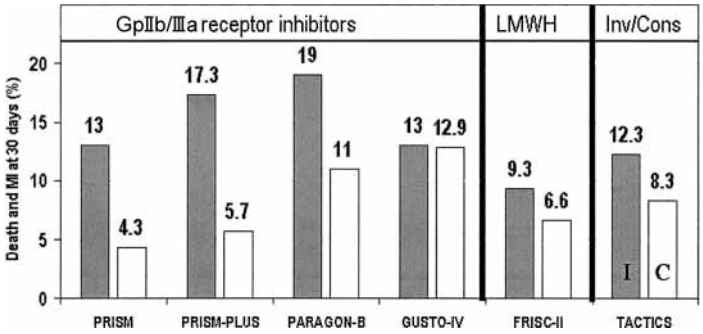

Figure 2 **Death or MI in patients with elevated troponins in contemporary trials. ■ = placebo; □ = GPIIb/IIIa.**

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[57,59,60]. However, in order to select the optimal treatment, other risk indicators also need to be taken into account[56,58].

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[61,62]. Some studies have cast doubt on the prognostic value of isolated T-wave inversion[63]. 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 CAD 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 off-line analysis, providing the results several hours or days after the recording. On-line continuous computer-assisted 12-lead ECG monitoring is the method of choice. Continuous ST-monitoring studies have revealed that 15–30% of patients with unstable CAD have transient episodes of ST-segment changes, predominantly ST-segment depression. These patients have an increased risk of subsequent cardiac events. ST-monitoring adds independent prognostic information to the ECG at rest and other common clinical parameters[64–69]. At 30 days, the rate of death/MI was 9·5% for patients with >0–2 ischaemic episodes per day, but 12·7% and 19·7% for patients with >2–5 or >5 episodes, respectively[70].

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[71–73]. In particular, these markers of myocardial necrosis are related to the risk for (re)infarction and cardiac death[74–84]. Any detectable elevation of cardiac troponin is associated with an increased risk of death and reinfarction. The risk of death is also correlated with the degree of troponin elevation[80,85], but Lindahl *et al.* showed that pronounced elevation of troponin is associated with high long-term mortality, reduced left ventricular function but a modest risk of reinfarction[86]. The increased risk associated with elevated troponin level is independent of and additive to other risk factors such as ECG changes at rest or on continuous monitoring, or markers of inflammatory activity[87,88]. Troponin point-of-care assays are useful to identify the short-term risk of patients with acute coronary syndromes. Furthermore, the identification of patients with elevated troponin levels (cTnT or cTnI) is also useful for selecting appropriate treatment in patients with unstable CAD. Recent trials have shown that patients with elevated troponin specifically benefit from treatment with low-molecular-weight heparin, GPIIb/IIIa blockers or an invasive strategy while no such benefit was observed in patients without troponin elevation[81,89–92] (Figs 2 and 3).

Markers of inflammatory activity

Increased fibrinogen levels and high-sensitivity CRP have been reported as risk markers in ACS, although the data are not consistent[86,93–95]. For example, 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 MI. The prognostic importance of fibrinogen was independent of ECG findings and troponin-levels[93]. However, 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 MI during the 42 days follow-up[94]. The prognostic value of increased CRP concentrations seems most prominent in patients with signs of myocardial damage[60,93]. In some studies, raised CRP 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[90,92,93,96].

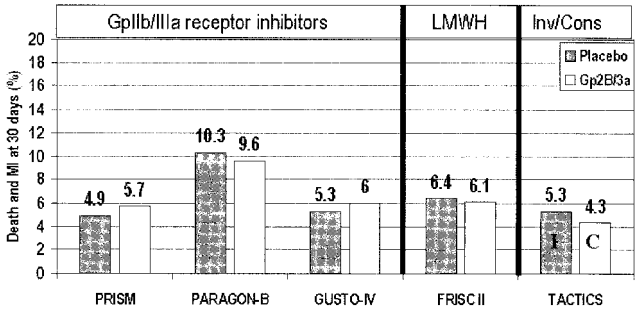

Figure 3 **Death or MI in patients with negative troponins in contemporary trials. Symbols as for Fig. 2.**

Troponin T and C-reactive protein levels are strongly related to the long-term risk of cardiac death and are independent risk factors but their effects are additive with respect to each other and other clinical markers. Elevated levels of brain natriuretic peptide (BNP) and interleukin-6 (IL-6) on admission are strongly related to mortality both in the short- and long-term[97].

Furthermore elevated IL-6 levels also seem to identify patients who derive the greatest benefit from both an early invasive strategy and from long-term antithrombotic treatment[98]. An early rise in soluble intercellular adhesion molecules (sICAM-1) and interleukin-6 have been shown in patients with acute coronary syndromes and more detailed study of these markers may provide additional insights into the pathogenesis of acute coronary syndromes[99].

Markers of thrombosis

An association between increased thrombin generation and an unfavourable outcome in unstable angina has been found in some although not all trials[100,101]. Protein C, protein S, resistance to APC and antithrombin deficiencies are defects in the anti-coagulant systems associated with the development of venous thromboembolism. However, so far none of these have 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[102–105]. Increased concentrations of PAI-1 have been reported to be related to an increased risk of new coronary events in MI survivors[106]. Increased D-dimer concentrations have been reported in unstable angina as well as in acute MI[107]. However, there are few large-scale trials of fibrinolytic activity in unstable CAD and its relation to acute phase proteins. Currently, haemostatic markers are not recommended for risk stratification or selection of treatment in individual patients with unstable CAD.

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 ventricle 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.

Predischarge stress testing

After stabilization and before discharge a stress test is useful to confirm the diagnosis of coronary artery disease in patients in whom such diagnosis has not yet been established and to predict the medium and long-term risk for subsequent coronary events.

Exercise testing has a high negative predictive value[108–111]. Parameters reflecting cardiac performance provide at least as much prognostic information as those reflecting ischaemia, while the combination of these parameters gives the best prognostic information[108,110,111]. 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, especially in women, although large long-term prognostic studies with stress echocardiography in patients after an episode of unstable CAD are still lacking[112–115].

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[116]. Angiographic assessment of the characteristics and location of the culprit lesion as well as other lesions is essential if revascularization 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:

- **(A) Markers of thrombotic risk, i.e. acute risk:**
  - **a. Recurrence of chest pain**
  - **b. ST-segment depression**
  - **c. Dynamic ST-segment changes**
  - **d. Elevated level of cardiac troponins**
  - **e. Thrombus on angiography**
- **(B) Markers of underlying disease i.e. long-term risk:**
  - **B1: Clinical markers**
    - **a. Age**
    - **b. History of previous MI, prior CABG, diabetes, congestive heart failure, hypertension**
  - **B2: Biological markers**
    - **a. Renal dysfunction (elevated creatinine or reduced creatinine clearance)**
    - **b. Inflammatory markers, CRP elevation, Fibrinogen elevation, IL-6 elevation**
  - **B3: Angiographical markers**
    - **a. LV dysfunction**
    - **b. 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 5. Five categories of treatment will be discussed: anti-ischaemic agents, antithrombin therapy antiplatelet agents, fibrinolytics and coronary revascularization.

Anti-ischaemic agents

These drugs decrease myocardial oxygen utilization (decreasing heart rate, lowering blood pressure or depressing LV 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 MI. Beta-blocking agents competitively inhibit the effects of circulating catecholamines. In acute coronary syndromes without ST-elevation, 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 IHD were small and uncontrolled. Three double-blind randomized trials have compared beta-blockers to placebo in unstable angina[117,118]. A meta-analysis suggested that beta-blocker treatment was associated with a 13% relative reduction in risk of progression to acute MI[119]. 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[120].

Beta-blockers are recommended in ACS in the absence of contraindications; the intravenous route should be preferred in patients at high risk (*level of evidence: 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 . min^{-1}. Patients with significantly impaired atrioventricular conduction, a history of asthma, or of acute LV dysfunction should not receive beta blockers[121].

Nitrates

The use of nitrates in unstable angina is largely based on pathophysiological considerations and clinical experience. The therapeutic benefits of nitrates and similar drug classes such as syndnonimines 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[121–123]. 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[124]. Another small randomized trial compared intravenous nitroglycerin with buccally administered nitroglycerin and found no difference[125]. There are no data from controlled trials to indicate the optimal intensity or duration of therapy.

In patients with ACS who require hospital admission, intravenous nitrates may be considered in the absence of contraindications (*level of evidence: 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[126–128].

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 potassium channel activators.

Potassium channel activators

A randomized, double-blind, placebo controlled trial (IONA study: Impact of Nicorandil in Angina) showed in 5126 patients with stable angina, that nicorandil (10 mg t.i.d. for 2 weeks increased to 20 mg t.i.d. for 1·6 years) reduced cardiovascular death, non-fatal MI and unplanned hospitalization for angina from 15·5% under placebo to 13·1% under nicorandil (hazard ratio: 0·83, (95% CI: 0·72–0·97), $P=0·014$). However, coronary heart disease mortality and non-fatal MI were not significantly reduced from 5·2% to 4·2% (hazard ratio: 0·79 (95% CI: 0·61–1·02), $P=0·068$) [129]. No specific data are available in acute coronary syndromes.

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 different 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 A-V conduction. A-V block may be induced by phenylalkylamines. Nifedipine and amlodipine produce the most marked peripheral arterial vasodilatation, whereas diltiazem has the least vasodilatory 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 appears equivalent to beta blockers[130,131]. The largest randomized trial, the HINT study, tested nifedipine and metoprolol in a 2×2 factorial design[118]. 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[132]. 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) but in two other trials it seems to be slightly beneficial[133,134].

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[135]. In particular, several analyses of 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[136,137]. On the other hand, there is evidence for a protective role of diltiazem in non-ST-segment elevation myocardial infarction[138] (*level of evidence: C*).

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. 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.

Anti-thrombin therapy

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, GPIIb/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 MI. Yet, the evidence for the use of unfractionated heparin is less robust than for other treatment strategies[139]. In clinical practice, maintenance of therapeutic anti-thrombin 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 endpoint) compared to placebo (relative risk reduction 0·29) while the relative 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[140]. 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 was 7·9% rate of death or

Table 2 Death and non-fatal MI

	Timing of end-point	LMWH	LMWH	UFH	OR	95% CI
Short-term						
FRIC	0–6 days	Dalteparin	3·9	3·6	1·07	0·63–1·8
ESSENCE	14 days	Enoxaparin	4·6	6·1	0·75	0·55–1·02
TIMI-11B	14 days	Enoxaparin	5·7	6·9	0·81	0·63–1·05
FRAXIS	14 days	Nadroparin	4·9	4·5	1·08	0·72–1·62
Total					0·86	0·72–1·02
Long-term						
FRISC	06–45 days	Dalteparin	4·3	4·7	0·92	0·54–1·57
ESSENCE	43 days	Enoxaparin	6·2	8·2	0·73	0·56–0·96
TIMI-11B	43 days	Enoxaparin	7·9	8·9	0·88	0·7–1·11
FRAXIS	90 days	Nadroparin	8·9	7·9	1·16	0·85–1·58
Total					0·89	0·77–1·03

myocardial infarction in the aspirin+heparin group and 10·3% in the aspirin alone group (absolute risk reduction=2·4%, OR: 0·74 (95% CI: 0·5–1·09), $P=0·10$)[139] (*level of evidence: B*). 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 anti-Xa activity in relation to anti-IIa (antithrombin) activity compared to unfractionated heparin. In addition, LMWHs 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. Different LMWHs appear to have similar activity in prevention and treatment of venous thrombosis, in spite of some differences in pharmacology and half-life. In ACS patients treated with aspirin, comparison between low-molecular-weight heparins and placebo or unfractionated heparins has been performed in several clinical trials.

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 has been demonstrated in the FRISC trial testing dalteparin against placebo in aspirin treated patients with unstable angina/non-ST-elevation MI[141].

Four randomized trials compared different low-molecular-weight heparins to unfractionated heparin. The design features of these trials with regard to entry criteria and study medication are summarized in Table 1 and the main results are summarized in Table 2.

This meta-analysis of the four trials shows no convincing evidence of difference in efficacy and safety between LMWH and unfractionated heparin[142]. The meta-analysis showed that long-term LMWH was associated with a significantly increased risk of major bleeding (OR=2·26 (95% CI: 1·63–3·41), $P<0·0001$.

In summary, there is convincing evidence in aspirin treated patients that low-molecular-weight heparin is better than placebo[141] (*level of evidence: A*). Two trials have provided data in favour of low-molecular-weight heparin (enoxaparin) over unfractionated heparin when administered as an acute regimen[55,143,144] (Fig. 4). These results have been confirmed at 1 year follow-up[145]. Thus, for LMW heparins overall it can be concluded that acute treatment is at least as effective as unfractionated heparin (*level of evidence: A*). However, enoxaparin was superior to unfractionated heparin in the two head-to-head comparisons (for the combined end-point of death/MI/recurrent angina).

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. Observational studies have also suggested similar safety profiles to unfractionated heparin when used with glycoprotein IIb/IIIa inhibitors (NICE studies)[146] and a moderate sized randomized trial (n=750 patients) of enoxaparin vs unfractionated heparin suggests superior safety and efficacy in eptifibatide treated patients (INTACT). However, the evidence to support longer-term out-patient treatment with low-molecular-weight heparin is less convincing.

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. Early benefits (24 h and 7 days) were observed, which were no longer significant at 30 days[147].

The OASIS-2 trial tested a higher dose of hirudin for 72 h against unfractionated heparin and the rate of cardiovascular death or new MI at 7 days was 4·2% for the unfractionated heparin group and 3·6% for hirudin ($P=0·077$). There was an excess of major bleeding (1·2%

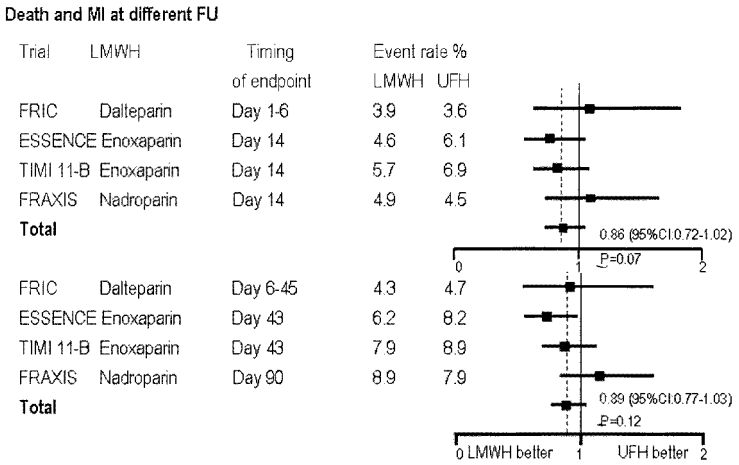

Figure 4 **Comparison of low-molecular-weight heparins to unfractionated heparins in patients with acute coronary syndromes. Odds ratio and 95% confidence interval.**

vs 0·7%) but no excess of life-threatening bleeds or strokes[148].

A combined analysis of the OASIS-1 pilot studies, OASIS-2, and GUSTO IIb indicates a 22% relative risk reduction in cardiovascular death or MI at 72 h, 17% at 7 days, and 10% at 35%[147,148] (*level of evidence: B*). 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, but none of the hirudins are 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. The risk of inducing a rebound thrombotic phenomenon should be assessed for such patients on an individual basis.

The anticoagulant and hemorrhagic 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 A2. Thus, platelet aggregation induced via this pathway is blocked. Three trials have consistently shown that aspirin decreases death or MI in patients with unstable angina[140,149,150]. A meta-analysis showed that 75–150 mg aspirin was as effective as higher doses. For acute MI, antiplatelet therapy (almost exclusively aspirin) results in fewer vascular events per 1000 treated patients[151]. In addition to the early benefit established in those studies, a long-term benefit is achieved by continuation of aspirin. Gastrointestinal side effects are relatively infrequent with these low doses, but there are few contraindications including active peptic ulcer, local bleeding or haemorrhagic diatheses. Allergy is rare. Accordingly, acute treatment with aspirin is recommended in all patients with suspected acute coronary syndromes in the absence of contraindications (*level of evidence: A*) and for long-term treatment thereafter (*level of evidence: A*).

ADP receptor antagonists: Thienopyridines

Ticlopidine and clopidogrel are inhibitors of ADP, resulting in inhibition of platelet aggregation. Ticlopidine has been investigated in a single study[152] but intolerance to this drug is relatively frequent because of gastrointestinal disorders, or allergic reactions. In addition, neutropenia or thrombocytopenia may occur. Ticlopidine has been superseded by clopidogrel.

Clopidogrel, has been investigated in aspirin (75–325 mg) treated ACS patients in a large clinical trial (CURE) of 12 562 patients[153]. Patients hospitalized within 24 h after the onset of symptoms with ECG changes or cardiac enzyme rise were randomized to a loading dose of 300 mg of clopidogrel followed by 75 mg once daily vs placebo for a median of 9 months. The first primary outcome (cardiovascular death, non-fatal myocardial infarction or stroke) was significantly reduced from 11·4% to 9·3% (ARR=2·1%, relative risk: 0·80; (95% CI: 0·72 to 0·90); $P<0·001$).The rate of each component also tended to be lower in the clopidogrel group but the most important difference was observed in the rates of myocardial infarction (ARR=1·5%, relative risk: 0·77; (95% CI: 0·67 to 0·89)). The rate of refractory ischaemia during initial hospitalization significantly ($P=0·007$) decreased from 2·0% to 1·4% (ARR=0·6%, relative risk: 0·68; 95% CI, 0·52 to 0·90) but did not significantly differ after discharge (7·6% in both groups).

Major bleeding was significantly more common in the clopidogrel group (3·7% vs 2·7%, (+1%, relative risk: 1·38; (95% CI: 1·13 to 1·67); $P=0·001$); the number of patients who required transfusion of two or more units was higher in clopidogrel group than in placebo group (2·8% vs 2·2%, $P=0·02$). Major bleedings were approximately as frequent during early treatment (<30 days) as later (>30 days after randomization) (2·0% and 1·7% respectively). Minor bleedings were significantly higher in the clopidogrel group than in the placebo group (5·1% vs 2·4%, $P<0·001$). Slightly fewer patients in the clopidogrel group underwent coronary revascularization (36% vs 36·9%) Nevertheless, it is of interest to consider the 1822 patients of the clopidogrel group who underwent by-pass surgery. Overall, there was no significant excess of major bleeding episodes after CABG (1·3% vs 1·1%). But in the 912 patients who did not stop study medication until 5 days before surgery, the rate of major bleeding was higher in the clopidogrel group (9·6% vs 6·3%, $P=0·06$).

A clear increase in bleeding risk occurred as the dose of aspirin increased from $\leq$100 mg to 100–300 mg to >300 mg in both placebo treated (2·0%, 2·2%, 4·0% major bleeds, respectively) and clopidogrel treated patients (2·5%, 3·5%, 4·9%. There was no clear evidence in CURE or in the Anti Platelet Triallist's Collaboration of improved outcome with higher doses of aspirin. Thus it is recommended that clopidogrel be used in conjunction with maintenance doses of $\leqslant$100 mg aspirin.

Recommendation

In ACS patients clopidogrel is recommended for acute treatment and for longer term treatment for at least 9–12 months (*evidence level B*). Beyond this level of evidence, treatment will depend on the risk status of the patient and individual clinical judgement. Clopidogrel should be given to ACS patients scheduled for angiography unless there is a likelihood that the patient will proceed to urgent surgery (within 5 days).

Clopidogrel may also be recommended for immediate and long-term therapy in patients who do not tolerate aspirin (CAPRIE)[154], and is recommended in patients receiving a stent[155] (*level of evidence: B*).

Glycoprotein IIb/IIIa receptor inhibitors

Activated GPIIb/IIIa receptors connect with fibrinogen to form bridges between activated platelets, leading to formation of platelet thrombi. Direct inhibitors of the glycoprotein IIb/IIIa receptors have been developed, and have been 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 patients receiving thrombolytic therapy for acute myocardial infarction.

Four intravenous GPIIb/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.

Eptifibatide is a cyclic peptide inhibiting selectively the glycoprotein IIb/IIIa receptors. It has short half-life and platelet function recovers 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.

Several oral GPIIb/IIIa receptor blockers have been recently studied: orbofiban, sibrafiban, lefradafiban, and others[156].

GPIIb/IIIa receptor blockers and percutaneous coronary intervention. In patients undergoing percutaneous coronary intervention (PCI) concomitant administration of GPIIb/IIIa receptor blockers consistently reduces thrombotic complications, in particular periprocedural myocardial infarction (EPIC, CAPTURE, EPILOG, EPISTENT, RESTORE, IMPACTII, ESPRIT trials)[157–].

The combined end-point of death, myocardial infarction and target vessel re-intervention was the primary end-point and was significantly reduced in most of these studies. A meta-analysis of all trials with abciximab also revealed a reduction in subsequent mortality if abciximab was given during and after PCI. The TARGET study compared two GPIIb/IIIa receptor antagonists, abciximab and tirofiban at the time of PCI in patients with acute coronary syndromes[163]. Abciximab appeared superior to tirofiban at 30 days (death and MI: 6·3% vs 9·3%, $P=0·04$) and at 6 months (7·1% vs 9·6%, $P=0·01$). But the difference was not statistically significant at 1 year follow up.

In view of the findings, treatment with a GPIIb/IIIa receptor blocker is recommended in all patients with ACS undergoing PCI (*level of evidence: A*). The infusion should be continued for 12 h (abciximab) or 24 h (eptifibatide, tirofiban) after the procedure.

GPIIb/IIIa receptor inhibitors in acute coronary syndromes. In patients admitted with acute coronary syndromes, systematic use of GPIIb/IIIa receptor blockers in addition to aspirin and 'standard' unfractionated heparin was studied in seven large randomized trials: CAPTURE, PRISM, PRISM-PLUS, PURSUIT, PARAGON-A, PARAGON-B, GUSTO-IV ACS[164,165–169] (Tables 3 and 4).

Abciximab. Two trials were performed with abciximab in ACS: CAPTURE enrolled 1265 patients with refractory unstable angina scheduled for percutaneous intervention and the drug was administered during, approximately the 24 h before intervention until 1 h afterwards[164]. In contrast, GUSTO-IV ACS studied the effect of abciximab on patients with ACS but not scheduled for early revascularization which was strongly discouraged. This trial included 7800 patients[169].

Tirofiban. 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[165].

PRISM-PLUS enrolled patients at somewhat higher risk, with unstable angina and 'ischaemic' ECG changes in the 12 h before enrolment[166]. 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[166].

Eptifibatide. In the largest trial (PURSUIT) 10 948 patients with ACS and symptoms within 24 h prior to enrolment with either an abnormal electrocardiogram or elevated cardiac enzymes were randomized to an eptifibatide bolus followed by an infusion up to 72 h, or to placebo[167].

Lamifiban. There were two trials with lamifiban: PARAGON-A enrolled 2282 patients and PARAGON B enrolled 5225 patients but the study medication was given at different doses (500 μg bolus followed by 1·0–2·0 μg . min^{-1} infusion vs 180 μg . kg^{-1} bolus followed by 1·3 or 2·0 μg . kg^{-1} min^{-1} infusion in PARAGON-A[168,170].

Tables 3–4 summarize the design, the clinical characteristics and the results of these trials. Overall the use of GPIIb/IIIa inhibitors is associated with a modest, but significant reduction in death or MI at 30 days in patients with acute coronary syndromes without persistent ST-segment elevation (Fig. 5). Medical therapy with a GPIIb/IIIa receptor blocker during the first days after admission, followed by percutaneous coronary intervention or bypass surgery, yields a significant reduction in death and non-fatal MI at 72 h, from 4·3 to 2·9% (Fig. 6).

Subsequently, in patients undergoing percutaneous coronary intervention in CAPTURE[164], as well as the subgroup of patients undergoing a similar procedure in PURSUIT[167] and PRISM-PLUS[166], a reduction from 8·0 to 4·9%, of procedure-related events was observed (P=0·001). Few events occurred more than 2 days after percutaneous coronary intervention in these patients, and no additional treatment effect was apparent at up to 30-days follow-up (Fig. 6).

In the larger placebo-controlled trials of GPIIb/IIIa receptor blockers in patients with acute coronary syndromes, the treatment benefit was particularly apparent in those patients who underwent early coronary revascularization[164,166,167]. A meta-analysis from Boersma[171] showed a strong treatment effect (death and MI in patients undergoing PCI but no effect in those not undergoing intervention (Fig. 7). Intervention (PCI or CABG) performed within 5 days in combination with GPIIb/IIIa receptor inhibitors induced a 3% absolute reduction of death and MI (relative risk reduction: 0·79; 95% CI: 0·68–0·91). When performed within 30 days, absolute risk reduction was 1·7% (relative risk reduction: 0·89; (95% CI: 0·80–0·98)).

In three trials (CAPTURE, PRISM, PARAGON-B)[164,165,170] the benefits of a treatment with a GPIIb/IIIa receptor blocker was particularly apparent among patients admitted with elevated levels of cardiac troponin T or cardiac troponin I (Figs 2 and 3). 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. In contrast, no benefit was observed in GUSTO IV patient with elevated troponin. Treatment with a GPIIb/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, who are scheduled for early revascularization (*level of evidence: A*). There was no benefit for patients with negative troponins.

From a meta-analysis of the six randomized trials, it was demonstrated that diabetic patients with acute coronary syndrome derive particular benefit from GPIIb/IIIa receptor inhibitors. Among 6458 diabetics, this antiplatelet treatment was associated with a significant mortality reduction at 30 days from 6·2% to 4·6% (relative risk 0·74; (95% CI: 0·59–0·92); P=0·007). Among 1279 diabetic patients undergoing PCI during index hospitalization, the use of GPIIb/IIIa receptor blockers was associated with a mortality reduction at 30 days, from 4·0% to 1·2% (ARR: 2·8%; relative risk: 0·30; (95% CI: 0·14–0·69); P=0·002)[172]. Thus, GPIIb/IIIa blockers are recommended, in particular in patients with diabetes and an acute coronary syndrome.

Finally, the level of platelet inhibition achieved with GPIIb/IIIa receptor inhibitors varies widely among patients undergoing percutaneous interventions. The GOLD multicenter study, conducted with a bedside machine showed that patients having less than 95% inhibition at the 10 min time point had the greatest incidence of in-hospital major cardiac events (14·4%) when compared to those with 95% or more platelet inhibition (6·4%; P=0·006)[173]. This approach to identify the therapeutic level of inhibition of GPIIb/IIIa binding activity could improve efficacy and reduce bleeding complications, but further studies are needed.

GPIIb/IIIa receptor inhibitors 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. GPIIb/IIIa receptor blockers should be discontinued before (4 h) or at the time of cardiac surgery. Eptifibatide and tirofiban have a short half-life, so that platelet function is 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.

Table 3

	CAPTURE	PRISM	PRISM-PLUS	PARAGON-A	PURSUIT	PARAGON-B	GUSTO-IV ACS
Enrolment period	1993–1995	1994–1996	1994–1996	1995–1996	1995–1997	1998–1999	1998–2000
No. of patients	1265	3232	1915	2282	10948	5225	7800
Last episode of chest pain	<48 h	<24 h	<12 h	<12 h	<24 h	<12 h	<24 h
Evidence of ischaemia							
ST-depression	Yes	>1·0 mm	>1·0 mm	>0·5 mm	>0·5 mm	>0·5 mm	>0·5 mm
T-wave inversion	Yes	Yes	>1·0 mm	>0·5 mm	>0·5 mm	>0·5 mm	>0·5 mm
CK-MB elevation	<2 ULN	Yes	Yes	No	>ULN	>ULN	No
Troponin elevation						>ULN	>ULN
Study drug	abciximab	Tirofiban	Tirofiban	Lamifiban	Eptifibatide	Lamifiban	abciximab
Bolus	0·25 mg . kg^{-1}	0·6 μg . kg^{-1}	0·4 μg . kg^{-1}	300 μg or 750 μg	180 μg . kg^{-1}	500 μg	250 μg . kg^{-1}
Infusion	10 μg . kg^{-1} min^{-1}	0·15 μg . kg^{-1} min^{-1}	0·1 μg . kg^{-1} min^{-1}	1 or 5 μg . kg^{-1} min^{-1}	1·3 or 2 μg . kg^{-1} min^{-1}	1·0–2·0 μg . kg^{-1} min^{-1}	0·125 μg . kg^{-1} min^{-1}
Heparin	Yes	No	Yes	Yes	Yes	Yes	Yes
Infusion duration	>1 h after PTCA	48 h	48–96 h	72–100 h	72–96 h	72–120 h	24 or 48 h
Aspirin	250 mg-minimum 50 mg	300–325 mg	325 mg	75–325 mg	80–325 mg	150–325 mg	150–325 mg
Control group							
ASA	250 mg-minimum 50 mg	300–325 mg	325 mg	75–325 mg	80–325 mg	150–325 mg	150–325 mg
Heparin	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Additional management							
PCI	All patients	Not scheduled	If indicated by angiography	Discretion invest	Discretion invest	Discretion invest	Not scheduled
CABG	If complicated PTCA	Discouraged <48 h	48–96 h post RDZ	Discouradged <24 h	Discretion invest	Discretion invest	Discouraged <48 h
Efficacy							
Primary EP	Death/MI/ Reintervention	Death/MI/RI	Death/MI/RI	Death/MI	Death/MI	Death/MI	Death/MI
Date	30 days	48 h	7 days	30 days	30 days	30 days	30 days
Definition MI (CK or CK-MB)	3 ULN	2 ULN	2 ULN	2 ULN	1 ULN	2 ULN	3 ULN
MI if PCI (CK or CK-MB)			3 ULN		3 ULN	3 ULN	3 ULN
MI if CABG (CK or CK-MB)						5 ULN	

Table 4

	Study drug	%	OR	95% CI
Death or MI at 120 h				
PRISM	Tirofiban	3	0·77	0·53–1·13
	Placebo	3·9		
PRISM-PLUS	Tirofiban	4·1	0·56	0·36–0·87
	Placebo	7·2		
PARAGON-A	Lamifiban	4·5	0·75	0·43–1·32
	Placebo	5·9		
PURSUIT	Eptifibatide	8·6	0·83	0·72–0·95
	Placebo	10·1		
PARAGON-B	Lamifiban	5·7	0·93	0·74–1·17
	Placebo	6·1		
GUSTO-IV ACS	Abciximab 24 h	3·2	0·85	0·63–1·15
	Abciximab 48 h	3·4	0·92	0·69–1·23
	Placebo	3·7		
All	Drug (n=15 562)	5·9	0·84	0·85–0·99
	Placebo (n=11 489)	7·3		
Death or MI at 30 days				
PRISM	Tirofiban	5·8	0·8	0·6–1·06
	Placebo	7·1		
PRISM-PLUS	Tirofiban	8·7	0·7	0·5–0·98
	Placebo	11·9		
PARAGON-A	Lamifiban	11·6	0·99	0·68–1·44
	Placebo	11·7		
PURSUIT	Eptifibatide	14·2	0·89	0·79–1·00
	Placebo	15·7		
PARAGON-B	Lamifiban	10·6	0·92	0·77–1·09
	Placebo	11·5		
GUSTO-IV ACS	abciximab 24 h	8·2	1·02	0·83–1·24
	abciximab 48 h	9·1	1·15	0·94–1·39
	Placebo	8		
All	Drug (n=15 562)	11·3	0·91	0·85–0·99
	Placebo (n=11 489)	12·5		

Table 5

Treatment	Early benefit Reduction of ischaemia	Early benefit Prevention death/MI	Sustained effects of early benefit	Additional long-term reduction death/MI	Class	References
Beta blockers	A	B	B	A	I	117, 118
Nitrates	C	—	—	—	I	121–128
Calcium antagonists	B	B	—	—	II	118, 132–138
Aspirin	—	A	A	A	I	139, 140
Thienopyridine	B	B	B	B	I	153
GpIIb/IIIa receptor inhibitors	A	A	A	A	II	160–182
Unfractionated heparin	C	B	—	—	I	139, 140, 149
LMWH	A	A	A	C*	I	141–145
Specific antithrombins	—	A	A	—	I	147, 148
Revascularization	C	B	B	B	I	52, 183, 157–163, 184

*In selected group of patients.

Oral GPIIb/IIIa receptor inhibitors. Four trials addressed prolonged treatment with oral GPIIb/IIIa receptor blockers in patients with acute coronary syndromes or after coronary intervention. Such prolonged treatment showed no evidence of benefit (OPUS-TIMI14- EXCITE, SYMPHONY 1 and 2). In fact, a modest but significant increase in mortality was apparent in a meta analysis of patients receiving oral GPIIb/IIIa receptor blockers[156].

Management of complications related to administration of GPIIb/IIIa inhibitors. With antiplatelet drugs and particularly with GPIIb/IIIa receptor inhibitors, the bleeding risk is clearly related to the dose of adjunctive

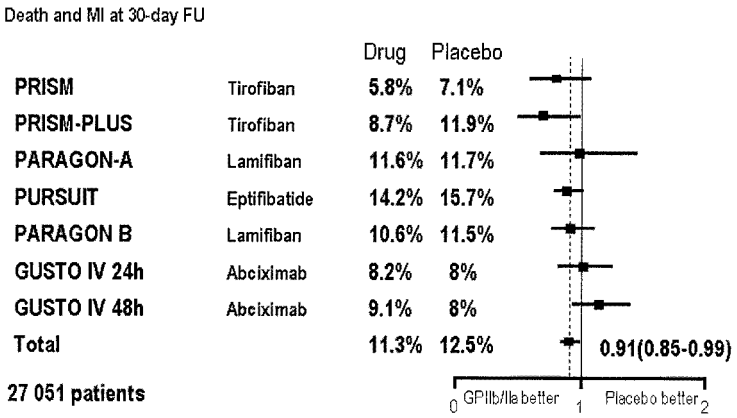

Figure 5 **GPIIb/IIIa inhibitors vs conventional treatment in six trials. Odds ratio and 95% confidence interval.**

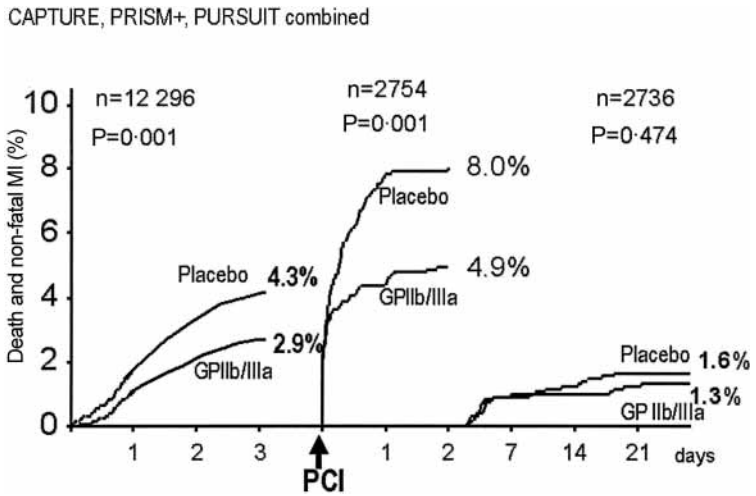

Figure 6 **GPIIb/IIIa inhibitors vs placebo in patients with acute coronary syndromes, undergoing percutaneous coronary interventions.**

heparin and specific reduced heparin dosing schedules are recommended. In the setting of percutaneous coronary intervention, it is recommended to significantly restrict the doses of heparin to 70 IU . kg^{-1} with a target ACT 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 GPIIb/IIIa receptor inhibitors: A decrease in platelet counts to less than 50 000 . mm^{-13} occurred in less than 1% of patients in PRISM-PLUS or GUSTO-IV-ACS (24 h). Stopping treatment usually results in a return to normal platelet levels[166,169]. Finally, re-administration might be an issue for abciximab, due to its inherent immunogenicity. In practice, the re-administration registry shows similar safety and efficacy for repeat administration as compared with first time administration[174,175].

Most of the trials with GPIIB/IIIA receptor inhibitors have been performed in combination with unfractionated heparin: However, the bleeding risk of combined low-molecular-weight heparin and GPIIB/IIIA receptor inhibitors must be assessed. In the ACUTE II trial conducted with tirofiban combined with enoxaparin, no difference was found in the rates of major and minor bleedings[176]. An observational study (NICE 3) showed that treatment with enoxaparin and GPIIB/IIIA receptor inhibitors (abciximab, eptifibatide or tirofiban) does not result in an excess of non-CABG major bleeding and that patients receiving this combination can safely undergo percutaneous coronary. However, in GUSTO-IV-ACS patients receiving abciximab, major bleeds tended to be more frequent for abciximab than placebo both in the dalteparin and unfractionated heparin cohort (3·8%)[169] and minor bleeds were considerably more frequent for abciximab in the dalteparin cohort (46·4% vs 27·4%, $P<0·001$). Minor bleeds were

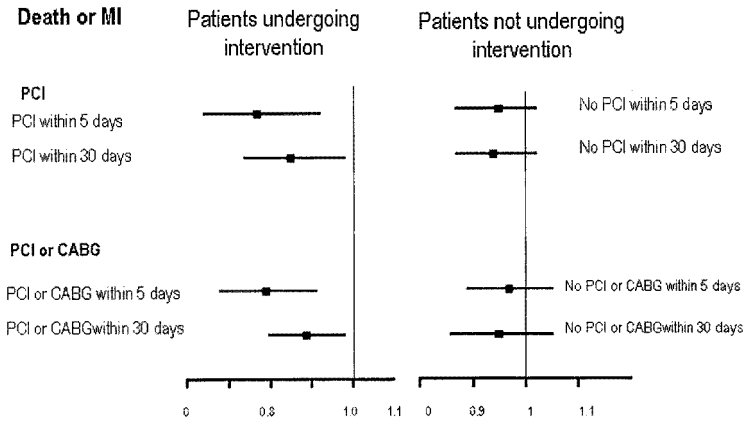

Figure 7 **GPIIb/IIIa inhibitors in patients with acute coronary syndromes: patients undergoing PCI and patients not undergoing PCI.**

considerably more common for elderly and females who constitute the greatest risk[177].

Fibrinolytic treatment

Fibrinolytic treatment has been shown to decrease the amount of intracoronary thrombus and to significantly improve survival in patients with acute coronary syndromes and ST-segment elevation[178]. 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[179–182]. The risk of death and MI 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[183]. 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.

Coronary angiography

Coronary angiography is the sole examination able to address the presence and extent of significant coronary disease. There is a wide variation among countries in the use of coronary angiography. The EuroHeart Survey demonstrated that among 5367 patients admitted with suspicion of acute coronary syndromes without ST-segment elevation, 52% underwent coronary angiography with significant regional variation[11].

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 II show that 30 to 38% of the patients with unstable coronary syndromes have single-vessel disease and 44 to 59% have multivessel disease. The rate of non-significant coronary disease varies from 14% up to 19%. The incidence of left main narrowing varies from 4% to 8%[63,184]. The pattern of ECG changes, when present, may help to identify the culprit lesion. The presence of thrombus at the lesion is an important risk marker. Eccentricity, irregular borders, ulceration, haziness and filling defects characteristic of intracoronary thrombus are markers of high-risk. However, coronary angiography has good specificity but poor sensitivity when compared to angioscopy for detection of thrombi[185].

Description of the culprit lesion is of paramount importance to choose the appropriate interventions. Extreme tortuosity, calcification, or location in a bend are important findings because they can preclude percutaneous coronary intervention with stent implantation. These aspects are frequent in elderly people.

Percutaneous coronary interventions

The safety and success of PCI in acute coronary syndromes have been markedly improved with the use

of stenting and administration of GPIIb/IIIa receptor inhibitors.

In the EuroHeart Survey, 25% of the total population had a PCI, with stent implantation in 74% of cases and administration of GPIIb/IIIa receptor inhibitors in 27% of cases[11].

Stent implantation in the setting of unstable coronary artery helps to mechanically stabilize the disrupted plaque at the site of the lesion: This benefit is particularly obvious in high-risk lesions. In a pre-specified 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[186]. Stent coated with different drugs are still more promising and in the RAVEL study, which included 220 patients with UA, there was no restenosis (re-occurrence of >50% stenosis) in the group treated with rapamycin-coated stent.

All patients undergoing PCI 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. This initial benefit was sustained at 6-month follow-up and beyond[157–159,164,187,188]. Similar but smaller reductions in acute complications were achieved with eptifibatide or tirofiban, but these initial effects were not sustained at 30 days[160,161].

From subanalyses of CAPTURE and PURSUIT, it appeared that the beneficial effect of GPIIb/IIIa inhibitors was already evident 6 to 12 h before and during planned PCI[164,167]. It is therefore recommended to begin adjunctive treatment with GPIIb/IIIa antagonists before PCI, and to continue abciximab for 12 h and other GPIIb/IIIa inhibitors for 24 h after the procedure[164,167].

The EPISTENT trial demonstrated that the combination of stent implantation and abciximab was associated with a significant 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[189]. These findings were also observed in the subset of patients with unstable coronary disease.

The ESPRIT trial confirmed the benefit of stent implantation and eptifibatide since the composite of death, myocardial infarction and urgent target vessel revascularization was reduced from 15% with placebo to 7·9% with eptifibatide ($P=0·0015$) within 48 h after randomization in patients with acute coronary syndromes[162].

The recently published PCI-CURE study (a subgroup pre-specified analysis of CURE) studied the benefit of a pre-treatment with clopidogrel[190]. At 30 days, there was a significant ($P=0·04$) reduction of cardiovascular death and MI (from 4·4% to 2·9%) and between 30 days and the end of follow-up long-term administration of clopidogrel also reduced the rate of cardiovascular death, myocardial infarction or re-hospitalization (25·3% vs 28·9%).

In all trials of ACS with PCI, the mortality rate associated with PCI is very low. After stent implantation, patients are usually discharged quickly on combination of clopidogrel and aspirin for 1 month[155]. PCI-CURE suggests that long-term (8 months on average in PCI-CURE) administration of clopidogrel after PCI is associated with a lower rate of cardiovascular death, myocardial infarction or any revascularization[190].

In a limited number of cases, special tools such as thrombectomy devices, distal protection devices etc. may be beneficial but properly randomized trials are needed to validate the use of such devices and to define the appropriate indications.

Coronary artery bypass surgery

The EuroHeart Survey showed that the current rate of CABG is overall very low[11]: 5·4%, although there is a large variation among countries. In contrast in the FRISC II and TACTICS trials, 35·2% and 20% of the patients in the invasive arm, respectively, had CABG[51,184]. Modern surgical techniques result in low operative mortality[191]. In FRISC II, the mortality rate of the surgically treated patients was 2% at 1 month FU and 1·7% in TACTICS. Surgery for post-infarction (<30 days) unstable angina has higher (6·8%) operative mortality rates (range 0 to 16%) and peri-operative myocardial infarction (5·9%) rates (range 0 to 15%). Patients with unstable coronary artery disease undergoing bypass grafting have varying risk profiles. Peri-operative mortality and morbidity is higher in patients with severe unstable angina and in patients with unstable angina after a recent (<7 days) myocardial infarction. Yet it is noteworthy that in the most recent trials of invasive treatment (FRISC-II, TACTICS), CABG was associated with a low risk of mortality (2·1%)[51,184], although the majority of these surgical procedures were performed in patients with left main or multivessel disease and early after infarction (<7 days).

It is important to consider the risk of bleeding complications in patients who underwent surgery and who were initially treated with aggressive antiplatelet treatment: In the PURSUIT trial, a total of 78 patients underwent immediate CABG within 2 h of cessation of study drug. Major bleeding was not different between groups occurring in 64% of patients receiving placebo and 63% of patients receiving eptifibatide[192]. The rate of blood transfusion was also similar (57% vs 59%). Similar observations were made by Bizzarri with tirofiban[193].

In the CURE study, 1822 patients of the clopidogrel group underwent bypass surgery. Overall, there was no significant excess of major bleeding episodes after CABG (1·3% vs 1·1%) but in the 912 patients who stopped clopidogrel within 5 days before surgery, the rate of major bleedings was higher in the clopidogrel group (9·6% vs 6·3%, $P=0·06$)[153].

Overall, pre-treatment with aggressive anti-platelet regimens should be considered as only a relative contraindication to early CABG, but may require specific surgical measures to minimize bleeding and, in

some instances may require platelet transfusions. Nevertheless, if an emergency operation is not required it is better to stop the drug and to perform intervention 5 days later.

Comparing patients with unstable angina undergoing CABG within or after 12 h after stopping fragmin, Clark *et al.* demonstrated that patients receiving dalteparin within 12 h of operation had significantly greater blood loss than the others and recommended to stop dalteparin more than 12 h before operation[194].

Respective indications for percutaneous coronary intervention or surgery

Patients with single-vessel disease and indication for revascularization are usually treated by percutaneous coronary intervention with stent implantation and adjunctive treatment with GPIIb/IIIa inhibitors. In these patients, surgical revascularization is only considered if unsuitable anatomy (extreme tortuosity of the vessel, marked angulation, etc.) 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[195,196]. Furthermore it is a more cost-effective alternative than PCI because of better symptom relief and a decreased need for repeat intervention[197–200].

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 trials did not shown a significant difference in the combined end-point of in-hospital mortality and myocardial infarction between the angioplasty and surgical groups[197–202]. 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 the patients for 7 years; during that period there was no difference in the mortality rate, except for patients with diabetes mellitus who had a better outcome with surgery than with PTCA[197].

Interventional cardiology is a continuously and rapidly evolving field; surgical techniques also continue to improve. Current state of the art practice of percutaneous coronary intervention is best presented in the ARTS trial[203]. This study was a randomized trial comparing the efficacy and cost-effectiveness of stenting vs CABG in patients with multivessel CAD. A total of 1200 patients were randomized. The proportion of unstable patients was around 36% in each group but there was no difference between stable and unstable patients. Treatment was successful in 97% of the stent group and 96% of the surgical group. The composite adverse event rate (death, MI, stroke, and need for revascularization) at 30 days was 8·7% in the stent group and 6·8% in the surgery group (P=ns). At 2-year follow-up, there was a difference (20·5% vs 15·2%) due to the need for subsequent revascularization in the stented group. Other trials have produced conflicting results: the SOS trial showed a higher cardiac mortality in the PCI group than in the surgery group at 1 year follow-up (1·6% vs 0·6%) whilst the ERACI II trial , came to the opposite conclusion (5·7% in the surgical group vs 0·9% in the PCI group)[202].

It is difficult to extrapolate from these results in highly selected patients, but overall there seems to be no firm evidence that one strategy is superior to the other. However, in many patients 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 PCI, 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 co-morbidity, 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.

In patients undergoing interventions (PCI or CABG) it is important to note that it is difficult to compare rates of peri-interventional MI. In previous trials (FRISC-II and TACTICS), different threshold for enzyme rise have been used after an intervention or in the conservative group[51,184]. In several trials, standardized but different definitions have been adopted for specific situations: an enzyme rise $\geq$3 times the upper limit of normal for percutaneous intervention, $\geq$2 times after medical treatment and, $\geq$5 times the upper limit of normal after CABG. There is however, no physiopathological basis for these different thresholds. Accordingly, the consensus document for the redefinition of myocardial infarction suggests to use similar thresholds for all conditions[5].

Invasive treatment strategy vs conservative strategy

Two randomized trials compared modern surgery and modern angioplasty with current medical therapy. The FRISC-II trial enrolled 2457 high-risk unstable patients with chest pain within 48 h of admission, who had ST-segment depression or T-wave inversion or biochemical markers above the normal range[184]. 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, PCI 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

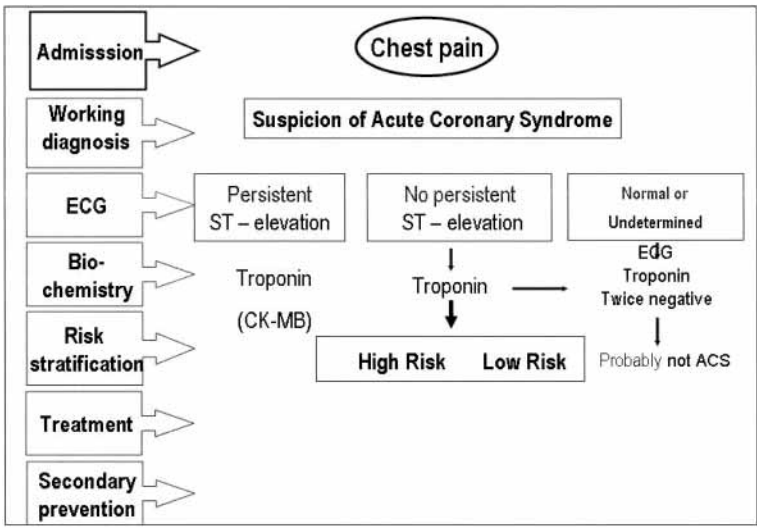

Figure 8 **Acute coronary syndromes: initial assessment.**

23% of those in the conservative arm. After 1-year follow-up there was a significant reduction in total mortality 2·2% vs 3·9% (relative reduction=0·57, (95% CI 0·36–0·90)) as well as a significant reduction in myocardial infarction 8·6% vs 11·6% (relative reduction=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% (relative risk=0·74 (95% CI 0·60–0·92)). This favourable effect was observed in men but not in women[204]. Furthermore the symptoms of angina and the need for readmissions were halved by the invasive strategy.

The TACTICS trial enrolled 2220 patients with acute coronary syndromes without persistent ST-segment elevation who were randomly assigned to an early (2–48 h) invasive strategy including routine coronary angiography followed by revascularization as appropriate or to a more conservative strategy in which catheterization was only performed if the patient had objective evidence of recurrent ischaemia or an abnormal stress test[51]. In the trial, 60% of patients allocated to invasive therapy underwent a procedure in hospital, while 36% in those allocated to medical therapy underwent a revascularization procedure. Nevertheless, the rate of the primary end-point (a composite of death, non-fatal MI, and rehospitalization for ACS) was significantly reduced at 6-month follow-up, from 19·4% to 15·4% (ARR: 4%, relative risk reduction: 0·78, (95% CI: 0·62–0·97; $P=0·025$)). The rate of death or non-fatal myocardial infarction at 6 months was similarly reduced (7·3% vs 9·5%; ARR: 2·2% relative risk reduction: 0·74; (95% CI: 0·54–1·00; $P<0·05$)). Patients with troponin T level $>0·01$ ng . ml^{-1} had a significant benefit from this invasive strategy that was not observed with troponin-T negative patients.

From FRISC II, and TACTICS it appears that a modern invasive strategy, preceded by modern anti-ischaemic and antithrombotic medication, in high risk patients with unstable coronary artery disease reduces death, myocardial infarction, symptoms and readmissions compared to a conservative strategy[51,184] (*level of evidence: A*).

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

In most patients only chest discomfort (chest pain) might be present and suspicion of acute coronary syndrome is only a working diagnosis. The initial assessment includes the four following steps (Fig. 8):
(1) It is important to obtain a careful history and a precise description of the symptoms. A physical examination with particular attention to the possible presence

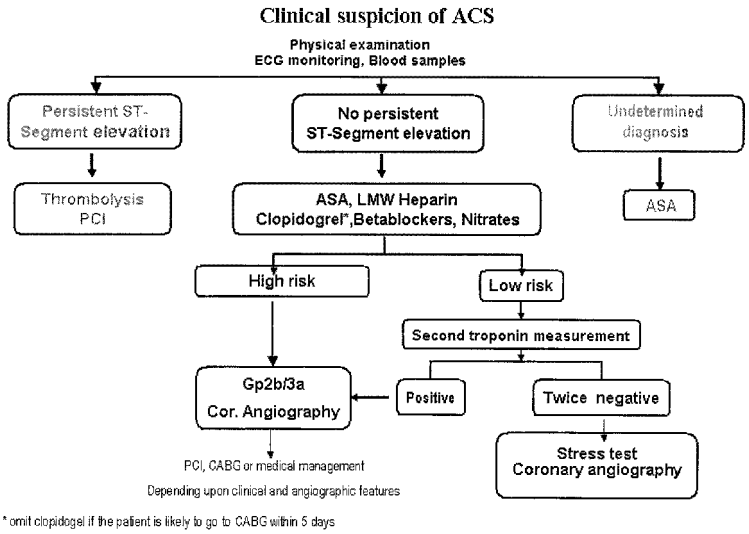

Figure 9 **Recommended strategy in acute coronary syndromes.**

of valvular heart disease (aortic stenosis), hypertrophic cardiomyopathy, heart failure, and pulmonary disease is required.

(2) An electrocardiogram is recorded : comparison with a previous ECG, if available, is very valuable, particularly in patients with pre-existing cardiac pathology such as left ventricular hypertrophy or known coronary disease. The ECG allows differentiation of patients with a suspicion of ACS in two categories requiring different therapeutic approaches:

(a) ST-segment elevation signifies complete occlusion of a major coronary artery and immediate reperfusion therapy is usually indicated. This represented 42% of the cases in the European Heart Survey on ACS[11]. Management of these patients falls outside the scope of the present guidelines and is addressed in the European Society Guidelines on Acute Myocardial Infarction[4].

(b) ST-segment changes but without persistent ST-segment elevation or a normal ECG (51% of cases).

(c) In a few cases (7%) there is no definite characterization and there are undetermined ECG changes such as bundle branch block or pacemaker rhythm.

(3) In the latter two cases, biochemical markers are required for further characterization: Laboratory assessments should include haemoglobin (to detect anaemia) and markers of myocardial damage, preferably cardiac troponin T or cardiac troponin I. If concentrations of troponins or cardiac enzymes rise, irreversible cell damage will have occurred and these patients must regarded as having had myocardial infarction according to the definition of the consensus conference[5].

(4) Then starts an observational period which includes a multi-lead ECG ischaemia monitoring. If the patient experiences a new episode of chest pain, a 12-lead ECG should be obtained and compared with a tracing obtained when symptoms have resolved spontaneously or after nitrates. In addition an echocardiogram may be recorded to assess left ventricular function and to eliminate other cardiovascular causes of chest pain. Finally a second troponin measurement should be obtained after 6 to 12 h.

Patients can then be classified as ACS, distinguishing myocardial infarction (with elevated markers of necrosis), and unstable angina (ECG changes but no signs of necrosis) with a remaining group of other disease or as yet undetermined cause of their symptoms.

Once diagnosed, acute coronary syndromes without persistent ST-segment elevation (ST-segment depression, negative T waves, pseudonormalization of T waves or normal ECG) require an initial medical treatment including aspirin 75 to 150 mg daily, clopidogrel (once registered for this indication), LMWH or unfractionated heparin, beta-blocker and oral or intravenous nitrates in cases of persistent or recurrent chest pain. Clopidogrel should replace aspirin in patients with hypersensitivity or major gastro-intestinal intolerance to aspirin. Calcium antagonists may be preferred over beta-blockers in those patients who have contra-indications to, or who are known not to tolerate, a beta-blocker. In the subsequent observation period (6–12 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.

Within this initial period risk assessment can be performed based on the clinical, electrocardiographical and biochemical data, and a further treatment strategy can be selected (Fig. 9). Risk stratification can identify two group of patients: high-risk and low-risk patients.

Strategies according to risk stratification

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

High-risk patients include those:

(a) with recurrent ischaemia (either recurrent chest pain or dynamic ST-segment changes (in particular ST-segment depression, or transient ST-segment elevation)
(b) with early post-infarction unstable angina
(c) with elevated troponin levels
(d) who develop haemodynamic instability within the observation period
(e) with major arrhythmias (repetitive ventricular tachycardia, ventricular fibrillation)
(f) with diabetes mellitus
(g) with an ECG pattern which precludes assessment of ST-segment changes

In these patients the following strategy is recommended:
(a) While waiting and preparing for angiography, treatment with LMWH should be continued. Administration of GPIIb/IIIa receptor inhibitor will be started and continued for 12 (abciximab) or 24 (tirofiban, eptifibatide) hours after the procedure if angioplasty is performed.
(b) Coronary angiography should be planned as soon as possible, but without undue urgency. A relatively small group of patients will require a coronary angiogram within the first hour. This includes patients with severe ongoing ischaemia, major arrhythmias, haemodynamic instability. In most cases coronary angiography is performed within the 48 h, or at least within hospitalization period. In patients with lesions suitable for myocardial revascularization, the decision regarding the most suitable procedure will be made after careful evaluation of the extent and characteristics of the lesions, where appropriate, in consultation with surgical colleagues. In general, recommendations for the choice of a revascularization procedure in unstable angina are similar to those for elective revascularization procedures. 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 case of serious co-morbidity, which contraindicates 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. If percutaneous intervention is the selected procedure, it may be performed immediately after angiography in the same session.

Patients with suitable lesions for PCI will receive clopidogrel. In patients planned for CABG clopidogrel will be stopped, except if the operation is deferred. In that case, clopidogrel should be stopped about 5 days before operation.

If angiography shows no options for revascularization, owing to the extent of the lesions and/or poor distal run-off, or 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 those:
(a) who have no recurrence of chest pain within the observational period
(b) without ST-segment depression or elevation but rather negative T waves, flat T waves or a normal ECG
(c) without elevation of troponin or other biochemical markers of myocardial necrosis on the initial and repeat measurement (performed between 6–12 h)

In these patients, oral treatment should be recommended, including aspirin, clopidogrel (loading dose of 300 mg followed by 75 mg daily), 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 observational period, no ECG changes are apparent and a second troponin measurement is negative.

A stress test is recommended. The purpose of such test is first, to confirm or establish a diagnosis of coronary artery disease and when this is yet uncertain, 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[205].

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

Observational studies show that most recurrent cardiac events occur within a few months following the initial

presentation of acute coronary syndromes[33,58]. 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. Some studies have shown sustained potential for rapid progression of culprit lesions in acute coronary syndromes despite initial clinical stability on medical therapy[206]. Increased thrombin generation has been observed for as long as 6 months following unstable angina or myocardial infarction[32].

In addition, trials that examined efficacy of heparin in addition to aspirin reported an increase in clinical events after heparin withdrawal[140,207]. Nevertheless, in FRISC II, continuation of low-molecular-weight heparin was only beneficial in patients waiting for an invasive procedure. Aggressive risk factor modification is warranted in all patients following diagnosis of ACS.

It is mandatory that patients quit smoking: patients should be clearly informed that smoking is a major risk factor. Referral to smoking cessation clinics is recommended and, the use of nicotine replacement therapy should be considered. Blood pressure control should be optimized. Aspirin should be prescribed (75–150 mg). According to the anti-platelet trialists meta-analysis, there is no advantage in higher doses of aspirin[208]. For patients with a history of MI, a mean of 27 months treatment results in 36 fewer vascular events per 1000 patients, including 18/1000 fewer non-fatal MI and 14/1000 fewer death with aspirin treatment[151].

Based on the results of the CURE trial, clopidogrel 75 mg should be prescribed for at least 9, possibly 12 months, and the dose of aspirin should be reduced to 75–100 mg[153]. Beta-blockers improve prognosis in patient after myocardial infarction and should be continued after acute coronary syndromes. Lipid lowering therapy should be initiated without delay. HMG-CoA reductase inhibitors substantially decrease mortality and coronary events in patients with high or intermediate or even low ($<3{\cdot}0$ mmol $.1^{-1}$) levels of LDL cholesterol (Heart Protection Study). Small subgroups of patients from PURSUIT, PRISM, PRISM-PLUS and TACTICS suggest that statins may provide an immediate benefit in acute coronary syndromes but these data are non-randomized. The MIRACL trial compared atorvastatin (80 mg daily given on average 63 h after admission and for 16 weeks) plus diet vs placebo in 3086 randomized patients[209]. The primary end-point (a composite end-point of death, non-fatal MI, rehospitalization for worsening angina at 16 weeks) was marginally ($P=0{\cdot}0459$) positive: 14·8% vs 17·4% but robust endpoints like death/MI were similar in both groups (10·1% vs 10·9%). The difference in the primary end-point was driven by rehospitalization for recurrent angina (6·2% vs 8·4%). In the RIKS-HIA registry (Register of Information and Knowledge about Swedish Intensive care Admissions) the 1 year-mortality rate was lower in patients with non-ST-elevation MI discharged with statin therapy than in the group without that treatment[210,211]. Other specific trials are ongoing to assess whether statins indeed provide immediate benefit in acute coronary syndromes (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 decrease in prothrombotic factors.

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 CAD treated with ACE inhibitors[212–214]. The decrease in MI rate became apparent after 6 months of active treatment. These data strongly suggest that beneficial effect of ACE inhibition goes beyond blood pressure control[215,216]. This concept is supported by experimental data indicative that the advantage may also be related to plaque stabilization and by the HOPE (Heart Outcomes Prevention Evaluation) trial which showed a reduction of cardiovascular death from 8·1% to 6·1% (ARR: 2%, relative risk: 0·4; (95% CI, 0·64–0·87); $P<0{\cdot}001$) and MI (relative risk: 0·80; (95% CI: 0·70–0·90); $P<0{\cdot}001$) over 4–6 years[217]. However, in HOPE, no benefit was demonstrated in the subcategory of unstable angina patients as defined by ST- and T-wave changes but this may be due to the play of chance[218]. 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 acute coronary syndromes.

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.

Summary statement

Acute coronary syndromes are a major healthcare problem and represent a large number of hospitalizations annually throughout Europe. In spite of modern treatment the rates of mortality, myocardial infarction and readmission with an acute coronary syndrome at 6-months follow-up remain still very high.

After clinical examination, it is necessary to record an electrocardiogram followed by continuous multi-lead ST-T segment monitoring, if possible. Blood samples should be obtained to determine troponin T or I, and CK-MB.

(A) *Patients with ST-segment elevation* require immediate coronary recanalization with PCI or thrombolysis

(B) *Patients without persistent ST-segment elevation* should receive baseline treatment including, aspirin,

low-molecular-weight heparin, clopidogrel, beta-blockers (if not contra-indicated) and nitrates. Risk stratification should be performed from clinical data, ECGs, troponins measurements.

Two categories of patients can be identified:
(1) High-risk patients (persistent or recurrent ischaemia, ST-segment depression, diabetes, elevated troponin, haemodynamic or arrhythmic instability) require on top of baseline treatment, infusion of GPIIb/IIIa receptor inhibitor followed by coronary angiography within the hospitalization period. This examination is performed as an emergency in patients with haemodynamic instability or recurrent life-threatening arrhythmias. Patients with suitable lesions for PCI will receive clopidogrel which will be also given to patients with coronary lesions not suitable for any form of revascularization. Patients scheduled for CABG will not receive clopidogrel, except if the operation is postponed, but in that case, clopidogrel should be stopped at least 5 days before operation. Clopidogrel should also be stopped if the coronary angiogram is completely normal.
(2) Low-risk patients include patients with no recurrent chest pain, T-wave inversion, flat T waves or normal ECG, and negative troponin. In such cases, troponin measurement should be repeated between 6–12 h. If this examination is twice negative, heparin may be discontinued, whilst aspirin, beta-blockers and nitrates are continued and clopidogrel is given. Before discharge, or in the following days if this is not possible, a stress test will be performed to assess the probability and the severity of coronary artery disease. Following this examination a coronary angiography may be performed.

In all cases, an aggressive management of risk factors: no smoking, regular exercise aspirin, clopidogrel for at least 9 months, beta-blockers (if no contra-indication) and statins must be continued during the follow-up.

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