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Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes

The Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology

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Preamble

Guidelines and Expert Consensus Documents summarize and evaluate all currently available evidence on a particular issue with the aim to assist physicians in selecting the best management strategies for a typical patient, suffering from a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes for textbooks. The legal implications of medical guidelines have been discussed previously.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines and Expert Consensus Documents can be found on the ESC website (http://www.escardio.org/knowledge/guidelines/rules).

In brief, experts in the field are selected and undertake a comprehensive review of the published evidence for management and/or prevention of a given condition. A critical evaluation of diagnostic and therapeutic procedures is performed including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger societies are included, where data exist. The level of evidence and the strength of recommendation of particular treatment options are weighed and graded according to pre-defined scales, as outlined in *Tables 1* and *2*.

The experts of the writing panels have provided disclosure statements of all relationships they may have which might be perceived as real or potential sources of conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. Any changes in conflict of interest that arise during the writing period must be notified to the ESC. The Task Force report was entirely

Table 1 Classes of recommendations

Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful

Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

supported financially by the ESC and was developed without any involvement of the industry.

The ESC Committee for Practice Guidelines (CPG) supervises and coordinates the preparation of new Guidelines and Expert Consensus Documents produced by Task Forces, expert groups, or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines and Expert Consensus Documents or statements. Once the document has been finalized and approved by all the experts involved in the Task Force, it is submitted to outside specialists for review. The document is revised, and finally approved by the CPG and subsequently published.

After publication, dissemination of the message is of paramount importance. Pocket-sized versions and personal digital assistant (PDA)-downloadable versions are useful at the point of care. Some surveys have shown that the intended end-users are sometimes not aware of the existence of guidelines, or simply do not translate them into practice, so this is why implementation programmes for new guidelines form an important component of the dissemination of knowledge. Meetings are organized by the ESC and directed towards its member National Societies and key opinion leaders in Europe. Implementation meetings can also be undertaken at national levels, once the guidelines have been endorsed by the ESC member societies and translated into the national language. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Thus, the task of writing Guidelines or Expert Consensus documents covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. The loop between clinical research, writing of guidelines, and implementing them into clinical practice can then only be completed if surveys and registries are performed to verify that real-life daily practice is in keeping with what is recommended in the guidelines. Such surveys and registries also make it possible to evaluate the impact of implementation of the guidelines on patient outcomes. Guidelines and recommendations should help physicians to make decisions in their daily practice; however, the ultimate judgement regarding the care of an individual patient must be made by the physician in charge of his/her care.

1. Introduction and definitions

Cardiovascular diseases are presently the leading causes of death in industrialized countries and expected to become so in emerging countries by 2020.[1] Among these, coronary artery disease (CAD) is the most prevalent manifestation and is associated with high mortality and morbidity. The clinical presentations of ischaemic heart disease include silent ischaemia, stable angina pectoris, unstable angina, myocardial infarction (MI), heart failure, and sudden death. Patients with chest pain represent a very large proportion of all acute medical hospitalizations in Europe. Distinguishing those with acute coronary syndrome (ACS) within the very large proportion with suspected cardiac pain represents a diagnostic challenge, especially in those without clear symptoms or electrocardiographic features. In spite of modern treatment, the rates of death, MI, and re-admission of patients with ACS remain high.

It is well established that ACS in their different clinical presentations share a widely common pathophysiological substrate. Pathological, angioscopic, and biological observations have demonstrated that atherosclerotic plaque rupture or erosion, with differing degrees of superimposed thrombosis and distal embolization, resulting in myocardial underperfusion, represent the basic pathophysiological mechanisms in most ACS.

As this is a life-threatening state of atherothrombotic disease, criteria for risk stratification have been developed to allow the clinician to make timely decisions on pharmacological management as well as on coronary revascularization strategies, tailored to the individual patient. The leading symptom that initiates the diagnostic and therapeutic cascade is chest pain, but the classification of patients is based on the electrocardiogram (ECG). Two categories of patients may be encountered:

(i) **Patients with typical acute chest pain and persistent (>20 min) ST-segment elevation.** This is termed ST-elevation ACS (STE-ACS) and generally reflects an acute total coronary occlusion. Most of these patients will ultimately develop an ST-elevation MI (STEMI). The therapeutic objective is to achieve rapid, complete, and sustained reperfusion by primary angioplasty or fibrinolytic therapy.[2]

(ii) **Patients with acute chest pain but without persistent ST-segment elevation.** They have rather persistent or transient ST-segment depression or T-wave inversion, flat T-waves, pseudo-normalization of T-waves, or no ECG changes at presentation. The initial strategy in these patients is to alleviate ischaemia and symptoms, to monitor the patient with serial ECG, and to

repeat measurements of markers of myocardial necrosis. At presentation, the working diagnosis of non-STE-ACS (NSTE-ACS), based on the measurement of troponins, will be further qualified into non-ST elevation MI (NSTEMI) or unstable angina. (*Figure 1*) In a certain number of patients, CAD will subsequently be excluded as the cause of symptoms. The therapeutic management is guided by the final diagnosis.

The management of patients with STEMI is addressed in the ESC Guidelines for management of ST-elevation acute MI.[2] The present document deals with the management of patients with suspected NSTE-ACS, replacing the document published in 2000 and last updated in 2002.[3] It includes all scientific evidence fully published as peer-reviewed papers in a journal, before 30 April 2007.

The class A level of recommendations of this document is based primarily on randomized, double-blind studies of adequate size using contemporary adjunctive treatment and endpoints that are not subject to observer bias, such as death and MI. These studies were considered to represent the greatest weight of evidence. Studies that were randomized, but not double blind, and/or studies using less robust endpoints (such as refractory ischaemia or need for revascularization) were considered to confer a lower weight of evidence. If only smaller studies were available, meta-analyses were used. However, even the largest controlled trials do not cover all aspects seen in real life. Therefore, some recommendations are derived from subset analyses of larger trials, in the absence of sufficiently powered independent studies. Furthermore, in this rapidly moving field, new studies will constantly challenge the current recommendations.

Costs of health care become an increasing issue in many countries. Although this should not play a role in decision-making, cost consciousness is necessary today. Therefore, we provide the numbers needed to treat (NNT) to prevent an event for the most important treatment options. The NNT seems to be the most transparent approach to compare studies of different size and different endpoints. For example, an NNT of 50 to prevent one death is to be interpreted differently from an NNT of 50 to avoid one rehospitalization.[4]

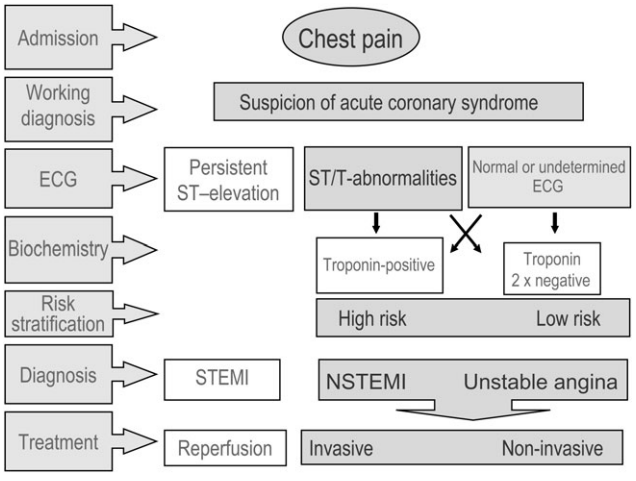

Figure 1 The spectrum of acute coronary syndromes.

2. Epidemiology and natural history

The diagnosis of NSTE-ACS is more difficult to establish than STEMI and therefore its prevalence is harder to estimate. In addition, in recent years, a new definition of MI has been introduced to take into account the use of more sensitive and more specific biomarkers of cell death.[5] In this context, the prevalence of NSTE-ACS, relative to STEMI, has been determined from multiple surveys and registries.[6–15] Overall, data suggest that the annual incidence of NSTE-ACS is higher than that of STEMI. The ratio between NSTE-ACS and STEMI has changed over time, as the rate of NSTE-ACS increased relative to STEMI, without any clear explanation for the reasons behind this evolution.[16] This change in the pattern of NSTE-ACS could actually be linked to changes in the management of disease and greater efforts in prevention of CAD over the last 20 years.[17–20] Overall, from these registries and surveys, it has been shown that the annual incidence of hospital admissions for NSTE-ACS is in the range of 3 per 1000 inhabitants. To date, there are no clear estimates for Europe as a whole, because of the absence of a common centre for centralized health statistics. However, the incidence of the disease is greatly variable among European countries, with a strong west-to-east gradient, the higher incidences and death rates occurring in Central-Eastern Europe.

Overall, the prognosis of NSTE-ACS can be derived from surveys carried out around the world that have included more than 100 000 patients. Data consistently show that the mortality rate at 1 and 6 months is higher in survey populations than in randomized clinical trials. Hospital mortality is higher in patients with STEMI than among those with NSTE-ACS (7 vs. 5%, respectively), but, at 6 months, the mortality rates are very similar in both conditions (12 vs. 13%, respectively).[21,22] Long-term follow-up of those who survive to reach hospital showed that death rates were higher among those with NSTE-ACS than with STE-ACS, with a two-fold difference at 4 years.[23] This difference in mid- and long-term evolution may be due to different patient profiles, since NSTE-ACS patients tend to be older, with more co-morbidities, especially diabetes and renal failure. The difference could also be due to the greater extent of coronary artery and vascular disease or persistent triggering factors such as inflammation.[24,25]

The implications for therapy are as follows.

- NSTE-ACS is more frequent than STEMI.
- In contrast to STEMI, where most events occur before or shortly after presentation, in NSTE-ACS these events continue over days and weeks.
- Mortality of STEMI and NSTE-ACS after 6 months is comparable.

This implies that treatment strategies for NSTE-ACS need to address the requirements of the acute phase as well as longer-term treatment.

3. Pathophysiology

Atherosclerosis is a chronic, multifocal immunoinflammatory, fibroproliferative disease of medium-sized and large arteries mainly driven by lipid accumulation.[26] CAD involves two distinct processes: a fixed and barely reversible

process that causes gradual luminal narrowing slowly over decades (atherosclerosis) and a dynamic and potentially reversible process that punctuates the slow progression in a sudden and unpredictable way, causing rapid complete or partial coronary occlusion (thrombosis or vasospasm, or both). Thus, symptomatic coronary lesions contain a variable mix of chronic atherosclerosis and acute thrombosis. Since the exact nature of the mix is unknown in the individual patient, the term atherothrombosis is frequently used. Generally, atherosclerosis predominates in lesions responsible for chronic stable angina, whereas thrombosis constitutes the critical component of culprit lesions responsible for the ACS.[27,28]

ACS represent a life-threatening manifestation of atherosclerosis usually precipitated by acute thrombosis, induced by a ruptured or eroded atherosclerotic plaque, with or without concomitant vasoconstriction, causing a sudden and critical reduction in blood flow. In the complex process of plaque disruption, inflammation was revealed as a key pathophysiological element. In rare cases, ACS may have a non-atherosclerotic aetiology such as arteritis, trauma, dissection, thrombo-embolism, congenital anomalies, cocaine abuse, and complications of cardiac catheterization. Some key pathophysiological elements will be described in more detail because they are important to understand the therapeutic strategies.

3.1 The vulnerable plaque

Atherosclerosis is not a continuous, linear process but rather a disease with alternate phases of stability and instability. Sudden and unpredictable changes in symptoms appear to be related to plaque disruption. The plaques prone to instability and rupture have a large lipid core, a low density of smooth muscle cells, a high concentration of inflammatory cells, and a thin fibrous cap covering the lipid core compared with stable plaques.[29] Plaque vulnerability may also depend on circumferential wall stress, on the location and size of the plaque, and on the impact of flow on the luminal plaque surface. In addition to plaque rupture, plaque erosion is another underlying mechanism in ACS. When erosion occurs, the thrombus adheres to the surface of the plaque, whereas in the case of plaque rupture, the thrombus involves the deeper layers down to the lipid core. This may contribute to the growth and rapid progression of the plaque, if the thrombus is not accommodated by positive remodelling.

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 in continuous equilibrium between growth factor-modulated collagen synthesis and its degradation by proteases arising from activated macrophages. The apoptosis of smooth muscle cells can also weaken cap tissue and favour plaque rupture. Macrophage infiltration has been consistently demonstrated in pathological studies; the proportion of macrophages is six to nine times greater in ruptured than in stable plaques and is characterized by the presence of activated T-lymphocytes at the site of plaque rupture that can release various cytokines that activate macrophages and promote smooth muscle cell proliferation.[30] These cells may produce proteases that digest the extracellular matrix. *In vitro*, macrophages induce the breakdown of collagen obtained from human fibrous caps, and protease inhibitors can block this process.

3.2 Coronary thrombosis

The central role of thrombosis in the development of ACS has been widely demonstrated by means of autopsy data[31,32] and angiographic and angioscopic detection of thrombi at the site of the culprit lesion.[33] In addition, the detection of markers of thrombin generation and platelet activation[34] and evidence of improved outcomes with antithrombotic treatments have contributed to our understanding of the role of thrombosis in ACS.

Coronary thrombosis in ACS usually develops at the site of a vulnerable plaque. The lipid-rich core exposed after plaque rupture is highly thrombogenic and has a high concentration of tissue factor.[35] Thrombosis is induced at the site of plaque rupture or erosion and may lead to rapid changes in the severity of stenosis that may cause subtotal or total vessel occlusion. The thrombus is fibrin-rich and completely occlusive in STEMI, whereas it is platelet-rich and partially or intermittently occlusive in NSTE-ACS.

Spontaneous thrombolysis may explain transient episodes of thrombotic vessel occlusion/subocclusion and the associated transient ischaemia. A platelet-rich thrombus at the site of plaque rupture may fragment into small particles, which embolize downstream and may occlude arterioles and capillaries. These platelet emboli may cause small areas of necrosis in the myocardium supplied by the culprit vessel, thus leading to the release of markers of myocardial necrosis.[31,32]

3.3 The vulnerable patient

There is increasing experimental and clinical evidence to suggest the diffuse nature of unstable plaques in patients with ACS. Multiple sites of plaque rupture with or without intracoronary thrombosis, along with elevated levels of various systemic markers of inflammation and thrombosis as well as coagulation system activation, have been documented in patients with ACS.[36–38] Hypercholesterolaemia, tobacco smoking, and increased fibrinogen levels have been reported to contribute to instability in these patients, leading to thrombotic complications.

The concept of widespread instability has important therapeutic implications, because beyond the focal revascularization strategies, such individuals should have systemic therapies aimed at stabilizing the high-risk profile that may cause recurrent ischaemic events.

3.4 Endothelial vasodilatory dysfunction

Minor changes in coronary tone may greatly affect myocardial blood supply and thus cause insufficient flow at rest or during exercise. Vasospasm most frequently occurs at the site of atherosclerotic plaques in which local vasoconstricting substances, such as serotonin, thromboxane A_2, and thrombin, are released locally by platelets and intracoronary thrombi. It has been shown that the endothelium is a multifunctional organ, the integrity of which is essential for normal tone modulation. Endothelial dysfunction is linked to prognosis and is unmasked by vasoconstriction induced by acetylcholine and methacholine.[39,40] The

prototype of dynamic coronary obstruction as a cause of ACS is Prinzmetal's variant angina, in which coronary vasospasm is the main determinant of an abrupt reduction in flow. This usually occurs at sites of critical or subcritical stenoses.[41]

3.5 Accelerated atherosclerosis

Severe endothelial injury appears to be the critical initiating event that causes smooth muscle cell proliferation in accelerated atherosclerosis. This is followed by intense platelet activation and thrombus formation leading to rapidly progressive coronary narrowing. An angiographic study of patients on the waiting list for percutaneous coronary revascularization has shown that rapid progression of pre-existing atherosclerotic stenoses is relatively common, and the risk arising from complex stenoses is greater than that associated with smooth lesions.[42]

3.6 Secondary mechanisms

A number of extra-cardiac mechanisms can cause a critical increase in myocardial oxygen consumption to above the supply threshold, and thus elicit an ACS episode with or without a pre-existing coronary stenosis. The mechanisms related to an increase in myocardial oxygen consumption are fever, tachycardia, thyrotoxicosis, a hyperadrenergic state, sudden emotional stress, and increased left ventricular (LV) afterload (hypertension, aortic stenosis), whereas those related to reduced myocardial oxygen delivery are anaemia, methaemoglobinaemia, and hypoxaemia. Triggers such as emotional upset, vigorous physical exercise, lack of sleep, or overeating have been shown to precipitate the onset of ACS.[43]

3.7 Myocardial injury

Pathological studies in patients with NSTE-ACS 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. 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.[31,32] Focal myocardial necrosis was shown to be surrounded by areas of inflammation.[44] In clinical practice, this minor damage may be detected only by cardiac troponin T (cTnT) or troponin I (cTnI) elevations and are classified as MI according to the ESC/AHA/ACC Consensus Document.[5] This concept is of clinical importance, because it has major practical implications with respect to short-term prognosis and the choice of the therapeutic regimen.

4. Diagnosis and risk assessment

Diagnosis and risk stratification are closely linked in ACS. During the process of establishing the diagnosis of ACS and excluding differential diagnoses, the risk is repeatedly assessed and serves as a guide for the therapeutic management. Patients with NSTE-ACS are at high risk for MI, recurrence of MI, or death. Risk must not be understood in a binary way, but rather as a continuum from patients with very high risk to patients with low risk.

4.1 Clinical presentation and history

The clinical presentation of NSTE-ACS 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 angina [Class III of the Classification of the Canadian Cardiovascular Society[45] (CCS)]
- Recent destabilization of previously stable angina with at least CCS III angina characteristics (crescendo angina), or
- Post-MI angina.

Prolonged pain is observed in 80% of patients, whereas *de novo* or accelerated angina is observed in only 20%.[46] It is important to note that a reliable distinction between ACS with or without ST-elevation cannot be based on symptoms.

The typical clinical presentation of NSTE-ACS is retrosternal pressure or heaviness ('angina') radiating to the left arm, neck, or jaw, which may be intermittent (usually lasting several minutes) or persistent. These complaints may be accompanied by other symptoms such as diaphoresis, nausea, abdominal pain, dyspnoea, and syncope. However, atypical presentations of NSTE-ACS are not uncommon.[47] These include epigastric pain, recent-onset indigestion, stabbing chest pain, chest pain with some pleuritic features, or increasing dyspnoea. Atypical complaints are often observed in younger (25–40 years) and older (>75 years) patients, in women, and in patients with diabetes, chronic renal failure, or dementia.[47,48] Absence of chest pain leads to under-recognition of the disease and undertreatment.[49] The diagnostic and therapeutic challenges arise especially when the ECG is normal or nearly normal, or conversely when the ECG is abnormal at baseline due to underlying conditions such as intraventricular conduction defects or LV hypertrophy.[13]

There are certain features regarding the symptoms that may support the diagnosis of CAD and guide the management. The exacerbation of symptoms by physical exertion or their relief at rest or after nitrates support a diagnosis of ischaemia. Symptoms at rest carry a worse prognosis than symptoms elicited only during physical exertion. In patients with intermittent symptoms, an increasing number of episodes preceding the index event may also have an impact on outcome. The presence of tachycardia, hypotension, or heart failure upon presentation indicates a poor prognosis and needs rapid diagnosis and management. It is important to identify clinical circumstances that may exacerbate or precipitate NSTE-ACS, such as anaemia, infection, inflammation, fever, and metabolic or endocrine (in particular thyroid) disorders.

A classification of unstable angina was introduced by Braunwald[50] and was based on the severity of pain, the circumstances under which it occurs, and precipitating factors associated with its onset, and was later validated as a prognostic tool.[51] However, its usefulness in the clinical setting is limited to the finding that patients with pain at rest during the last 48 h are at increased risk, particularly if troponins are elevated.[52]

When faced with a symptomatic patient, there are several clinical findings that increase the probability of a diagnosis of CAD and therefore NSTE-ACS. These include older age, male gender, and known atherosclerosis in non-coronary

territories, such as peripheral or carotid artery disease. The presence of risk factors, in particular diabetes mellitus and renal insufficiency as well as prior manifestation of CAD, i.e. previous MI, percutaneous coronary intervention (PCI), or coronary bypass graft surgery (CABG), also raises the likelihood of NSTE-ACS. However, all of these factors are not specific, so that their diagnostic value should not be overestimated.

4.2 Diagnostic tools

4.2.1 Physical examination

The physical examination is frequently normal. Signs of heart failure or haemodynamic instability must prompt the physician to expedite the diagnosis and treatment of patients. An important goal of the physical examination is to exclude non-cardiac causes of chest pain and non-ischaemic cardiac disorders (e.g. pulmonary embolism, aortic dissection, pericarditis, valvular heart disease), or potentially extra-cardiac causes, such as acute pulmonary diseases (e.g. pneumothorax, pneumonia, pleural effusion). In this regard, differences in blood pressure between the upper and lower limbs, an irregular pulse, heart murmurs, a friction rub, pain on palpation, and abdominal masses are physical findings that may suggest a diagnosis other than NSTE-ACS. Other physical findings such as palor, increased sweating, or tremor may orientate towards precipitating conditions, such as anaemia and thyrotoxicosis.

4.2.2 Electrocardiogram

The resting 12-lead ECG is the first-line diagnostic tool in the assessment of patients with suspected NSTE-ACS. It should be obtained within 10 min after first medical contact upon arrival of the patient in the emergency room and immediately interpreted by a qualified physician.[53] The finding of persistent ($>$20 min) ST-elevation suggests STEMI which requires different treatment.[2] In the absence of ST-elevation, additional recordings should be obtained when the patient is symptomatic and compared with recordings obtained in an asymptomatic state. Comparison with a previous ECG, if available, is valuable, particularly in patients with co-existing cardiac disorders such as LV hypertrophy or a previous MI. ECG recordings should be repeated at least at 6 and 24 h, and in the case of recurrence of chest pain/symptoms. A pre-discharge ECG is advisable.

ST-segment shifts and T-wave changes are the ECG indicators of unstable CAD.[21,54] The number of leads showing ST-depression and the magnitude of ST-depression are indicative of the extent and severity of ischaemia and correlate with prognosis.[55] ST-segment depression $\geq$0.5 mm (0.05 mV) in two or more contiguous leads, in the appropriate clinical context, is suggestive of NSTE-ACS and linked to prognosis.[56] Minor (0.5 mm) ST-depression may be difficult to measure in clinical practice. More relevant is ST-depression of $\geq$1 mm (0.1 mV) which is associated with an 11% rate of death and MI at 1 year.[54] ST-depression of $\geq$2 mm carries about a six-fold increased mortality risk.[57] ST-depression combined with transient ST-elevation also identifies a high-risk subgroup.[58]

Patients with ST-depression have a higher risk for subsequent cardiac events compared with those with isolated T-wave inversion ($>$1 mm) in leads with predominant R-waves, who in turn have a higher risk than those with a normal ECG on admission. Some studies have cast doubt on the prognostic value of isolated T-wave inversion. However, deep symmetrical inversion of the T-waves in the anterior chest leads is often related to a significant stenosis of the proximal left anterior descending coronary artery or main stem.[59]

It should be appreciated that a completely normal ECG does not exclude the possibility of NSTE-ACS. In several studies, around 5% of patients with normal ECG who were discharged from the emergency department were ultimately found to have either an acute MI or an unstable angina.[60,61] Particularly, ischaemia in the territory of the circumflex artery frequently escapes the common 12-lead ECG, but may be detected in lead V_4R and V_3R as well as in leads V_7–V_9. Transient episodes of bundle branch block occasionally occur during ischaemic attacks.

Continuous ST-segment monitoring

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 the phase of instability are clinically silent and, hence, not likely to be detected by conventional ECG. On-line continuous computer-assisted 12-lead ST-segment monitoring is a valuable diagnostic tool. Several studies revealed that 15–30% of patients with NSTE-ACS 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, troponins, and other clinical parameters.[62–65]

Exercise or other stress testing

In patients who continue to have typical ischaemic chest pain, no stress test should be performed. However, a stress test has a predictive value and is therefore useful before discharge in patients with non-diagnostic ECG provided there is no pain, no signs of heart failure, and normal biomarkers (repeat testing). Early exercise testing has a high negative predictive value. 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.[66]

4.2.3 Biochemical markers

Several biomarkers have been investigated in recent years to be used for diagnostic and risk stratification. These reflect different pathophysiological aspects of NSTE-ACS, such as minor myocardial cell injury, inflammation, platelet activation, or neurohormonal activation. For the long-term prognosis, indicators of LV and renal dysfunction or diabetes also play an important role.

Markers of myocardial injury

cTnT or cTnI are the preferred markers of myocardial injury, because they are more specific and more sensitive than the traditional cardiac enzymes such as creatinine kinase (CK) or its isoenzyme MB (CK-MB). In this setting, myoglobin is not specific and sensitive enough to allow the detection of myocardial cell injury and therefore not recommended for routine diagnosis and risk stratification.[67]

It is believed that the elevation of cardiac troponins reflects irreversible myocardial cellular necrosis typically

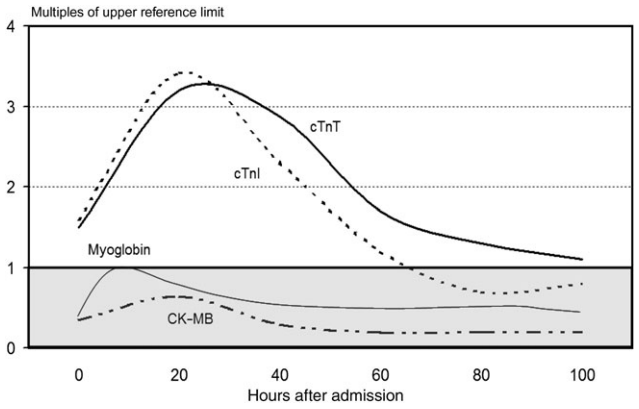

Figure 2 Example of release of cardiac markers in a patient with non-ST-elevation acute coronary syndrome (shaded area indicates normal range).

Table 3 Non-coronary conditions with troponin elevations[68]

Severe congestive heart failure: acute and chronic
Aortic dissection, aortic valve disease, or hypertrophic cardiomyopathy
Cardiac contusion, ablation, pacing, cardioversion, or endomyocardial biopsy
Inflammatory diseases, e.g. myocarditis, or myocardial extension of endocarditis/pericarditis
Hypertensive crisis
Tachy- or bradyarrhythmias
Pulmonary embolism, severe pulmonary hypertension
Hypothyroidism
Apical ballooning syndrome
Chronic or acute renal dysfunction
Acute neurological disease, including stroke, or subarachnoid haemorrhage
Infiltrative diseases, e.g. amyloidosis, haemochromatosis, sarcoidosis, scleroderma
Drug toxicity, e.g. adriamycin, 5-fluorouracil, herceptin, snake venoms
Burns, if affecting >30% of body surface area
Rhabdomyolysis
Critically ill patients, especially with respiratory failure, or sepsis

resulting from distal embolization of platelet-rich thrombi from the site of a ruptured plaque. Accordingly, troponins may be seen as a surrogate marker of active thrombus formation. In the setting of myocardial ischaemia (chest pain, ST-segment changes) troponin elevation has to be labelled as MI according to the ESC/ACC/AHA Consensus Document[5] currently under revision.[68]

Troponins are the best biomarker to predict short-term (30 days) outcome with respect to MI and death.[69–72] The prognostic value of troponin measurements has also been confirmed for the long term (1 year and beyond). The increased risk associated with elevated troponin levels is independent of and additive to other risk factors such as ECG changes at rest or on continuous monitoring, or markers of inflammatory activity.[52,71] Furthermore, the identification of patients with elevated troponins levels is also useful for selecting appropriate treatment in patients with NSTE-ACS.[73–75]

In patients with MI, an initial rise in troponins in peripheral blood occurs after 3–4 h. Troponin levels may persist elevated for up to 2 weeks caused by proteolysis of the contractile apparatus. In NSTE-ACS, minor elevation of troponins may be measurable only over 48–72 h (*Figure 2*). The high sensitivity of troponin tests allows the detection of myocardial damage undetected by CK-MB in up to one-third of patients presenting with NSTE-ACS. Minor or moderate elevations of troponins appear to carry the highest early risk in patients with NSTE-ACS.[72]

A single negative test for troponins on arrival of the patient in hospital is not sufficient for ruling out an elevation, as in many patients an increase in troponins can be detected only in the subsequent hours. In order to demonstrate or to exclude myocardial damage, repeated blood sampling and measurements are required 6–12 h after admission and after any further episodes of severe chest pain.[76] A second sample in the absence of any other suspicious findings may be omitted only if the patient's last episode of chest pain was more than 12 h prior to the initial determination of troponins.

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 troponins and should always be considered as a differential diagnosis. Elevation of cardiac troponins also occurs in the setting of non-coronary-related myocardial injury (*Table 3*). This reflects the sensitivity of the marker for myocardial cell injury and should not be labelled as false-positive test results. True 'false-positive' results have been documented in the setting of skeletal myopathies or chronic renal failure. Elevation of troponins is frequently found when serum creatinine level is >2.5 mg/dL (221 μmol/L) in the absence of proven ACS, and is also associated with adverse prognosis.[77,78] Troponin elevations that cannot be explained are rare.

There is no fundamental difference between troponin T and troponin I. Differences between study results are predominantly explained by varying inclusion criteria, differences in sampling patterns, and the use of assays with different diagnostic cut-offs. The diagnostic cut-off for MI using cardiac troponins should be based on the 99th percentile of levels among healthy controls as recommended by the Consensus committee. Acceptable imprecision (coefficient of variation) at the 99th percentile for each assay should be $\leq$10%.[5] Each individual laboratory should regularly assess the range of reference values in their specific setting.

The diagnosis of NSTE-ACS should never be made only on the basis of cardiac biomarkers, whose elevation should be interpreted in the context of other clinical findings.

Markers of inflammatory activity

Of the numerous inflammatory markers that have been investigated over the past decade, C-reactive protein measured by high-sensitive (hsCRP) assays is the most widely studied and linked to higher rates of adverse events. The exact source of elevated hsCRP levels among patients with NSTE-ACS remains unclear. Given that myocardial damage is also a major inflammatory stimulus, an acute inflammatory process induced by myocardial damage is

superimposed on a chronic inflammatory condition, both of which might influence long-term outcome in NSTE-ACS.

There is robust evidence that even among patients with troponin-negative NSTE-ACS, elevated levels of hsCRP are predictive of long-term mortality (>6 months).[37,71,79,80] The FRISC study confirmed that mortality is associated with elevated hsCRP levels at the time of the index event and continues to increase over 4 years.[36] This was also observed in large cohorts of patients submitted to planned PCI.[81] However, hsCRP has no role for the diagnosis of ACS.

Markers of neurohumoral activation

Neurohumoral activation of the heart can be monitored by measurements of systemic levels of natriuretic peptides secreted from the heart. Natriuretic peptides, such as brain-type [B-type natriuretic peptide (BNP)] or its N-terminal prohormone fragment (NT-proBNP), are highly sensitive and fairly specific markers for the detection of LV dysfunction. There are robust retrospective data in NSTE-ACS showing that patients with elevated BNP or NT-proBNP levels have a three- to five-fold increased mortality rate when compared with those with lower levels.[82,83] The level is strongly associated with the risk of death even when adjusted for age, Killip class, and LV ejection fraction (EF).[71] Values taken a few days after onset of symptoms seem to have superior predictive value when compared with measurements on admission.[84,85] Natriuretic peptides are useful markers in the emergency room in evaluating chest pain or dyspnoea and were shown to be helpful in differentiating between cardiac and non-cardiac causes of dyspnoea. However, they are markers of long-term prognosis, but have limited value for initial risk stratification and hence for selecting the initial therapeutic strategy in NSTE-ACS.[86]

Markers of renal function

Impaired renal function is a strong independent predictor for long-term mortality in ACS patients.[71,87,88] Serum creatinine concentration is a less reliable indicator of renal function than creatinine clearance (CrCl) or glomerular filtration rate (GFR), because it is affected by a multitude of factors, including age, weight, muscle mass, race, and various medications.[89] Several formulae have been devised to improve the accuracy of serum creatinine level as a surrogate of GFR, including the Cockcroft–Gault[90] and the abbreviated Modification of Diet in Renal Disease (MDRD) equations.[91] Long-term mortality is influenced by the degree of renal function, as it increases exponentially with decreasing GFR/CrCl. When compared with patients with normal renal function, the odds ratio (OR) for death at 1 year was 1.76 for mild renal dysfunction, 2.72 for moderate renal dysfunction, and 6.18 for severe renal dysfunction.[88] (see section 7.4 Chronic kidney disease).

Cystatin C is considered to be a surrogate marker of renal function superior to CrCl or GFR estimation.[93,94] Cystatin C is a cysteine proteinase inhibitor produced by all nucleated cells at a constant rate and excreted into the bloodstream. Because of its low molecular weight (13 kDa), it is freely filtered at the glomerulus and is almost completely reabsorbed and catabolized, but not secreted, by tubular cells. Cystatin C levels have been shown to be good markers of prognosis,[95] although not widely available yet.

Novel biomarkers

A considerable number of patients can still not be identified as being at high risk by today's routine biomarkers. Accordingly, a great number of novel biomarkers have been investigated in recent years to explore their usefulness as diagnostic tools and for risk stratification in addition to established markers. Several novel biomarkers have been studied. These include markers of oxidative stress (myeloperoxidase),[96,97] markers of thrombosis and inflammation (e.g. soluble CD40 ligand),[98,99] or markers involved more upstream in the inflammation cascade, i.e. markers specific of vascular inflammation. All have shown their incremental value over troponins in retrospective analyses, but have not been tested prospectively and are not yet available for routine use.

Multimarker approach

Since NSTE-ACS is a complex event, several markers reflecting the respective pathophysiological pathways may be advantageous for risk stratification. It is useful to distinguish between markers for the acute risk of MI and for long-term mortality. The combined use of markers for myocardial necrosis, inflammation, myocardial and renal dysfunction, and neurohumoral activation may significantly add to our ability to identify correctly patients who are at high risk for future cardiovascular events. Several studies demonstrated that a multimarker approach improves risk stratification.[71,79,98]

Currently, it is recommended to use troponins (cTnT or cTnI) for the acute risk stratification on arrival of the patient in the hospital. At the same time or during the subsequent days, CrCl and BNP or NT-pro-BNP allow estimation of any renal or myocardial dysfunction with its inherent impacts on treatment and long-term outcome. Currently, only hsCRP is available on a routine basis for the detection of the underlying inflammatory activity responsible for long-term mortality.

Point-of-care (bedside) biomarker testing

The diagnosis of NSTE-ACS and the assignment to a risk group should be undertaken as rapidly as possible (see section 8 Management strategies). Point-of-care testing for biochemical markers is advantageous to establish diagnosis. These tests 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.[76,100,101] Point-of-care tests for troponins should be implemented when a central laboratory cannot consistently provide test results within 60 min.[102] No special skill or prolonged training is required to read the result of these assays. Accordingly, these tests can be performed by various members of the health-care team after adequate training.[103] However, reading of these mostly qualitative tests is performed visually and therefore is observer-dependent. Some companies provide optical reading devices for the emergency room setting.[104] The tests are usually reliable when positive. However, in the presence of a remaining suspicion of unstable CAD, negative tests should be repeated at a later time point and verified by a central laboratory.

4.2.4 Echocardiography and non-invasive myocardial imaging

LV systolic function is an important prognostic variable in patients with ischaemic heart disease and can be easily and accurately assessed by echocardiography. In

experienced hands, 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. Furthermore, differential diagnoses such as aortic stenosis, aortic dissection, pulmonary embolism, or hypertrophic cardiomyopathy may be identified.[105] Therefore, echocardiography should routinely be used in emergency units.

Stress echocardiography is helpful in stabilized patients to obtain objective evidence of ischaemia and has the same indications as other exercise modalities.[106] Similarly, stress scintigraphy[107,108] or magnetic resonance imaging (MRI)[109] may be used, if available. MRI is useful to assess myocardial viability. Rest myocardial scintigraphy was shown to be helpful for initial triage of patients presenting with chest pain without ECG changes or evidence of ongoing MI.[110]

4.2.5 Imaging of the coronary anatomy

Imaging modalities provide unique information on the presence and the severity of CAD. The gold standard is still conventional invasive coronary angiography.

Patients with multiple vessel disease as well as those with left main stenosis are at the highest risk of serious cardiac events.[111] 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. Highest risk is associated with the occurrence of filling defects indicating intracoronary thrombus formation.

At the current state of development, cardiac computed tomography (CT) cannot be recommended as the coronary imaging modality in NSTE-ACS, because of suboptimal diagnostic accuracy. Fast technical evolution may result in improved diagnostic accuracy in the near future and lead to reconsideration of the use of this tool in the decision-making process.[112] Furthermore, because of the high likelihood of PCI, time is lost and the patient is exposed to unnecessary radiation and contrast medium utilization if CT is used as the first diagnostic option.

MRI is not established as an imaging tool for coronary arteries. It may only be useful in the course of hospitalization in quantifying myocardial injury or excluding myocarditis.[109] CT or MRI may, however, be indicated for evaluation of differential diagnoses, such as pulmonary embolism or aortic dissection.

4.3 Differential diagnoses

There are several cardiac and non-cardiac conditions that may mimic NSTE-ACS (*Table 4*).

Underlying chronic heart conditions such as hypertrophic cardiomyopathy and valvular heart disease (i.e. aortic stenosis, aortic regurgitation) may be associated with typical symptoms of NSTE-ACS, elevated cardiac biomarkers, and ECG changes.[113] Since some patients with these underlying conditions also have CAD, the diagnostic process can be difficult.

Myocarditis, pericarditis, or myopericarditis of different aetiologies may be associated with chest pain that resembles the typical angina of NSTE-ACS and be associated with a rise in cardiac biomarker levels, ECG changes, and wall motion abnormalities. A flu-like, febrile condition with symptoms attributed to the upper respiratory tract often precedes or accompanies these conditions. However, infections, especially of the upper respiratory tract, also often precede or accompany NSTE-ACS.[114] The definitive diagnosis of myocarditis or myopericarditis may frequently only be established during the course of hospitalization.

Non-cardiac, life-threatening conditions may mimic NSTE-ACS and must be diagnosed. Among these, pulmonary embolism may be associated with dyspnoea, chest pain, ECG changes, as well as elevated levels of cardiac biomarkers similar to those of NSTE-ACS.[115] Chest X-ray, CT, or MRI angiography of the pulmonary arteries, pulmonary perfusion scans, and blood levels of D-dimer are the recommended diagnostic tests. Aortic dissection is another condition to be considered as an important differential diagnosis. NSTE-ACS may be a complication of aortic dissection when the dissection involves the coronary arteries. In a patient with undiagnosed aortic dissection, the current therapies for NSTE-ACS may exacerbate the patient's condition and result in detrimental outcomes. Stroke may be accompanied by ECG changes, wall motion abnormalities, and a rise in cardiac biomarker levels.[116] Conversely, atypical symptoms such as headache and vertigo may in rare cases be the sole presentation of myocardial ischaemia.

Table 4 Cardiac and non-cardiac conditions that can mimic non-ST-elevation acute coronary syndromes

Cardiac	Pulmonary	Haematological	Vascular	Gastrointestinal	Orthopaedic
Myocarditis	Pulmonary embolism	Sickle cell anaemia	Aortic dissection	Oesophageal spasm	Cervical discopathy
Pericarditis	Pulmonary infarction		Aortic aneurysm	Oesophagitis	Rib fracture
Myopericarditis	Pneumonia Pleuritis		Aortic coarctation	Peptic ulcer	Muscle injury/ inflammation
Cardiomyopathy	Pneumothorax		Cerebrovascular disease	Pancreatitis	Costochondritis
Valvular disease				Cholescystitis	
Apical ballooning (Tako-Tsubo syndrome)					

4.4 Risk scores

Several risk stratification scores have been developed and validated in large patient populations. In clinical practice, only simple risk scores are useful.

The GRACE risk scores[8,117,118] are based upon a large unselected population of an international registry of the full spectrum of ACS patients. The risk factors were derived with independent predictive power for in-hospital deaths[118] and post-discharge deaths at 6 months.[8] Easy to assess clinical/ECG/laboratory variables such as age, heart rate, systolic blood pressure, serum creatinine level, Killip class at admission, presence of ST-depression, and elevated cardiac biomarkers as well as cardiac arrest are included in the calculation. The models were validated in GRACE and GUSTO-2B, as well as externally in a Mayo Clinic population, a Canadian ACS Registry, and a Portuguese Registry. The GRACE models have very good discriminative power. Their complexity, however, requires special tools (graphs, tables, or computer programs) to estimate risk at the bedside. Computer or PDA software of a simplified nomogram are freely available at http://www.outcomes.org/grace. According to the GRACE risk score, three risk categories have been developed (*Table 5*). On the basis of direct comparisons,[119] the GRACE risk score is recommended as the preferred classification to apply on admission and at discharge in daily clinical routine practice.

The TIMI risk score[120] is derived from the TIMI-11B trial population and was validated in the TIMI-11B and ESSENCE patients, as well as externally such as in a Mayo Clinic population, in the TIMI-3 and Portuguese Registries. The TIMI risk score was applied in analysing treatment efficacy in various risk groups. It is less accurate in predicting events, but its simplicity makes it useful and widely accepted. The FRISC score is based on similar variables and was derived from the 1-year outcome of the FRISC-2 trial.[121] This is the only risk score that has repeatedly been shown to identify patients with a long-term benefit of an early invasive treatment strategy in a randomized trial.[122] The PURSUIT risk score is based upon the PURSUIT trial population and was validated externally in the Canadian ACS Registry, a Mayo Clinic population, and in a Portuguese Registry.[123] It allows separate risk stratification of patients with unstable angina and NSTE-MI. It is a complex model with high discriminative power, but poor calibration in the Canadian ACS Registry.

Table 5 Mortality in hospital and at 6 months in low-, intermediate-, and high-risk categories in registry populations according to the GRACE risk score[8,117]

Risk category (tertiles)	GRACE risk score	In-hospital deaths (%)
Low	≤108	<1
Intermediate	109–140	1–3
High	>140	>3
Risk category (tertiles)	**GRACE risk score**	**Post-discharge to 6 months deaths (%)**
Low	≤88	<3
Intermediate	89–118	3–8
High	>118	>8

For calculations, see http://www.outcomes.org/grace.

Recommendations for diagnosis and risk stratification

- **Diagnosis and short-term risk stratification of NSTE-ACS should be based on a combination of clinical history, symptoms, ECG, biomarkers, and risk score results (I-B).**
- **The evaluation of the individual risk is a dynamic process that is to be updated as the clinical situation evolves.**
  - **A 12-lead ECG should be obtained within 10 min after first medical contact and immediately read by an experienced physician (I-C). Additional leads (V_3R and V_4R, V_7—V_9) should be recorded. ECG should be repeated in the case of recurrence of symptoms, and at 6 and 24 h and before hospital discharge (I-C).**
  - **Blood must be drawn promptly for troponin (cTnT or cTnI) measurement. The result should be available within 60 min (I-C). The test should be repeated after 6—12 h if the initial test is negative (I-A).**
  - **Established risk scores (such as GRACE) should be implemented for initial and subsequent risk assessment (I-B).**
  - **An echocardiogram is recommended to rule in/out differential diagnoses (I-C).**
  - **In patients without recurrence of pain, normal ECG findings, and negative troponins tests, a non-invasive stress test for inducible ischaemia is recommended before discharge (I-A).**
- **The following predictors of long-term death or MI should be considered in risk stratification (I-B).**
  - **Clinical indicators: age, heart rate, blood pressure, Killip class, diabetes, previous MI/CAD;**
  - **ECG markers: ST-segment depression;**
  - **Laboratory markers: troponins, GFR/CrCl/cystatin C, BNP/NT-proBNP, hsCRP;**
  - **Imaging findings: low EF, main stem lesion, three-vessel disease;**
  - **Risk score result.**

5. Treatment

The treatment options described in this section are based on evidence from numerous clinical trials or meta-analyses.

Four categories of acute treatment are discussed: anti-ischaemic agents, anticoagulants, antiplatelet agents, and coronary revascularization. Generally, the therapeutic approach is based on whether the patient is to be only medically treated, or in addition referred to angiography and revascularization. Many of the treatment options were evaluated more than two decades ago or tested only in specific subsets of patients. The recommendations take these circumstances into account.

5.1 Anti-ischaemic agents

These drugs decrease myocardial oxygen consumption (decreasing heart rate, lowering blood pressure, or depressing LV contractility) and/or induce vasodilatation.

5.1.1 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 STEMI. Beta-blockers competitively inhibit the myocardial effects of circulating catecholamines. In NSTE-ACS, the primary benefits of beta-blockers are related to their effects on beta-1 receptors that result in a decrease in myocardial oxygen consumption.

Two double-blind, randomized trials have compared beta-blockers with placebo in unstable angina.[124,125] A meta-analysis suggested that beta-blocker treatment was associated with a 13% relative reduction in risk of progression to STEMI.[126] Although no significant effect on mortality in NSTE-ACS has been demonstrated in these relatively small trials, the results may be extrapolated from larger randomized trials of beta-blockers in patients with unselected MI.[127]

Beta-blockers are recommended in NSTE-ACS in the absence of contraindications and are usually well tolerated. In most cases, oral treatment is sufficient. The target heart rate for a good treatment effect should be between 50 and 60 b.p.m. Patients with significantly impaired atrioventricular conduction and a history of asthma or of acute LV dysfunction should not receive beta-blockers.

5.1.2 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 sydnonimines are related to their effects on the peripheral and coronary circulation. The major therapeutic benefit is probably related to the venodilator effects that lead to a decrease in myocardial pre-load and LV end-diastolic volume, resulting in a decrease in myocardial oxygen consumption. In addition, nitrates dilate normal as well as atherosclerotic coronary arteries and increase coronary collateral flow.

Studies of nitrates in unstable angina have been small and observational.[128–130] 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. Only very scarce data exist about the best route for administrating nitrates (intravenous, oral, sublingual, or topical) and about the optimal dose and duration of therapy.[131,132]

In patients with NSTE-ACS who require hospital admission, intravenous nitrates may be considered in the absence of contraindications. The dose should be titrated upwards until symptoms (angina and/or dyspnoea) are relieved unless side effects (notably headache or hypotension) occur. A limitation of continuous nitrate therapy is the phenomenon of tolerance, which is related to both the dose administered and the duration of treatment. When symptoms are controlled, intravenous nitrates may 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. Nitric oxide donor therapy (nitrates and sydnonimines) is contraindicated in patients taking phosphodiesterase-5 inhibitors (sildenafil, vardenafil, tadalafil) because of the risk of profound vasodilatation and blood pressure drop in the case of concomitant administration.

5.1.3 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 cause vasodilatation, decrease myocardial contractility, and delay atrioventricular (A-V) conduction. A-V block may be induced by non-dihydropyridines. 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 only small randomized trials testing calcium channel blockers in NSTE-ACS. Generally, they show efficacy in relieving symptoms that appear equivalent to beta-blockers.[133,134] The HINT study, the largest randomized trial, tested nifedipine and metoprolol in a 2×2 factorial design.[125] Although no statistically significant differences were observed, there was a trend towards an increased risk of MI or recurrent angina with nifedipine (compared with placebo), whereas treatment with metoprolol, or with a combination of both drugs, was associated with a reduction in these events.

The beneficial effect after discharge is somewhat controversial.[135,136] A meta-analysis of the effects of calcium channel blockers on death or non-fatal MI in unstable angina suggests that this class of drugs does not prevent the development of acute MI or reduce mortality.[137] 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 CAD.[138,139] On the other hand, there is evidence for a protective role of diltiazem in NSTEMI in one trial.[140]

Calcium channel blockers, particularly dihydropyridines, are the drugs of choice in vasospastic angina.

5.1.4 New drugs

New antianginal drugs with different modes of action have been investigated in recent years. Ivabradine selectively inhibits the primary pacemaker current in the sinus node and may be used in patients with beta-blocker contraindications.[141] Trimetazidine exerts metabolic effects without haemodynamic changes.[142] Ranolazine exerts antianginal effects by inhibiting the late sodium current.[143] It was not effective in reducing major cardiovascular events in MERLIN-TIMI 36.[92] Nicorandil has nitrate-like properties. Nicorandil significantly reduced the rate of occurrence of the primary composite endpoint (coronary death, non-fatal MI, or unplanned hospital admission for cardiac pain) in chronic stable angina patients in the IONA study,[144] but has never been tested in the setting of NSTE-ACS.

Recommendations for anti-ischaemic drugs

- **Beta-blockers are recommended in the absence of contraindications, particularly in patients with hypertension or tachycardia (I-B).**
- **Intravenous or oral nitrates are effective for symptom relief in the acute management of anginal episodes (I-C).**
- **Calcium channel blockers provide symptom relief in patients already receiving nitrates and beta-blockers; they are useful in patients with contraindications to**

beta-blockade and in the subgroup of patients with vasospastic angina (I-B).
- **Nifedipine, or other dihydropyridines, should not be used unless combined with beta-blockers (III-B).**

5.2 Anticoagulants

Anticoagulants are used in the treatment of NSTE-ACS to inhibit thrombin generation and/or activity, thereby reducing thrombus-related events. There is clear evidence that anticoagulation is effective in addition to platelet inhibition and that the combination of the two is more effective than either treatment alone.[145,146] With all anticoagulants, there is an increased risk of bleeding. The risk factors for bleeding are well defined (see section 6.1 Bleeding complications). Several anticoagulants, which act at different levels of the coagulation cascade, have been investigated in NSTE-ACS:

- unfractionated heparin (UFH) as intravenous infusion;
- low molecular weight heparin (LMWH) as subcutaneous injection;
- fondaparinux as subcutaneous injection;
- direct thrombin inhibitors (DTIs) as intravenous infusion;
- vitamin K antagonists (VKAs) as oral medication.

5.2.1 Unfractionated heparin

Pharmacology

UFH is a heterogeneous mixture of polysaccharide molecules, with a molecular weight ranging from 2000 to 30 000 (mostly 15–18 000) Da. One-third of the molecules found within a standard UFH preparation contain the pentasaccharide sequence, which binds to antithrombin and accelerates the rate at which antithrombin inhibits factor-Xa. Inhibition of factor-IIa requires heparin to bind to both thrombin and antithrombin to bridge them. This can only be achieved if the chains containing the pentasaccharide sequence comprise at least 18 saccharide units to provide sufficient length to bridge to factor-IIa. UFH is poorly absorbed by the subcutaneous route, so that intravenous infusion is the preferred route of administration. The therapeutic window is narrow, requiring frequent monitoring of the activated partial thromboplastin time (aPTT), with an optimal target level of 50–75 s, corresponding to 1.5–2.5 times the upper limit of normal. At higher aPTT values, the risk of bleeding complications is increased, without further antithrombotic benefits. At aPTT values lower than 50 s, the antithrombotic effect is limited and the number of ischaemic events not reduced. A weight-adjusted dose of UFH is recommended, at an initial bolus of 60–70 IU/kg with a maximum of 5000 IU, followed by an infusion of 12–15 IU/kg/h, to a maximum of 1000 IU/h. This regimen is that currently recommended as being the most likely to achieve the target aPTT values.[145,146]

The maintenance of a well-controlled anticoagulation is difficult by UFH infusion in NSTE-ACS patients, especially as the clinical condition usually improves within the first 24 h, when the patients often are mobilized and even ambulatory. The anticoagulant effect of UFH is rapidly lost within a few hours after interruption. During the first 24 h after termination of treatment, there is a risk of reactivation of the coagulation process and thereby a transiently increased risk of recurrence, despite simultaneous acetylsalicylic acid (aspirin) treatment.[147]

Treatment effects

A pooled analysis of six trials testing short-term UFH vs. placebo or untreated controls showed a significant risk reduction for death and MI of 33% (OR 0.67, 95% CI 0.45–0.99, $P = 0.045$).[148] The risk reduction for MI accounted for practically all of the beneficial effect. When the data from FRISC, which compared LMWH with placebo, are added to this pooled analysis, the risk reduction is even greater (*Figure 3*). In trials comparing the combination of UFH plus aspirin vs. aspirin alone in NSTE-ACS, a trend towards a benefit was observed in favour of the UFH–aspirin combination, but at the cost of an increase in the risk of bleeding. Recurrence of events after interruption of UFH explains why this benefit is not maintained over time, unless the patient is revascularized before the interruption of UFH[148–150] (*Figure 3*).

5.2.2 Low molecular weight heparin

Pharmacology

LMWH represents a class of heparin-derived compounds with molecular weights ranging from 2000 to 10 000 Da. LMWHs have pharmacological advantages over UFH. They link to antithrombin through the pentasaccharide sequence. This is the basis of anti-Xa activity. The anti-IIa activity is lower than that with UFH and depends on the molecular weight of the molecule, with greater anti-IIa activity with increasing molecular weight. The advantages of LMWH are an almost complete absorption after subcutaneous administration, less protein binding, less platelet activation, and, thereby, a more predictable dose–effect relationship.[145,146] Furthermore, there is a lower risk of heparin-induced thrombocytopenia (HIT) with LMWH when compared with UFH due to less interaction with platelet factor 4 (PF4) (see section 6.2 Thrombocytopenia). LMWHs are eliminated at least partially by the renal route. They are contraindicated in the case of renal failure with CrCl $<$30 mL/min (in certain countries such as the USA, dose adaptation in the case of renal failure is recommended; see section 7.4 Chronic kidney disease).

The LMWH dosages used in NSTE-ACS are body weight adjusted and are of the same magnitude as those used in the treatment of venous thrombo-embolism (VTE), which are higher than the doses used in prophylaxis of deep vein thrombosis (DVT). LMWHs are commonly administered subcutaneously every 12 h in NSTE-ACS to avoid the risk of inadequate anti-Xa level during treatment.[149,151–155] An initial intravenous bolus in high-risk patients has also been advocated.[151] From VTE studies, the therapeutic range of anti-Xa activity has been considered to be 0.6–1.0 IU/mL, without any clear relationship between anti-Xa activity and clinical outcome. However, the bleeding risk increases above 1.0 IU/mL of anti-Xa activity.[145,146] In TIMI-11A, where the enoxaparin dose was 1.5 mg/kg twice daily, patients with major haemorrhage had anti-Xa activity in the range of 1.8–2.0 IU/mL. Excess bleeding led to a reduction in the dosage.[156] With the current doses used in clinical practice, monitoring of anti-Xa activity is not necessary, except in special populations of patients, such as those with renal failure and obesity.

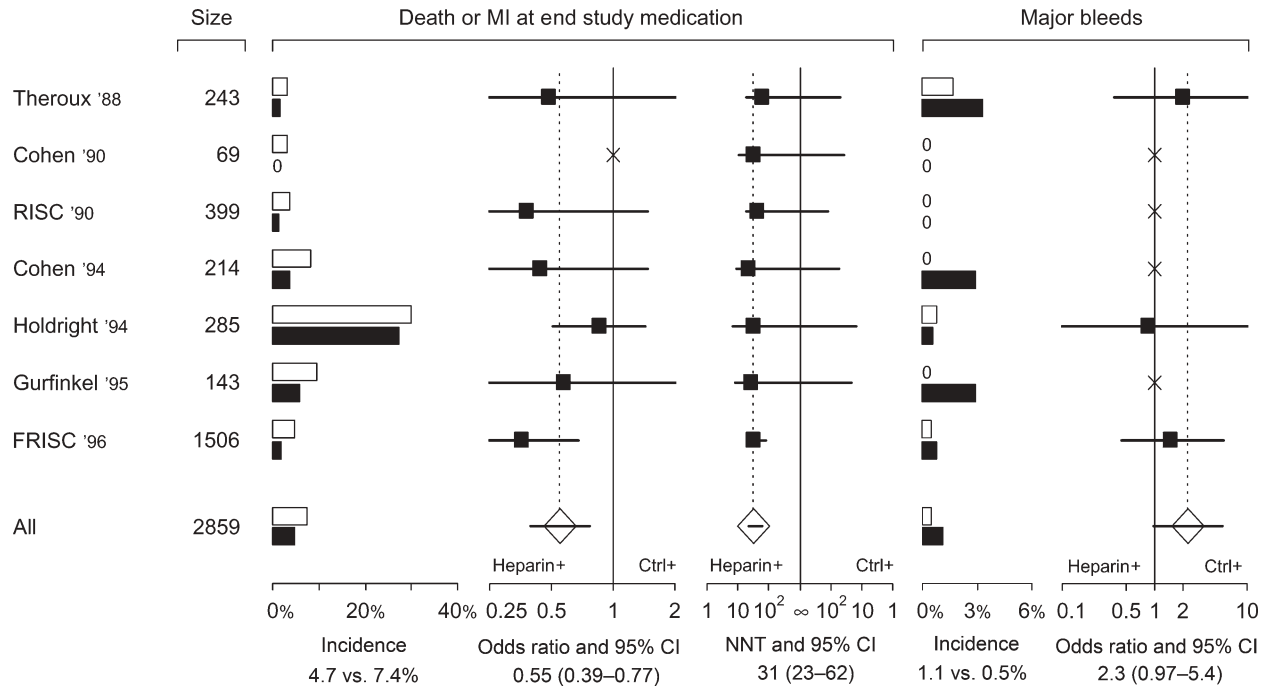

Figure 3 Death, myocardial infarction, and major bleeds at the completion of study medication in randomized trials of unfractionated heparin/low molecular weight heparin (filled bars) vs. control (open bars). NNT = number of patients who needed to be treated to avoid one event.

The treatment can be prolonged without immobilization of the patient.[153,157] This allows treatment to be continued until a decision on early coronary angiography is made.[153] As no superior protection against recurrence of ischaemic events and more bleeding occurred with prolonged treatment, discontinuation of LMWH is recommended at hospital discharge.[157] The risk of bleeding with LMWH is dose-related and is increased with higher age, female gender, lower body weight, reduced renal function, and interventional procedures.[146]

Treatment effects

The efficacy of LMWH in aspirin-treated patients with NSTE-ACS has been evaluated vs. placebo in FRISC[157] with dalteparin 120 U/kg twice daily, and in another smaller study.[158] The results showed a substantial risk reduction of death and MI associated with a modest increase in bleeding risk. Several trials have assessed the respective efficacy and safety of various LMWHs in comparison with UFH. Dalteparin and nadroparin were shown to be equally efficacious and safe as UFH in aspirin-treated patients.[155,159] Dalteparin was shown to have greater efficacy in troponin-positive than in troponin-negative patients.[160] Enoxaparin has been compared with UFH in several trials. In ESSENCE and TIMI-11B, an invasive strategy was not encouraged and as a result the revascularization rate was low in both trials when compared with contemporary practice.[151,152]

A pooled analysis of both trials showed a significant risk reduction of death and MI at the end of the study period, achieved at the cost of a significant increase in minor (but not major) bleeding complications. In INTERACT and ACUTE-2, a regimen of enoxaparin plus eptifibatide or tirofiban was compared with a regimen of UFH plus eptifibatide or tirofiban in aspirin-treated patients.[161–163] These two trials were insufficiently powered to draw definitive conclusions as to whether enoxaparin regimen had a better efficacy/safety profile than the UFH regimen. In A to Z, enoxaparin plus tirofiban was shown to be non-inferior to a regimen of UFH plus tirofiban.[161] SYNERGY was the largest trial to test enoxaparin against UFH in a contemporary approach with a high rate of invasive procedures, use of PCI/revascularization, stent implantation, and active antiplatelet therapy with aspirin, clopidogrel, and a high rate of glycoprotein IIb/IIIa (GP IIb/IIIa) receptor inhibitors. It included 10 027 high-risk patients undergoing early invasive evaluation/revascularization, of whom 76% received anticoagulants pre-randomization. No significant difference was observed in terms of death and MI at 30 days (14.0 vs. 14.5%, OR 0.96; 95% CI 0.86–1.06, P = NS) for enoxaparin vs. UFH.[164] More bleeding occurred with enoxaparin, with a statistically significant increase in TIMI major bleeding (9.1 vs. 7.6%, $P = 0.008$) but non-significant excess in GUSTO severe bleeding (2.7 vs. 2.2%, $P = 0.08$) and transfusions (17.0 vs. 16.0%, $P = 0.16$).

The meta-analysis of these six trials, totalling 21 946 patients, showed no significant difference between the two compounds for death at 30 days (3.0 vs. 3.0%, OR 1.00, 95% CI 0.85–1.17, P = NS).[165] A significant reduction in the combined endpoint of death or MI at 30 days was observed in favour of enoxaparin vs. UFH (10.1 vs. 11.0%, OR 0.91, 95% CI 0.83–0.99). *Post hoc* subgroup analysis showed a significant reduction in death or MI at 30 days in enoxaparin-treated patients, who did not receive UFH prior to randomization, vs. the UFH group (8.0 vs. 9.4%, respectively, OR 0.81, 95% CI 0.70–0.94). No significant differences in blood transfusions (7.2 vs. 7.5%, OR 1.01, 95% CI 0.89–1.14) or in major bleeding (4.7 vs. 4.5%, OR 1.04, 95% CI 0.83–1.30) were observed at 7 days after randomization in the overall population, as well as in the

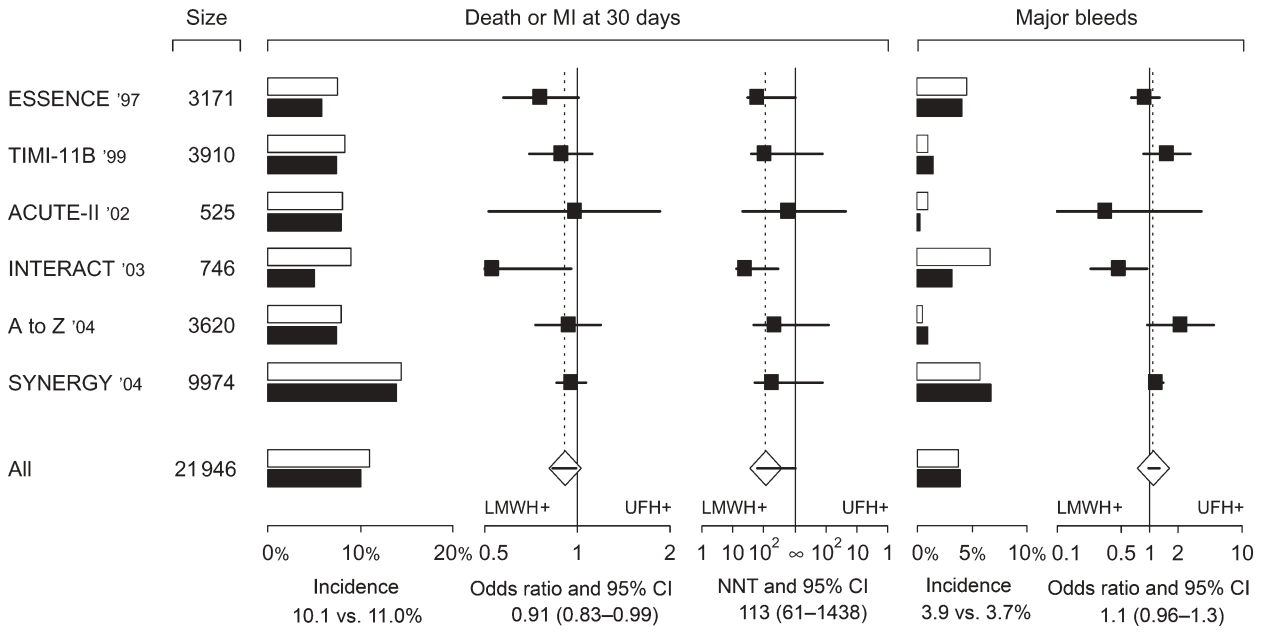

Figure 4 Death, myocardial infarction, and major bleeds at 30 days in randomized trials of enoxaparin (filled bars) vs. unfractionated heparin (open bars). NNT = number of patients who needed to be treated to avoid one event.

population of patients who received no anticoagulant therapy prior to randomization (*Figure 4*).

Enoxaparin has been used in combination with aspirin and thienopyridines in many recent trials or observational studies apparently without safety concerns, particularly bleeding complications.[164,167] However, as the bleeding risk specifically incurred by this combination of different antithrombotic agents was not the main objective of these studies, it is difficult to extract specific data on safety. However, it is known from registry data that combination of antithrombotic drugs is a predictor of increased risk of bleeding[168] (see section 6.1 Bleeding complications). Enoxaparin and other LMWHs have also been tested in combination with GP IIb/IIIa inhibitors in several trials or observational studies, in most without dose adaptation. No complications of excess bleeding were reported, except in SYNERGY where high rates of pre-randomization administration of anticoagulants and crossover from one anticoagulant to the other may have played a role in the excess bleeding observed with enoxaparin compared with heparin.[161–165,169–171] In INTERACT, eptifibatide and enoxaparin in aspirin-treated patients demonstrated better efficacy than UFH plus eptifibatide, but the sample size was too small to draw any definitive conclusion.[163]

Registry data have shown that the use of enoxaparin in an unselected cohort of patients with NSTE-ACS may lead to a significant risk reduction for death or MI when compared with UFH.[172]

5.2.3 Factor-Xa inhibitors

Pharmacology

The only selective factor-Xa inhibitor available for clinical use is fondaparinux. This is a synthetic pentasaccharide modelled after the antithrombin-binding sequence of UFH. It exerts a selective antithrombin-mediated inhibition of factor-Xa, a dose-dependent inhibition of thrombin generation without inhibition of the thrombin molecule *per se*. It has a 100% bioavailability after subcutaneous injection with an elimination half-life of 17 h and can therefore be given once daily. It is eliminated mainly by the renal route. It is contraindicated if CrCl is lower than 30 mL/min. It is insensitive to inactivation by platelet-released heparin neutralization proteins. Because it does not induce the formation of heparin–PF4 complexes, HIT is unlikely to occur with fondaparinux. No case of HIT has been reported with this drug, even after extensive use in the setting of prevention and treatment of VTE. Therefore, monitoring of platelet count is not necessary. In ACS, a 2.5 mg fixed dose is recommended. No dose adjustment and no monitoring of anti-Xa activity is required. Fondaparinux has no significant influence on the usual variables that monitor anticoagulant activity, such as aPTT, activated clotting time (ACT), prothrombin, and thrombin times.

Clinical studies have shown advantageous effects compared with UFH and LMWH in the settings of prevention of DVT in orthopaedic and general surgery, in acutely ill medical patients, and in the treatment of VTE. In two small, phase II studies, fondaparinux also showed promising results as a substitute for enoxaparin or UFH in NSTE-ACS[173] and PCI.[174]

Treatment effects

In a double-blind dose-ranging study of fondaparinux vs. enoxaparin in the setting of NSTE-ACS involving 1147 patients, the 2.5 mg dose of fondaparinux was shown to have the best efficacy/safety profile when compared with 4, 8, and 12 mg doses of fondaparinux and with enoxaparin 1 mg/kg twice daily, and was then chosen as the dose for subsequent phase III trials.[173] Fondaparinux was also tested in a phase II trial in the setting of PCI, at doses of 2.5 or 5 mg, vs. the standard dose of UFH, and was shown to have comparable efficacy and safety to UFH.[174] In this study, catheter thrombi were reported in both UFH and

fondaparinux groups, but with a higher frequency with fondaparinux. There was no impact on the rate of clinical events, including peri-procedural MI, but the study was underpowered to detect significant differences in the rate of events.[174]

In the OASIS-5 study,[175,176] 20 078 patients with NSTE-ACS were randomized to receive 2.5 mg subcutaneous fondaparinux once daily vs. subcutaneous enoxaparin 1 mg/kg twice daily for 8 days maximum (average 5.2 vs. 5.4 days). The primary efficacy outcome of death, MI, or refractory ischaemia at 9 days was 5.7 vs. 5.8% for enoxaparin vs. fondaparinux, respectively (HR 1.01, 95% CI 0.90–1.13). The upper limit of the CI was well below the pre-specified boundary of 1.185 for non-inferiority ($P = 0.007$). At the same time point, major bleeds were halved with fondaparinux, 2.2% compared with 4.1% with enoxaparin (HR 0.52, 95% CI 0.44–0.61, $P < 0.001$), and the composite outcome of death, MI, refractory ischaemia, or major bleeding also favoured fondaparinux, 7.3 vs. 9.0% for fondaparinux vs. enoxaparin (HR 0.81, 95% CI 0.73–0.89, $P < 0.001$). Major bleeding was an independent predictor of long-term mortality, which was significantly reduced with fondaparinux at 30 days (2.9 vs. 3.5%, HR 0.83, 95% CI 0.71–0.97, $P = 0.02$) and at 6 months (5.8 vs. 6.5%, HR 0.89, 95% CI 0.80–1.00, $P = 0.05$). The composite outcome of death, MI, or stroke was significantly lower with fondaparinux at 6 months (11.3 vs. 12.5%, HR 0.89, 95% CI 0.82–0.97, $P = 0.007$). In summary, at 30 days, 167 patients needed to be treated to avoid one death or one death/MI, and 53 patients to avoid one major bleed. In the population submitted to PCI, a significantly lower rate of major bleeding complication (including access site complications) was observed in the fondaparinux group vs. enoxaparin at 9 days, 2.3 vs. 5.1%, respectively (HR 0.45, 95% CI 0.34–0.59, $P < 0.001$).[176] Catheter thrombus formation during PCI was observed in both groups, though at a significantly higher rate with fondaparinux than with enoxaparin (see section 5.2.6 Anticoagulants during percutaneous coronary intervention). On the basis of OASIS-5, if fondaparinux is chosen as anticoagulant therapy, it should be maintained for up to 5 days or until hospital discharge, and cannot be used as sole anticoagulant during PCI procedures (see section 5.2.6 Anticoagulants during percutaneous coronary intervention).

5.2.4 Direct thrombin inhibitors

Pharmacology

DTIs bind directly to thrombin (factor-IIa) and thereby inhibit the thrombin-induced conversion of fibrinogen to fibrin. They inactivate fibrin-bound, as well as fluid-phase thrombin. As they do not bind to plasma proteins, the anticoagulant effect is more predictable. Unlike heparin, DTIs do not interact with PF4. The model compound for this treatment principle is hirudin extracted from the medical leech (*Hirudo medicinalis*). Currently, several DTIs (hirudin, argatroban, bivalirudin) are available. Hirudin and its derivatives are eliminated by the renal route. Hirudin and bivalirudin prolong aPTT and ACT. Coagulation tests correlate well with plasma concentrations. Therefore, these two tests can be used to monitor the anticoagulant activity of these compounds.

Treatment effects

Intravenous direct thrombin inhibition with hirudin has been compared with aPTT-monitored UFH infusion in several large-scale randomized trials. In a meta-analysis including all these trials, there was a significantly lower event rate with hirudin vs. UFH infusion[149,177,178] (*Figure 5*). However, these differences were not sustained during long-term follow-up. Furthermore, the use of hirudin as the primary treatment of NSTE-ACS has been associated with a higher bleeding rate (1.7 vs. 1.3%, OR 1.28, 95% CI 1.06–1.55)[177] and therefore its use in this indication has not been approved. Bivalirudin compared with UFH in the setting of PCI significantly reduced the rate of major adverse cardiac

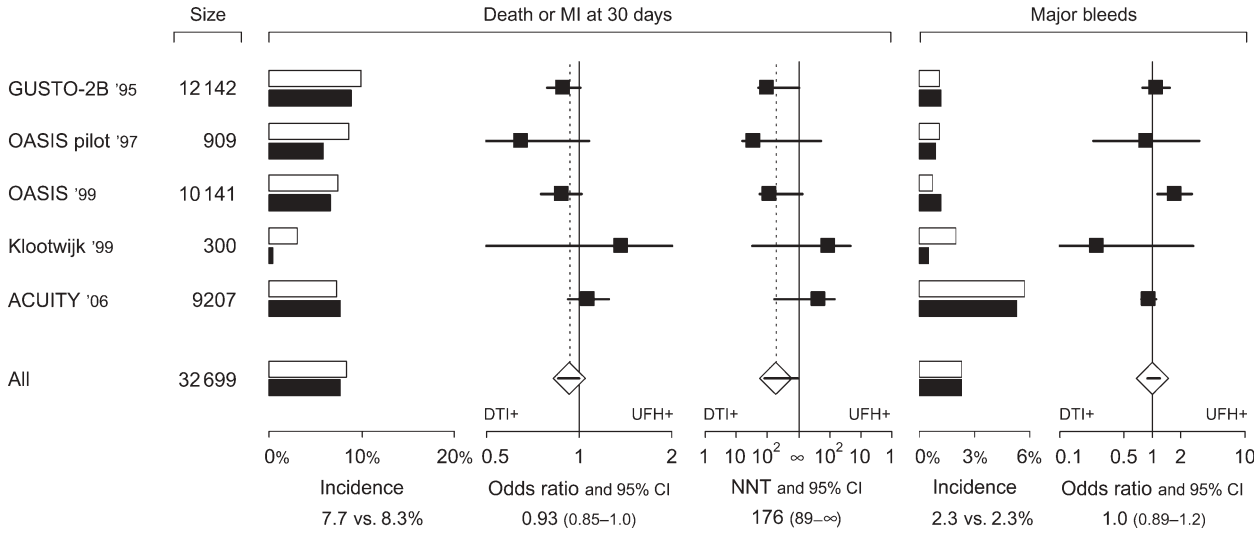

Figure 5 Death, myocardial infarction, and major bleeds at 30 days in randomized trials of direct thrombin inhibitors (filled bars) vs. unfractionated heparin/low molecular weight heparin (open bars). NNT = number of patients who needed to be treated to avoid one event. (For Acuity, the arms unfractionated heparin/low molecular weight heparin and bivalirudin both with glycoprotein IIb/IIIa inhibitors as background therapy are presented. In addition, the composite ischaemic endpoint includes unplanned revascularization.)

events (death, MI, or repeat revascularization) (6.2 vs. 7.9%; OR 0.78% CI 0.62–0.99, $P = 0.039$) and of bleeding (3.5 vs. 9.3%; OR 0.34 95% CI 0.26–0.45, $P < 0.001$ for bivalirudin vs. UFH) at 7 days in one trial.[179] More recently, bivalirudin plus provisional GP IIb/IIIa inhibitors was shown to be non-inferior to UFH plus GP IIb/IIIa inhibitors in the protection against ischaemic events during PCI procedures, but with a significantly lower rate of major bleeding complications (2.4 vs. 4.1%, $P < 0.001$ for bivalirudin vs. UFH plus GP IIb/IIIa inhibitors).[180,181] Bivalirudin is currently recommended as an alternative anticoagulant for urgent and elective PCI.[182] Hirudin, bivalirudin, and argatroban have been used for treatment of HIT complicated by thrombotic events.[183–185]

The ACUITY trial was a randomized, open-label trial in 13 819 patients with moderate to high risk NSTE-ACS planned for an invasive strategy.[186,187] Three primary 30-day endpoints were pre-specified, some of them including not so robust components: composite ischaemia (death from any cause, MI, or unplanned revascularization for ischaemia), major bleeding (non-CABG-related), and net clinical outcome (composite ischaemia or major bleeding). Major bleeding definition included intracranial or intraocular bleeding, haemorrhage at the access site requiring intervention, haematoma >5 cm in diameter, haemoglobin level drop >4 g/dL without or >3 g/dL with overt bleeding, reoperation for bleeding, or transfusion. Some elements of the definition such as haematoma >5 cm in diameter were never used in any other definition of major bleeding and may have left room for potential biased assessment in a non-blinded trial.

Patients were randomized to one of three unblinded treatment groups: standard combination treatment with either UFH or LMWH with GP IIb/IIIa inhibitor (control arm) ($n = 4603$) or bivalirudin with GP IIb/IIIa inhibitor ($n = 4604$) or bivalirudin alone ($n = 4612$). A pre-specified non-inferiority hypothesis with a boundary of 1.25 was generated to compare the relative efficacy of the two test arms vs. the control arm as to the composite ischaemia endpoint. In the two arms with GP IIb/IIIa inhibitors, patients were randomized to receive GP IIb/IIIa inhibitors either upstream of the catherization laboratory, or after angiography if PCI were to be undertaken. The randomization was stratified for pre-treatment with clopidogrel, which was administered prior to PCI in 62.3% of patients. Coronary angiography was performed in 98.9%, PCI in 56.3%, and CABG in 11.1%, whereas 32.6% had no revascularization procedure. There was no significant difference between standard UFH/LMWH plus GP IIb/IIIa inhibitors, and the combination of bivalirudin and GP IIb/IIIa inhibitors for the composite ischaemia endpoint at 30 days (7.3 vs. 7.7%, respectively, RR 1.07, 95% CI 0.92–1.23, $P = 0.39$), or for major bleeding (5.7 vs. 5.3%, RR 0.93, 95% CI 0.78–1.10, $P = 0.38$). Bivalirudin alone was shown to be non-inferior to the standard UFH/LMWH combined with GP IIb/IIIa inhibitors as to the composite ischaemia endpoint (7.8 vs. 7.3%, RR 1.08, 95% CI 0.93–1.24, $P = 0.32$ for bivalirudin alone vs. UFH/LMWH plus GP IIb/IIIa inhibitors), but with a significantly lower rate of major bleeding (3.0 vs. 5.7%, RR 0.53, 95% CI 0.43–0.65, $P < 0.001$ for bivalirudin alone vs. UFH/LMWH plus GP IIb/IIIa inhibitors). Therefore, the rate of 30-day net clinical outcome was significantly lower (10.1 vs. 11.7%, RR 0.86 95% CI 0.77–0.94, $P = 0.015$) with bivalirudin alone vs. UFH/LMWH plus GP IIb/IIIa inhibitors. It has to be stressed that in ACUITY, about 41% of patients had no troponin elevation. Therefore, in the two groups where UFH/LMWH or bivalirudin were combined with GP IIb/IIIa inhibitors, the risk of bleeding may have been increased, without any beneficial effect on the ischaemic side in troponin-negative patients. This may have favoured the group bivalirudin alone. The treatment effects of bivalirudin monotherapy as regards net clinical outcome were consistent among most pre-specified subgroups, including patients who had positive tests for biomarkers, those undergoing PCI, those who were randomly assigned to immediate or deferred treatment with GP IIb/IIIa inhibitors, and those who did or did not undergo early angiography. However, in patients not pre-treated with clopidogrel prior to PCI, a significant excess of composite ischaemia endpoints was observed (9.1 vs. 7.1%, RR 1.29, 95% CI 1.03–1.63) for bivalirudin alone vs. UFH/LMWH plus GP IIb/IIIa inhibitors, with borderline significant interaction ($P = 0.054$) between pre-treatment with clopidogrel and the effect of bivalirudin alone. The lack of efficacy in patients not pre-treated with clopidogrel suggests that a potent antiplatelet therapy remains necessary for PCI. This is consistent with the results of ISAR-REACT 2 that show that GP IIb/IIIa inhibitors in addition to aspirin plus clopidogrel are beneficial in troponin-positive NSTE-ACS patients.[188] In retrospect, the margins of non-inferiority as regards the composite ischaemia endpoint might have been too liberal and did not meet the approach recommended by regulatory authorities.[189–197]

The risk reduction for bleeding with bivalirudin alone compared with UFH/LMWH plus GP IIb/IIIa inhibitors was significant in all subgroups, except in patients submitted to CABG surgery. The reduction in bleeding with bivalirudin alone did not translate at 30-day follow-up into a risk reduction of death or ischaemic events as observed in OASIS-5.

5.2.5 Vitamin K antagonists

The VKAs produce their anticoagulant effect by interfering with the hepatic metabolism of vitamin K that results in the production of partially carboxylated and decarboxylated proteins with reduced coagulant activity. Their therapeutic effects are not observed until after 3–5 days of treatment. This treatment is therefore not useful in the acute phase of NSTE-ACS. In order to maintain anticoagulation efficacy without an excessive risk of bleeding, laboratory monitoring of the prothrombin time aiming for international normalized ratio (INR) levels 2.0–3.0 is required in the setting of MI.[198] The level of anticoagulation requires continuous monitoring as it is influenced by several food–drug and drug–drug interactions. VKA treatment, especially VKAs in combination with aspirin, was shown to be more effective than aspirin alone in the long-term prevention of death, re-MI, and stroke,[199] but at the cost of a higher risk of major bleeding.[200] Better efficacy and safety of VKAs plus aspirin over aspirin alone can only be obtained if good compliance is achieved.[201] In the current era of combining aspirin with clopidogrel in NSTE-ACS, VKAs are mostly used in the presence of other indications for anticoagulation, such as atrial fibrillation, or after implantation of a mechanical heart valve.

The optimal antithrombotic therapy post-PCI in patients on ongoing anticoagulation therapy, for example because

of atrial fibrillation, remains to be defined. Administration of aspirin and clopidogrel to patients already on VKA increases the risk of bleeding, whereas withholding antiplatelet therapy increases the risk of thrombotic events, particularly if a stent has been implanted. Discontinuation of VKAs in turn increases the risk of thrombo-embolic events. There are no data from randomized trials to clarify the optimum treatment in these patients and the feasibility of such studies is questionable. Hence, treatment decisions continue to be made on an individualized basis and should include information on key factors, including bleeding and thrombo-embolic risks. On the basis of experiences from clinical practice, it seems that antiplatelet and VKA combinations lead to only modest increases in bleeding risk in elderly patients, provided tight control of INR can be obtained[200,202] (see section 5.3.4 Resistance to antiplatelet agents/drug interactions for recommendations for association of a VKA and dual antiplatelet therapy). In patients with active VKA treatment presenting with ACS, initiation of the anticoagulants recommended during the acute phase (UFH, LMWH, fondaparinux, or bivalirudin) should be withheld as long as the INR is not known, and not started before the INR is <2.0. Reversal of anticoagulation with vitamin K supplements is not recommended unless necessary for bleeding complications.

5.2.6 Anticoagulants during percutaneous coronary intervention procedures in non-ST-segment elevation acute coronary syndromes

The use of platelet inhibition with aspirin and systemic anticoagulation with UFH has been the standard of care for PCI from the beginning.[182] The current recommendation, based on empiric evidence, is to give UFH as an intravenous bolus of 100 IU/kg or 50–60 IU/kg if GP IIb/IIIa inhibitors are given.[182] The efficacy of UFH is monitored by ACT. However, the relationship between ACT and the rate of clinical events, and the real utility of ACT monitoring remain controversial.

Direct thrombin inhibition with bivalirudin and provisional GP IIb/IIIa inhibitor infusion has been shown to be at least as effective as and associated with a lower risk of bleeding than UFH/LMWH plus GP IIb/IIIa inhibitors in the setting of planned PCI.[181] In addition, bivalirudin during PCI procedures was tested in comparison with UFH/LMWH or bivalirudin plus GP IIb/IIIa inhibitors in the ACUITY trial. As already mentioned, a significant risk reduction for bleeding was observed with bivalirudin alone when compared with UFH/LMWH or bivalirudin with GP IIb/IIIa inhibitors, but with a significantly higher rate of ischaemic events in patients not pre-treated with clopidogrel.[187]

As most of the data and evidence in the setting of PCI have been collected so far with UFH and bivalirudin, including in NSTE-ACS, either drug can be recommended as first choice if the patient is directed immediately to the catherization laboratory because of life-threatening condition or refractory ischaemia and/or angina (see section 8 Management strategies).

LMWH have been used in the setting of PCI, but most of the data have been obtained with enoxaparin.[164,203] Until recently, because of the lack of the clinical studies, it was recommended to add UFH in enoxaparin-treated patients taken to the catherization laboratory for PCI.[152] More recent data have shown that no additional UFH is needed if PCI is carried out within 6–8 h following the last subcutaneous dose of enoxaparin. After 6–8 h, an additional 0.3 mg/kg intravenous bolus of enoxaparin is recommended.[204]

Enoxaparin (1 mg/kg twice daily) was compared with UFH as antithrombotic agent in a PCI setting in 4687 NSTE-ACS in the SYNERGY trial. There was no difference in outcome during or after PCI, whatever the drug used in the catherization laboratory (UFH or enoxaparin). However, there was a strong trend towards an excess of bleeding (non-CABG-related TIMI major bleeds) with enoxaparin, when compared with UFH, possibly augmented by post-randomization crossover antithrombotic therapy.[164] A recent trial (STEEPLE) involving 3258 patients undergoing elective PCI suggests that lower doses of enoxaparin may be favourable with respect to bleeding.[205]

Enoxaparin and fondaparinux were used in the setting of PCI in 6239 patients in OASIS-5.[176] There was a significantly higher risk of vascular access site complications (8.1 vs. 3.3%, RR 0.41, 95% CI 0.33–0.51, $P < 0.001$) with enoxaparin than with fondaparinux. Catheter thrombus was significantly more common with fondaparinux (0.4 vs. 0.9%, RR 2.25, 95% CI 1.64–7.84, $P = 0.001$ for enoxaparin vs. fondaparinux). Per protocol in OASIS-5, patients taken to the catheterization laboratory more than 6 h after the last enoxaparin injection received an additional dose of UFH. In the fondaparinux group, no additional UFH was given. This may have generated a protective effect against catheter thrombus formation in the enoxaparin group. The excess of catheter thrombus had no impact on the rate of PCI-related coronary complications (8.6 vs. 9.5%, RR 1.11 95% CI 0.94–1.29, $P = 0.21$) for enoxaparin vs. fondaparinux and no significant impact on clinical events at 9 days. Peri-procedural complications, in terms of death, MI, stroke, and major bleeding, were significantly more frequent with enoxaparin compared with fondaparinux (20.6 vs. 16.6%, RR 0.81, 95% CI 0.73–0.90, $P = 0.001$) at 9 days as well as at 30 days (11.7 vs. 9.5%, RR 0.81, 95% CI 0.70–0.93, $P = 0.004$ for enoxaparin vs. fondaparinux).

Fondaparinux has also been used in the setting of PCI in ASPIRE and OASIS-6 in addition to OASIS-5.[166,174,176] Catheter thrombus was also observed in the setting of primary PCI in STEMI in the OASIS-6 study.[166] Catheter thrombus formation was reduced in OASIS-5 and eliminated in OASIS-6 by the administration of UFH upstream of or during PCI. Adding UFH to fondaparinux did not increase bleeding risk in OASIS-5, but a larger data set of patients is needed to confirm the safety of this association.[206] Until new data are available, a standard dose of UFH (50–100 IU/kg bolus)[182] is needed in addition to fondaparinux at the time of PCI, if fondaparinux was initiated prior to the procedure.

Recommendations for anticoagulation

- **Anticoagulation is recommended for all patients in addition to antiplatelet therapy (I-A).**
- **Anticoagulation should be selected according to the risk of both ischaemic and bleeding events (I-B) (see also section 6.1 Bleeding complications, section 7.4 Chronic kidney disease, and section 7.5 Anaemia).**
- **Several anticoagulants are available, namely UFH, LMWH, fondaparinux, and bivalirudin. The choice depends on the initial strategy (see section 8 Management strategies: urgent invasive, early invasive, or conservative strategies) (I-B).**
- **In an urgent invasive strategy, UFH (I-C), enoxaparin (IIa-B), or bivalirudin (I-B) should be immediately started.**

- **In an non-urgent situation, as long as a decision between an early invasive or conservative strategy is pending (see section 8 Management strategies):**
  - **Fondaparinux is recommended on the basis of the most favourable efficacy/safety profile (I-A) (see sections 5.2.3 Factor-Xa inhibitors and 6.1 Bleeding complications).**
  - **Enoxaparin with a less favourable efficacy/safety profile than fondaparinux should be used only if the bleeding risk is low (IIa-B).**
  - **As the efficacy/safety profile of LMWH (other than enoxaparin) or UFH relative to fondaparinux is unknown, these anticoagulants cannot be recommended over fondaparinux (IIa-B).**
  - **At PCI procedures, the initial anticoagulant should also be maintained during the procedure regardless of whether this treatment is UFH (I-C), enoxaparin (IIa-B), or bivalirudin (I-B), whereas addititional UFH in standard dose (50—100 IU/kg bolus) is necessary in the case of fondaparinux (IIa-C).**
  - **Anticoagulation can be stopped within 24 h after an invasive procedure (IIa-C). In a conservative strategy, fondaparinux, enoxaparin, or other LMWH may be maintained up to hospital discharge (I-B).**

5.3 Antiplatelet agents

Platelet activation plays a key pathophysiological role in NSTE-ACS. The time course of events following presentation with NSTE-ACS necessitates immediate treatment with antiplatelet therapy, once the diagnosis is made. Platelet activation needs to be seen not only in the context of an acute plaque rupture event, but also as a contributor to subsequent atherothrombotic events in patients with up-regulated inflammation in the arterial wall and systemic circulation. Thus, antiplatelet therapy is necessary for the acute event, and subsequent maintenance therapy. Three related but complementary strategies provide effective antiplatelet therapy: cyclooxygenase (COX)-1 inhibition (aspirin), inhibition of adenosine diphosphate (ADP)-mediated platelet aggregation with thienopyridines (ticlopidine and clopidogrel), and GP IIb/IIIa inhibition (tirofiban, eptifibatide, abciximab).

5.3.1 Acetylsalicylic acid (aspirin)

Aspirin irreversibly inhibits COX-1 in platelets, thereby limiting the formation of thromboxane A_2, thus inhibiting platelet aggregation. Three trials have consistently shown that aspirin decreases death or MI in patients with unstable angina.[147,207,208] In the meta-analysis of the Antithrombotic Trialists Collaboration, a 46% reduction in the rate of vascular events was evidenced.[209] This meta-analysis suggested that 75–150 mg aspirin was as effective as higher doses. No robust relationship between dose and efficacy has been demonstrated. Initial doses of chewed, non-enteric aspirin from 160 to 325 mg are recommended to minimize delay before COX-1 inhibition occurs.[209] In another meta-analysis, including four studies, the reduction in the rate of vascular events was 53% (*Figure 6*). Intravenous aspirin is an alternative mode of application, but has never been validated in trials.

The most common side effect of aspirin is gastrointestinal intolerance, reported in 5–40% of aspirin-treated patients. Gastrointestinal bleeding appears to increase with higher doses. In the CAPRIE study, the rate of gastrointestinal bleeding leading to aspirin discontinuation was 0.93%.[210] Hypersensitivity ('allergy') to aspirin is rare, but its prevalence depends on the clinical manifestation. Desensitization may be an option in selected patients.[211] Most frequent is aspirin-exacerbated respiratory tract disease. Aspirin-induced rash or skin manifestations occur in 0.2–0.7% of the general population. More serious reactions such as anaphylactic shock are extremely rare.[212,213]

In the CURE trial, aspirin was given in combination with clopidogrel at doses ranging from 75 to 325 mg.[167] The incidence of major bleeding increased as a function of the aspirin dose, both in patients treated with aspirin alone and in patients treated with a combination of aspirin and clopidogrel. The risk of bleeding was lowest with doses up

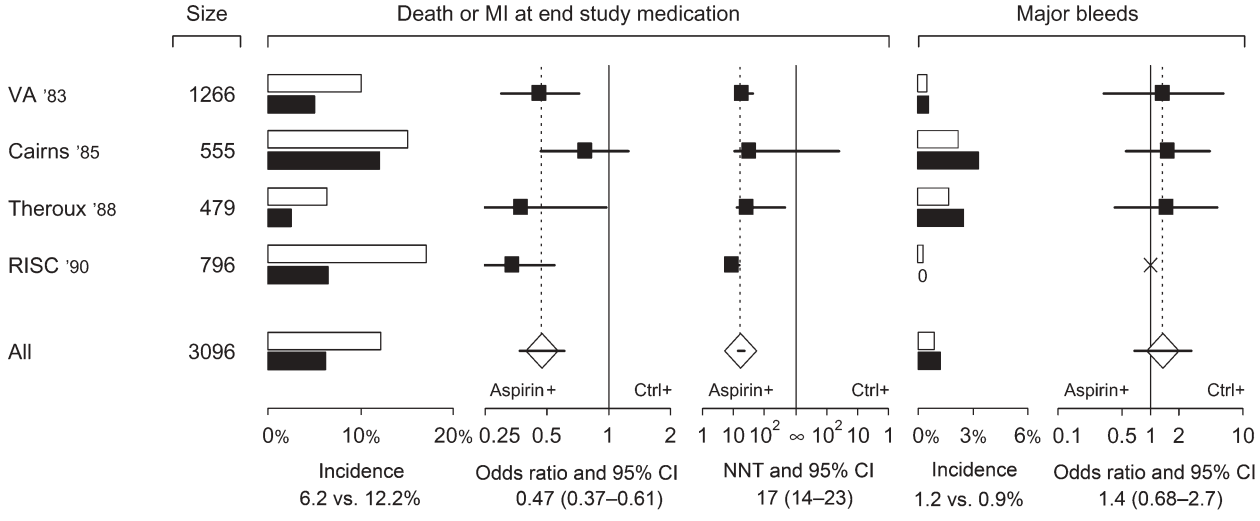

Figure 6 Death, myocardial infarction, and major bleeds at the end of study medication in four randomized trials of aspirin (filled bars) vs. control (open bars). NNT = number of patients who needed to be treated to avoid one event.

to 100 mg of aspirin, and there was no evidence of improved efficacy with higher doses of aspirin.[214]

5.3.2 Thienopyridines

Both ticlopidine and clopidogrel are ADP receptor antagonists, which block the ADP-induced pathway of platelet activation by specific inhibition of the $P2Y_{12}$ ADP receptor. Ticlopidine has been investigated in the setting of NSTE-ACS in only one study, in which a significant 46% risk reduction of death and MI at 6 months has been documented.[215] However, the use of ticlopidine has declined because of potentially serious side effects, in particular gastrointestinal, and risk of neutropenia or thrombocytopenia, and slower onset of action. As a result, ticlopidine was replaced by clopidogrel over time.

In the CURE trial, clopidogrel was administered for 9–12 months in addition to aspirin (75–325 mg) vs. aspirin alone in 12 562 patients suffering from NSTE-ACS. Patients received placebo or a loading dose of 300 mg clopidogrel followed by 75 mg daily, in addition to conventional therapy. A significant risk reduction for death from cardiovascular causes, non-fatal MI, or stroke was observed in the treatment arm (9.3 vs. 11.4%, RR 0.80, 95% CI 0.72–0.90, $P < 0.001$). The risk reduction was significant for MI, and there was a trend towards reduction of death and stroke. The risk reduction was consistent across all risk groups (low, moderate, or high) and among all subsets of patients (elderly, ST-deviation, with or without elevated cardiac biomarkers, diabetic patients). The benefit was obtained early, with a significant 34% risk reduction of cardiovascular death, MI, stroke, or severe ischaemia at 24 h in the clopidogrel group (1.4 vs. 2.1%, OR 0.66, 95% CI 0.51–0.86, $P < 0.01$) and throughout the 12 months of the study period.[167,216]

In non-acute settings, two other mega-trials tested clopidogrel against aspirin[210] and clopidogrel plus aspirin against placebo plus aspirin.[217] In CAPRIE, clopidogrel 75 mg once daily was compared with 325 mg of aspirin once daily in a population of 19 185 patients suffering from documented atherosclerotic disease, manifested as either recent ischaemic stroke, recent MI, or symptomatic peripheral arterial disease. The mean follow-up was 23 months. A significant relative risk reduction of 8.7% in favour of clopidogrel was observed vs. aspirin (95% CI 0.3–16.5, $P = 0.043$). There was no significant difference in the rate of major bleeding, particularly intracranial or gastrointestinal haemorrhage.[210]

The CHARISMA study included 15 603 patients, of whom 12 153 had documented cardiovascular disease, including 10.4% with prior MI. In this trial, clopidogrel was added to low-dose aspirin (75–160 mg daily). There was no difference with respect to the primary endpoint (cardiovascular death, MI, or stroke).[217] In the pre-specified subgroups of patients with documented cardiovascular disease, the composite endpoint was significantly reduced with dual antiplatelet therapy, when compared with aspirin (6.9 vs. 7.9%, RR 0.88, 95% CI 0.77–0.99, $P = 0.046$). There was a non-significant increase in the risk of GUSTO major bleeding complications (1.7 vs. 1.3%, RR 1.25, 95% CI 0.97–1.61, $P = 0.09$). Although clopidogrel cannot be recommended for long-term treatment for the full spectrum of patients investigated in the CHARISMA trial, subsidiary analyses suggest that among those with documented cardiovascular disease, benefits may outweigh risks.

Limited data are available about the combination of aspirin, clopidogrel, and GP IIb/IIIa inhibitors in the setting of NSTE-ACS. In the CURE study, the need for GP IIb/IIIa inhibitors was considered as a surrogate marker of anti-ischaemic efficacy. Overall, 5.9% of patients received GP IIb/IIIa inhibitors in conjunction with clopidogrel plus aspirin, when compared with 7.2% in the placebo group (RR 0.82, 95% CI 0.72–0.93, $P = 0.003$). No specific data have been reported about the safety and efficacy of this triple association. Triple antiplatelet therapy has been shown to be superior in preventing ischaemic events without compromising safety in *post hoc* analyses of PCI trials and in the ISAR-REACT-2 trial[188,218,219] (see section 5.3.3 Glycoprotein IIb/IIIa receptor inhibitors).

Newer $P2Y_{12}$ inhibitors with more potent receptor affinity and more rapid onset of action are currently under evaluation (e.g. prasugrel, cangrelor, AZD6140).

Risk of bleeding

In CURE, an increase in the rate of major bleeding was observed in clopidogrel-treated patients (3.7 vs. 2.7%, RR 1.38, 95% CI 1.13–1.67, $P = 0.001$), but with a non-significant increase in life-threatening and fatal bleeds.[167] Bleeding rates were higher in patients who underwent CABG, but this reached only borderline significance in 912 patients submitted to surgery less than 5 days after cessation of clopidogrel treatment (9.6 vs. 6.3%, RR 1.53, 95% CI 0.97–2.40, $P = 0.06$). For those treated more than 5 days after interruption of clopidogrel, there was no significant increase in bleeding.[220] There is no known antidote to clopidogrel or other ADP receptor antagonists (see section 6.1 Bleeding complications).

However, in the entire cohort, the benefit of clopidogrel treatment, including among patients submitted to revascularization by both PCI and CABG, outweighed the risk of bleeding, since overall, treating 1000 patients resulted in 21 fewer cardiovascular deaths, MI, or stroke, at the cost of an excess of seven patients requiring transfusion, and a trend for four patients to experience life-threatening bleeds.[220]

Overall, the benefit of clopidogrel treatment outweighs the risk in all patients with NSTE-ACS, including those submitted to CABG. The excess bleeding risk in patients submitted to surgery may be attenuated or eliminated by stopping clopidogrel for 5 days before surgery. However, it has not been investigated whether this results in increased complication rates during washout.

Dose and timing of clopidogrel

A number of studies have employed higher loading doses of clopidogrel (usually 600 mg), and these have demonstrated more rapid inhibition of platelet aggregation than that achieved with 300 mg. However, no large-scale outcome clinical trials have tested higher doses of clopidogrel in the setting of NSTE-ACS. Nevertheless, experience in other clinical settings suggests that faster platelet inhibition with higher loading doses ($\geq$600 mg) may be more effective in reducing clinical endpoints.[221–225] Definitive evidence of risk vs. benefit will be provided by ongoing large-scale clinical trials.

Pre-treatment of unselected patients with clopidogrel before angiography results in better outcome of

PCI.[218,219,226] The approach of postponing clopidogrel administration until coronary anatomy is known in patients submitted to very early invasive angiography is not based on evidence. The potential advantage of this approach is to avoid increased bleeding risk in patients requiring immediate surgery. However, this situation is rare, and frequently surgery can be deferred for a few days. Therefore, postponing clopidogrel to after angiography cannot be recommended, because the highest rates of events are observed in the early phase of NSTE-ACS. In patients who cannot be given clopidogrel before PCI, GP IIb/IIIa inhibitors should be administered.

Recommendations for oral antiplatelet drugs (Table 6)

- **Aspirin is recommended for all patients presenting with NSTE-ACS without contraindication at an initial loading dose of 160—325 mg (non-enteric) (I-A), and at a maintenance dose of 75—100 mg long-term (I-A).**
- **For all patients, an immediate 300 mg loading dose of clopidogrel is recommended, followed by 75 mg clopidogrel daily (I-A). Clopidogrel should be maintained for 12 months unless there is an excessive risk of bleeding (I-A).**
- **For all patients with contraindication to aspirin, clopidogrel should be given instead (I-B).**
- **In patients considered for an invasive procedure/PCI, a loading dose of 600 mg of clopidogrel may be used to achieve more rapid inhibition of platelet function (IIa-B).**
- **In patients pre-treated with clopidogrel who need to undergo CABG, surgery should be postponed for 5 days for clopidogrel withdrawal if clinically feasible (IIa-C).**

Table 6 Clinical use of antithrombotic therapy

Oral antiplatelet therapy
Aspirin initial dose: 160–325 mg non-enteric formulation, followed by 75–100 mg daily Clopidogrel 75 mg/day after a loading dose of 300 mg (600 mg when rapid onset of action is wanted)
Anticoagulants
Fondaparinux[a] 2.5 mg subcutaneously daily Enoxaparin[a] 1 mg/kg subcutaneously every 12 h Dalteparin[a] 120 IU/kg every 12 h Nadroparin[a] 86 IU/kg every 12 h UFH intravenous bolus 60–70 U/kg (maximum 5000 IU) followed by infusion of 12–15 IU/kg/h (maximum 1000 U/h) titrated to aPTT 1.5–2.5 times control Bivalirudin[a] intravenous bolus of 0.1 mg/kg and infusion of 0.25 mg/kg/h. Additional intravenous bolus of 0.5 mg/kg and infusion increased to 1.75 mg/kg/h before PCI
GP IIb/IIIa inhibition[a]
Abciximab 0.25 mg/kg intravenous bolus followed by infusion of 0.125 μg/kg/min (maximum 10 μg/min) for 12–24 h Eptifibatide 180 μg/kg intravenous bolus (second bolus after 10 min for PCI) followed by infusion of 2.0 μg/kg/min for 72–96 h Tirofiban 0.4 μg/kg/min intravenously for 30 min followed by infusion of 0.10 μg/kg/min for 48–96 h. A high-dose regimen (bolus 25 μg/kg +0.15 μg/kg/min infusion for 18 h) is tested in clinical trials

[a]See Chronic kidney disease for specific rules of prescription in the case of renal failure.

5.3.3 Glycoprotein IIb/IIIa receptor inhibitors

Three GP IIb/IIIa inhibitors have been approved for clinical use, namely abciximab, eptifibatide, and tirofiban. They block the final common pathway of platelet activation by binding to fibrinogen and, under high shear conditions, to von Willebrand factor, and thus inhibiting the bridging between activated platelets. Abciximab is a monoclonal antibody fragment, eptifibatide is a cyclic peptide, and tirofiban a peptido-mimetic inhibitor. Clinical studies with oral GP IIb/IIIa inhibitors were stopped because of an excess of ischaemic events and/or excess bleeding.[227,228]

The results obtained with the use GP IIb/IIIa inhibitors differed according to whether their use was associated with a conservative or an invasive strategy.

Glycoprotein IIb/IIIa inhibitors in a conservative strategy

All three GP IIb/IIIa inhibitors were tested in trials where an invasive strategy was not encouraged. A meta-analysis including 31 402 NSTE-ACS patients treated in clinical trials using GP IIb/IIIa inhibitors showed a 9% significant risk reduction for death and MI at 30 days with GP IIb/IIIa inhibitors (11.8 vs. 10.8%, OR 0.91, 95% CI 0.84–0.98, $P = 0.015$).[229] This risk reduction was consistent across multiple subgroups and was evident particularly in high-risk patients, (diabetic patients, ST-segment depression, and troponin-positive patients) and in patients submitted to PCI during initial hospitalization. GP IIb/IIIa inhibitors had no effects in troponin-negative patients and in women. However, most of them were actually troponin negative,[229] and women with troponin release derived the same benefit as men. The use of GP IIb/IIIa inhibitors was associated with an increase in major bleeding complications, but intracranial bleeding was not significantly increased[229] (*Figure 7*).

Outcome as a function of the utilization of GP IIb/IIIa inhibitors in patients initially medically managed, and submitted to PCI, was explored in a further meta-analysis involving 29 570 patients.[230] A 9% risk reduction overall was confirmed, but the benefit was non-significant in purely medically managed patients receiving GP IIb/IIIa inhibitors vs. placebo, with a rate of death and MI at 30 days of 9.3 vs. 9.7% (OR 0.95, 95% CI 0.86–1.04, $P = 0.27$). The only significant beneficial effect was observed when GP IIb/IIIa inhibitors were maintained during PCI (10.5 vs. 13.6%, OR 0.74, 95% CI 0.57–0.96, $P = 0.02$). These data confirm previous reports showing a risk reduction for ischaemic events in patients pre-treated with GP IIb/IIIa inhibitors before PCI.[231,232] In diabetic patients, a meta-analysis showed a highly significant risk reduction for death at 30 days with the use of GP IIb/IIIa inhibitors,[233] particularly pronounced when submitted to PCI. This confirmed previous reports on this issue.[229,231,233]

Abciximab. Abciximab was tested in the GUSTO-4-ACS trial.[234] In this trial, an invasive strategy and revascularization were discouraged during the acute phase. Seven thousand patients on aspirin and UFH were randomized to one of three drug regimens: placebo, abciximab bolus plus 24 h infusion, or abciximab bolus plus 48 h infusion.

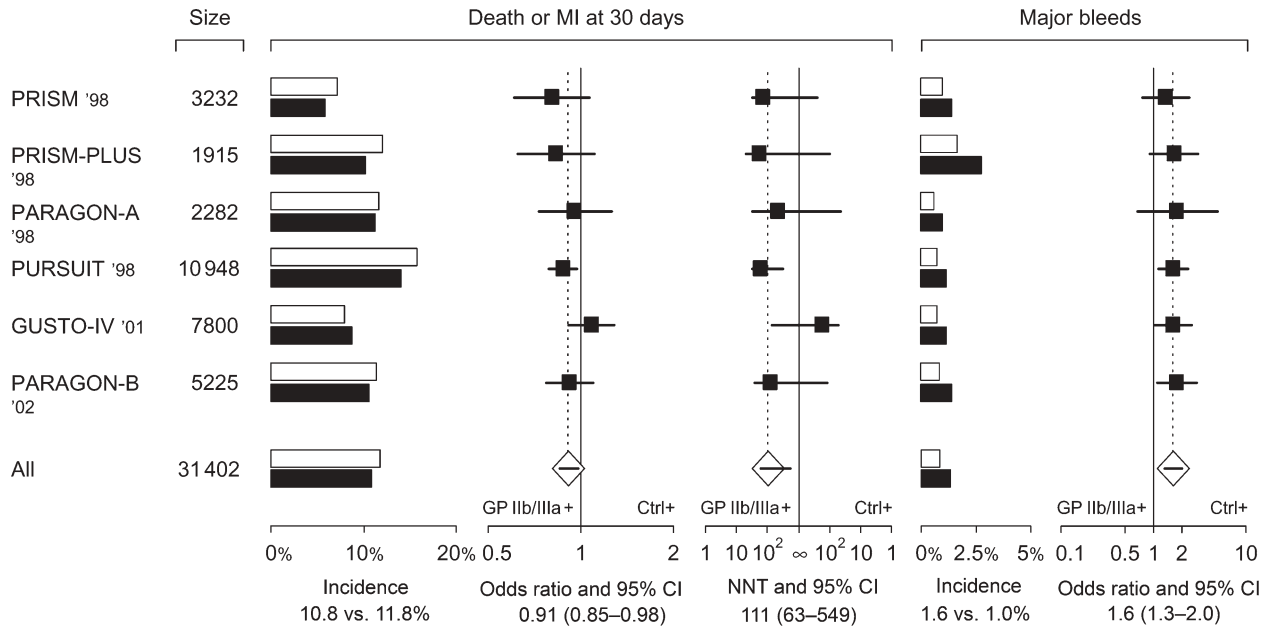

Figure 7 Death, myocardial infarction, and major bleeds at 30 days in randomized trials of glycoprotein IIb/IIIa inhibitors (filled bars) vs. control (open bars) in a conservative strategy. NNT = number of patients who needed to be treated to avoid one event.

No significant benefit was demonstrated for the two groups treated with abciximab, and an increased bleeding risk was observed. Thrombocytopenia (defined as platelet count $<50\,000\ \mu L^{-1}$) was observed in 1.5% of patients receiving abciximab vs. 1% in the placebo group. Thus, abciximab cannot be recommended for patients with NSTE-ACS, unless in the context of PCI (discussed subsequently).

Eptifibatide. In the PURSUIT trial,[235] 10 948 patients were enrolled and randomized into three arms. In addition to conventional therapy including aspirin and UFH, patients were randomized to placebo or two different regimens of eptifibatide infusion, after the same initial bolus. The lower dose of eptifibatide was dropped because of lack of efficacy. The comparison involved the high-dose eptifibatide regimen vs. placebo. A significant reduction of the 30-day composite endpoint of death or non-fatal MI was observed (14.2 vs. 15.7%, eptifibatide vs. placebo, $P = 0.04$). The benefit was maintained at 6 months. This benefit was obtained at the cost of an excess risk of TIMI major bleeding (10.6 vs. 9.1%, $P = 0.02$), but no excess of intracranial bleeding. Thrombocytopenia (defined as platelet count of $<100\,000\ mm^{-3}$ or nadir $<50\%$ of baseline value) occurred at a similar rate in both arms (6.8% eptifibatide vs. 6.7% placebo). The rate of profound thrombocytopenia (defined as platelet count $<20\,000\ mm^{-3}$) was low in both treatment arms (0.2 vs. $<0.1\%$, eptifibatide vs. placebo, P = NS).

Tirofiban. Tirofiban has been tested in two separate randomized trials.[236,237] In the PRISM trial, 3231 patients presenting with NSTE-ACS were randomized to receive either tirofiban or UFH for 48 h. A significant reduction in the composite endpoint of death, MI, or refractory ischaemia was observed at 48 h and maintained at 30 days, but not thereafter (3.8 vs. 5.6%, RR 0.67, 95% CI 0.48–0.92, $P = 0.01$ at 48 h). The rate of thrombocytopenia (defined as platelet count $<90\,000\ mm^{-3}$) was significantly more frequent with tirofiban than with UFH (1.1 vs. 0.4%, $P = 0.04$).

In the PRISM-PLUS trial, 1915 patients at higher risk than in the PRISM trial were randomized to three different arms: tirofiban alone, tirofiban plus UFH, or UFH alone. The tirofiban-alone arm was stopped soon after the start of the trial, because of an excess of adverse events. A significant reduction of the risk of death, MI, and refractory ischaemia was obtained at 7 days (12.9 vs. 17.9%, RR 0.68, 95% CI 0.53–0.88, $P = 0.004$) and maintained at 30 days and 6 months in the tirofiban plus UFH group, when compared with UFH alone. Major bleeds (according to the TIMI criteria) were not statistically more frequent in the tirofiban group, despite a trend towards an increase (1.4 vs. 0.8%, $P = 0.23$).

Glycoprotein IIb/IIIa inhibitors in an invasive strategy

Consistent results have been obtained in three different meta-analyses exploring the impact of the use of GP IIb/IIIa inhibitors in the setting of PCI. Two meta-analyses showed that a significant risk reduction for death and MI at 30 days could be achieved when GP IIb/IIIa inhibitors were administered before taking patients to the catherization laboratory and maintained during PCI.[230,231] Kong *et al.*[238] reported a significant risk reduction in 30-day mortality among a total of 20 186 patients (0.9 vs. 1.3%, OR 0.73, 95% CI 0.55–0.96, $P = 0.024$). Importantly, thienopyridines and stents were not routinely used in these trials.

Abciximab. Abciximab has been tested in three trials as an adjunct to PCI in the setting of ACS.[239–241] Altogether, 7290 patients were included in these three trials, which convincingly showed a significant reduction in the combination of death and MI or need for urgent revascularization at 30 days. Pooled data from these three trials showed a significant late mortality benefit (HR 0.71, 95% CI 0.57–0.89, $P = 0.003$).[242]

In CAPTURE, abciximab has also been tested in patients with NSTE-ACS with planned PCI pre-treated with abciximab for 24 h and maintained for 12 h. In this trial without routine use of stents and clopidogrel, abciximab significantly

reduced the rate of death, MI, and need for urgent intervention for recurrent ischaemia when compared with placebo at 30 days (11.3 vs. 15.9%, $P = 0.012$).[243] The benefit was restricted to patients with elevated TnT levels.[74]

More recently, in ISAR-REACT-2, 2022 high-risk NSTE-ACS patients were randomized following pre-treatment with aspirin and 600 mg of clopidogrel to either abciximab or placebo.[188] There was a similar proportion of diabetic patients in each group (average 26.5%); 52% of patients had elevated troponins and 24.1% had previous MI. The 30-day composite endpoint of death, MI, or urgent target vessel revascularization (TVR) occurred significantly less frequently in abciximab-treated patients vs. placebo (8.9 vs. 11.9%, RR 0.75, 95% CI 0.58–0.97, $P = 0.03$). Most of the risk reduction generated by abciximab resulted from a reduction in the occurrence of death and MI. The effect was more pronounced in certain pre-specified subgroups, particularly troponin-positive patients (13.1 vs. 18.3%, RR 0.71, 95% CI 0.54–0.95, $P = 0.02$). The duration of pre-treatment with clopidogrel had no influence on outcome, and there was no detectable effect in troponin-negative patients or among diabetic patients. However, the number of diabetic patients included in this trial may have been too low to provide robust statistical power to detect any effect.

Abciximab was tested in a head-to-head comparison vs. tirofiban in the TARGET trial, in which two-thirds of the patients had recent or ongoing NSTE-ACS. Abciximab was shown to be superior to tirofiban in standard doses in reducing the risk of death, MI, and urgent revascularization at 30 days, but the difference was not significant at 6 months and 1 year.[244,245]

Eptifibatide. Eptifibatide has been tested in patients undergoing PCI including 38% with unstable angina (IMPACT-2) and exhibited no significant benefit when compared with placebo.[246] Subsequently, eptifibatide was tested in the ESPRIT trial, in which the dose was increased to a double bolus of 180 μg/kg followed by an infusion of 2.0 μg/kg/min for 18–24 h vs. placebo.[247] In this trial, a significant reduction in the risk of death, MI, urgent TVR, and bail-out use of GP IIb/IIIa inhibitors was demonstrated at 48 h, maintained at 30 days and at 6 months (6.6 vs. 10.5%, RR 0.63, 95% CI 0.47–0.84, $P = 0.0015$ at 48 h for eptifibatide vs. placebo). The secondary composite endpoint of death, MI, or urgent TVR was also significantly reduced at the same time point (6.0 vs. 9.3%, RR 0.65, 95% CI 0.47–0.87, $P = 0.0045$). However, in this study, a smaller proportion (46%) of patients with recent or ongoing NSTE-ACS was included when compared with TARGET.

Tirofiban. Tirofiban was tested in the RESTORE trial, involving 2139 patients suffering from recent NSTE-ACS. In this trial, a significant 38% relative risk reduction in the primary composite endpoint of death, MI, repeat revascularization, or recurrent ischaemia at 48 h was observed at 7 days but not at 30 days.[248] Tirofiban was used at the same dose in the TARGET and RESTORE trials. In retrospect, the dose may have been too low.

Further trials explored higher doses of tirofiban in various clinical settings. In a small trial of 202 patients, high-dose bolus (25 μg/kg) and infusion (0.15 μg/kg/min for 24–48 h) was shown to reduce the incidence of ischaemic thrombotic complications during high-risk PCI vs. placebo.[249] TENACITY, a large-scale study testing high-dose tirofiban against abciximab, was stopped for financial reasons after inclusion of only 383 patients.

Use of glycoprotein IIb/IIIa inhibitors prior to revascularization

Glycoprotein IIb/IIIa inhibitors and percutaneous coronary intervention. Two GP IIb/IIIa inhibitors (tirofiban and eptifibatide) have shown efficacy in reducing ischaemic events in NSTE-ACS, particularly in high-risk subgroups, such as troponin-positive or diabetic patients, and in patients submitted to revascularization.[73,235] Therefore, they may be used as first-line treatment in addition to other antithrombotic agents, before invasive evaluation of the patient is undertaken. This so-called 'upstream' use of GP IIb/IIIa inhibitors prior to revascularization has been shown in meta-analyses to further reduce the risk of death and MI at 30 days, if GP IIb/IIIa inhibitors are prescribed upstream of and maintained during the PCI procedure.[230,231] However, this question will be further explored in upcoming trials (EARLY-ACS).[250]

In ACUITY-TIMING, deferred selective vs. routine upstream administration of GP IIb/IIIa inhibitors was tested in a 2 × 2 factorial design. GP IIb/IIIa inhibitors were used in 55.7% of patients for 13.1 h in the deferred selective and in 98.3% of patients for 18.3 h in the routine upstream strategy.[251] Deferred selective vs. routine upstream strategy resulted in a reduced 30-day major bleeding rate (4.9 vs. 6.1%, RR 0.80, 95% CI 0.67–0.95) but the rate of ischaemic events did not meet the criteria for non-inferiority, with a trend towards a higher rate (7.9 vs. 7.1%, RR 1.12, 95% CI 0.97–1.29; $P = 0.13$ deferred selective vs. routine upstream strategy). TIMI major bleeding rate was not significantly different in both groups (1.6 vs. 1.9%, $P = 0.20$) for deferred selective vs. routine upstream, whereas TIMI minor bleeding rate was significantly lower (5.4 vs. 7.1%, $P < 0.001$) for deferred selective vs. routine upstream. Ischaemic composite endpoint was achieved significantly more frequently in patients submitted to PCI with deferred selective vs. routine upstream GP IIb/IIIa inhibitors (9.5 vs. 8.0%, RR = 1.19, 95% CI 1.00–1.42, $P = 0.05$). Considering these results, it can be concluded that more frequent and more prolonged use of GP IIb/IIIa inhibitors with upstream treatment leads to an excess risk of major bleeding, but with potentially greater protection against ischaemic events in patients submitted to PCI.

In routine practice, as shown by several registries,[252,253] patients are often taken to the catherization laboratory without prior infusion of GP IIb/IIIa inhibitors. In this setting, if there is a need for immediate PCI, the administration of GP IIb/IIIa inhibitors in the catherization laboratory is recommended on the basis of ISAR-REACT-2 as an alternative strategy, which, however, has no proven superiority when compared with upstream administration.

Glycoprotein IIb/IIIa inhibitors and coronary artery bypass graft. Inhibition of platelet aggregation may result in bleeding complications, either spontaneously or at the time of cardiac surgery. However, surgery in patients receiving GP IIb/IIIa inhibitors has been shown to be safe when appropriate measures are taken to ensure adequate haemostasis. GP IIb/IIIa inhibitors should be discontinued at the time of cardiac surgery. Eptifibatide and tirofiban have a short half-life, so platelet function should recover by the end of CABG. Abciximab has a longer effective half-life, and

earlier discontinuation may be needed. If excessive bleeding occurs, fresh platelet transfusions may be administered (see section 6.1 Bleeding complications). Fibrinogen supplementation with fresh–frozen plasma or cryoprecipitate either alone or in combination with platelet transfusion can also be considered for restoring haemostatic potential and managing major haemorrhagic complications associated with the administration of small-molecule, GP IIb/IIIa inhibitors.[254]

Adjunctive therapy

All trials carried out with GP IIb/IIIa inhibitors used UFH. Nowadays, the use of LMWH, particularly enoxaparin, is more widespread. Several trials in the field of NSTE-ACS, as well as observational studies in PCI, have shown that LMWH, predominantly enoxaparin, can be safely used with GP IIb/IIIa inhibitors without compromising efficacy.[162–172,255,256] In OASIS-5, GP IIb/IIIa inhibitors were used with aspirin, clopidogrel, and fondaparinux in 1308 patients or enoxaparin in 1273 patients. Overall, bleeding complications were lower with fondaparinux than with enoxaparin (see section 5.2 Anticoagulants).

Thienopyridines were not used in earlier trials testing GP IIb/IIIa inhibitors. Therefore, the efficacy and safety of a triple association of aspirin, clopidogrel, and GP IIb/IIIa inhibitors was not clearly defined. Recently, the ISAR-REACT-2 study has confirmed that better outcome can be obtained with abciximab added to pre-treatment with aspirin and a 600 mg loading dose of clopidogrel, when compared with a dual regimen with only aspirin plus clopidogrel in the setting of high-risk PCI patients with NSTE-ACS.[188] Other trials testing the same hypothesis are ongoing (e.g. Early-ACS).[250]

Bivalirudin and UFH/LMWH were shown to have equivalent safety and efficacy when used with triple antiplatelet therapy, including GP IIb/IIIa inhibitors in the ACUITY trial. However, bivalirudin alone was associated with a lower bleeding risk when compared with any combination with GP IIb/IIIa inhibitors.[257]

Recommendations for glycoprotein IIbIIIa inhibitors (Table 6)

- **In patients at intermediate to high risk, particularly patients with elevated troponins, ST-depression, or diabetes, either eptifibatide or tirofiban for initial early treatment is recommended in addition to oral antiplatelet agents (IIa-A).**
- **The choice of combination of antiplatelet agents and anticoagulants should be made in relation to risk of ischaemic and bleeding events (I-B).**
- **Patients who receive initial treatment with eptifibatide or tirofiban prior to angiography should be maintained on the same drug during and after PCI (IIa-B).**
- **In high-risk patients not pre-treated with GP IIb/IIIa inhibitors and proceeding to PCI, abciximab is recommended immediately following angiography (I-A). The use of eptifibatide or tirofiban in this setting is less well established (IIa-B).**
- **GP IIb/IIIa inhibitors must be combined with an anticoagulant (I-A).**
- **Bivalirudin may be used as an alternative to GP IIb/IIIa inhibitors plus UFH/LMWH (IIa-B).**
- **When anatomy is known and PCI planned to be performed within 24 h with GP IIb/IIIa inhibitors, most secure evidence is for abciximab (IIa-B).**

5.3.4 Resistance to antiplatelet agents/drug interactions

Resistance to antiplatelet agents describes partial or total failure of an antiplatelet agent to achieve the expected inhibition of platelet function and would therefore be better named low or hypo-responsiveness. The term refers to the variability in the magnitude of platelet aggregation inhibition measured *ex vivo* achieved in a population of treated patients. Resistance to antiplatelet agents is often confused with recurrence of events despite antiplatelet treatment. This does not necessarily imply that antiplatelet resistance is the causal phenomenon, since atherothrombosis is multifactorial, and the recurrence of events may be due to a mechanism other than resistance to treatment. Resistance to antiplatelet agents may be assessed by various tests of platelet function. The magnitude of true resistance to antiplatelet agents remains poorly defined. No simple test has been reliably validated to assess the level of platelet function inhibition for any antiplatelet agent used in atherothrombosis.[258,259]

In addition, drug interactions may result in partial or total inhibition of the activity of a given compound. As the prescription list for patients suffering from NSTE-ACS at the acute phase and for the long term involves several different pharmacological classes, caution has to be exerted before deciding on a polypharmacy prescription. Only few interactions have been reported for the drugs used in this setting. The most serious interactions have recently been suspected with non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin (discussed subsequently).

Aspirin resistance/drug interactions

Resistance to aspirin describes a range of phenomena, including inability to protect individuals from thrombotic complications, inability to cause prolongation of the bleeding time, inability to reduce thromboxane A_2 production, and failure to produce an anticipated effect on one or more *in vitro* tests of platelet function, including in particular aggregometry, shear stress-induced activation, and expression of platelet surface receptors.[259] A proportion of patients treated for any clinical manifestation of atherothrombosis, CAD, cerebrovascular disease, or peripheral artery disease may develop treatment failure over time, even with increasing doses.[260–266]

However, few studies have shown that aspirin resistance could lead to treatment failure. One HOPE substudy showed that different degrees of thromboxane A_2 inhibition were associated with a significant difference in rate of events. However, these differences may reflect different levels of treatment compliance.[267,268]

There are at least three potential mechanisms that may lead to aspirin resistance, namely transient expression of COX-2 in newly formed platelets,[269] extra-platelet sources of thromboxane A_2, [270] and interference with NSAIDs. Concomitant administration of NSAIDs, such as ibuprofen, may interfere with the inactivation of COX-1 due to a competitive action on the docking site of aspirin in the COX channel.[271] This possible interaction is not observed with selective COX-2 inhibitors or other anti-inflammatory drugs such as diclofenac. Nevertheless, in some reports, it has

been shown that more events occur in patients treated with this association.[258,272,273] Recently, a retrospective analysis of a large cohort of patients discharged from hospital after MI showed that the use of selective COX-2 inhibitors and non-selective NSAIDs in the post-MI period led to a higher risk of death, with any of these agents.[274] There was also an increased risk of hospitalization for MI with the use of selective COX-2 inhibitors and NSAIDs. This and other studies indicate that anti-inflammatory drugs should be avoided in the post-MI period, whatever the mechanism for the increased risk of death and MI may be.

Clopidogrel resistance/drug interactions

Clopidogrel is an inactive compound, which needs oxidation by hepatic cytochrome P450 to generate an active metabolite. CYP3A4 and CYP3A5 are the P450 isoforms responsible for the oxidation of clopidogrel, which, through a multistage metabolic degradation, leads to the active form of the drug. The standard dose of clopidogrel achieves, through antagonism of the $P2Y_{12}$ platelet ADP receptor, approximately 30–50% inhibition of ADP-induced platelet aggregation.[275]

Clopidogrel resistance is an inappropriate terminology which refers actually to the variability in the clopidogrel-induced inhibition of platelet aggregation. Light transmission aggregometry is the most frequently used test to measure platelet inhibition. However, there is no unanimity on how to define clopidogrel resistance with regard to the cut-off value. With these restrictions, clopidogrel resistance was shown to occur in 4–30% of patients.[258,275] The mechanisms of clopidogrel resistance are currently under investigation. Despite small studies that have shown a higher rate of events associated with low inhibition of platelet aggregation, there is little tangible evidence that clopidogrel resistance results in treatment failure.[276–278] There are still efforts to overcome this problem by raising and/or tailoring the clopidogrel dose. Newer ADP receptor antagonists (e.g. prasugrel, cangrelor, and AZD6140) are currently under clinical investigation.

In some instances, reduced bioavailability through drug interactions has been elicited, particularly with some statins which are metabolized by CYP3A4 and CYP3A5. They have been shown in *in vitro* studies to limit by 90% the degradation of clopidogrel in its active metabolite form.[258,275] However, in clinical practice, this has not been translated into any demonstrable negative effect.[279] Indeed, in the GRACE registry, the association of clopidogrel and statins is suggestive of an additive beneficial effect on outcome.[280]

In vitro, clopidogrel metabolites can inhibit enzymatic activity of cytochrome P4502C9 and lead to increased plasma levels of NSAIDs, which are metabolized by this cytochrome. This could lead to an increased risk of gastrointestinal bleeding in the case of concomitant administration of clopidogrel and NSAIDs (particularly naproxen).[281]

Lastly, the association of clopidogrel with a VKA is not recommended, since it may potentially increase the risk of bleeding. This combination can, however, be necessary in the context of mechanical heart valve or in the case of high risk of thrombo-embolic events, where VKAs cannot be interrupted and clopidogrel is mandatory. In these cases, the lowest efficacious INR and shortest duration for the prescription should be targeted. Strict control of the INR is necessary.

Recommendations for resistance to antiplatelet treatment/drug interactions

- **Routine assessment of platelet aggregation inhibition in patients submitted to either aspirin or clopidogrel the-rapy, or both, is not recommended (IIb-C).**
- **NSAIDs (selective COX-2 inhibitors and non-selective NSAIDs) should not be administered in combination with either aspirin or clopidogrel (III-C).**
- **Clopidogrel can be administered with all statins (I-B).**
- **The triple association of aspirin, clopidogrel, and a VKA should only be given if a compelling indication exists, in which case, the lowest efficacious INR and shortest duration for the triple association should be targeted (IIa-C).**

5.3.5 Withdrawal of antiplatelet agents

Some recent reports have shown that, in patients with CAD, withdrawal of antiplatelet agents, whatever the reason, may lead to an increased rate of recurrence of events.[282] In a recently published multicentre prospective cohort of 1521 patients with recent MI, 184 patients discontinued all three recommended medications (aspirin, beta-blockers, and statins), 56 two medications, and 272 only one medication during a 12-month follow-up period. Patients who discontinued all three medications had the lowest 12-month survival rate (88.5 vs. 97.7%; log-rank $P < 0.001$) compared with patients who maintained at least one medication. In multivariate analysis, medication discontinuation was independently associated with higher mortality rates (HR 3.81; 95% CI 1.88–7.72). Results were consistent when evaluating aspirin, beta-blockers, and statins separately.[283]

Interruption of dual antiplatelet therapy soon after stent implantation increases the risk of acute stent thrombosis, which carries a particularly adverse prognosis, with mortality varying from 15 to 45% at 1 month.[284–286] In addition, interruption of antiplatelet agents long after implantation of drug-eluting stents (DES) may expose the patient to late stent thrombosis.[285,287–289] Similarly, interruption of dual antiplatelet treatment soon after the acute phase of NSTE-ACS may expose the patients to a high risk of recurrence of events even in non-stented patients, though only few data are available to support this notion. However, interruption of dual antiplatelet therapy in the case of a necessary surgical procedure more than 1 month after ACS in patients without DES may be reasonable.

If interruption of dual antiplatelet therapy becomes mandatory, such as need for urgent surgery or major bleeding that cannot be controlled by local treatment, no proven efficacy alternative therapy can be proposed as a substitute. Different alternatives to dual antiplatelet treatment have been proposed depending on the clinical setting, the type of stent and date of implantation, and type of surgery. None of them was formerly proven efficacious, and all are based on experts' consensus opinion. LMWH have been advocated without tangible proof of efficacy.[290,291]

Recommendations for withdrawal of antiplatelet treatment

- **Temporary interruption of dual antiplatelet therapy (aspirin and clopidogrel) within the first 12 months after the initial episode is discouraged (I-C).**

- **Temporary interruption for major or life-threatening bleeding or for surgical procedures where even minor bleeding may result in severe consequences (brain or spinal surgery) is mandatory (IIa-C).**
- **Prolonged or permanent withdrawal of aspirin, clopidogrel, or both is discouraged unless clinically indicated. Consideration should be given to the risk of recurrence of ischaemic events which depends (among other factors) on initial risk, on the presence and type of stent implanted, and on the time window between proposed withdrawal and the index event and/or revascularization (I-C).**

5.4 Coronary revascularization

Revascularization for NSTE-ACS is performed to relieve angina and ongoing myocardial ischaemia and to prevent progression to MI or death. The indications for myocardial revascularization and the preferred approach (PCI or CABG) depend on the extent and severity of the lesions as identified by coronary angiography, the patient's condition, and co-morbidity.

5.4.1 Coronary angiography

Invasive coronary angiography remains pivotal in determining suitability for percutaneous and/or surgical revascularization. It is recommended to perform angiograms after intracoronary administration of vasodilators (nitrates) in order to attenuate vasoconstriction and offset the dynamic component that is frequently present in ACS.[292] In haemodynamically compromised patients (pulmonary oedema, hypotension, severe life-threatening arrhythmias), it may be advisable to perform the examination after placement of an intra-aortic balloon pump, to limit the number of coronary injections and to omit LV angiography.

Data from TIMI-3B[293] and FRISC-2[294] show that 30–38% of the patients with unstable coronary syndromes have single-vessel disease and 44–59% have multivessel disease (>50% diameter stenosis). The incidence of left main narrowing varies from 4 to 8%. Although stenosis severity is usually well determined by angiography, sometimes intravascular ultrasound may be useful.[295] Coronary angiography in conjunction with ECG findings and wall motion abnormalities frequently allows identification of the culprit stenosis that often shows eccentricity, irregular borders, ulceration, haziness, and filling defects suggestive of the presence of intracoronary thrombus.[296] However, sometimes it may be difficult to determine the culprit lesion because the above-mentioned features are either present in more than one vessel or absent. Diffuse atherosclerotic infiltration without significant narrowing is found in 14–19% of cases.[253] A number of new investigational invasive diagnostic tools are currently being tested for their ability to identify the presence of one or more vulnerable segments, monitor changes that occur either spontaneously or under medical treatment, and relate those markers of plaque vulnerability to patient outcome.[297,298] Focal accumulation of specific plaque components such as lipid necrotic core and weakening of the fibrous cap are associated with instability.[299,300] At this point in time, it remains undetermined whether non-culprit coronary segments showing vulnerable features will merit mechanical intervention.[301]

5.4.2 Invasive vs. conservative strategy

Choice of strategy

Coronary angiography should be planned as soon as possible (urgent invasive strategy) in patients with severe ongoing angina, profound or dynamic ECG changes, major arrhythmias, or haemodynamic instability upon admission or thereafter. These patients represent 2–15% of the patients admitted with NSTE-ACS.[302–304] In patients with intermediate to high-risk features, but without the aforementioned life-threatening features, early coronary angiography (within 72 h) followed by revascularization when possible and indicated, or initial medical stabilization and selective performance of coronary angiography based on the clinical course have been tested as alternative strategies. In low-risk patients, a non-invasive assessment of inducible ischaemia should be performed prior to discharge. If this is positive, coronary angiography should be performed[305] (see section 8 Management strategies).

A meta-analysis of seven randomized trials (including early studies prior to the widespread use of stents and multidrug adjunctive therapy) comparing routine angiography ($n = 4608$) followed by revascularization with a more conservative strategy (invasive care only in patients with recurrent or inducible ischaemia, $n = 4604$) showed reduced rate of death and MI at the end of follow-up (12.2 vs. 14.4%, OR 0.82, 95% CI 0.72–0.93, $P = 0.001$) for routine invasive vs. selective invasive.[306] At the same time point, there was a non-significant trend towards fewer deaths (5.5 vs. 6.0%, OR 0.92, 95% CI 0.77–1.09), whereas a significant reduction in MI alone was observed (7.3 vs. 9.4%, OR 0.72, 95% CI 0.65–0.88, $P < 0.001$) for routine invasive vs. selective invasive. These results were obtained despite an early hazard observed during initial hospitalization in the routine invasive group, where a significantly higher risk of death, and death and MI was noted (1.8 vs. 1.1%, OR 1.6, 95% CI 1.14–2.25, $P = 0.007$ for death; 5.2 vs. 3.8%, OR 1.36, 95% CI 1.12–1.66, $P = 0.002$ for death and MI) for routine invasive vs. selective invasive. The beneficial effect was actually achieved from hospital discharge to the end of follow-up, where a significant risk reduction in death and death and MI was observed (3.8 vs. 4.9%, OR 0.76, 95% CI 0.62–0.94, $P = 0.01$ for death; 7.4 vs. 11.0%, OR 0.64, 95% CI 0.55–0.75, $P < 0.001$ for death and MI) routine invasive vs. selective invasive. Over a mean follow-up of 17 months, recurrent angina was reduced by 33% and rehospitalization by 34% in the routine invasive group. In another meta-analysis including six contemporary trials, the OR was 0.84, 95% CI 0.73–0.97 for early invasive vs. conservative strategy (*Figure 8*). The benefit of the routine invasive strategy was present in patients with elevated troponins at baseline, but not in troponin-negative patients (from the analysis of the three most recently performed trials with available troponin data).[122,307,308] A more recent meta-analysis including seven trials with 8375 patients available for analysis showed after a mean follow-up of 2 years a significant risk reduction for all-cause mortality (4.9 vs. 6.5%, RR 0.75, 95% CI 0.63–0.90, $P = 0.001$) for early invasive vs. conservative, without excess of death at 1 month (RR = 0.82, 95% CI 0.50–1.34, $P = 0.43$). At 2 years of follow-up, the incidence of non-fatal MI was 7.6 vs. 9.1% (RR = 0.83, 95% CI 0.72–0.96, $P = 0.012$), without excess at 1 month (RR = 0.93, 95% CI 0.73–1.19, $P = 0.57$.[309] Long-term mortality reduction has been

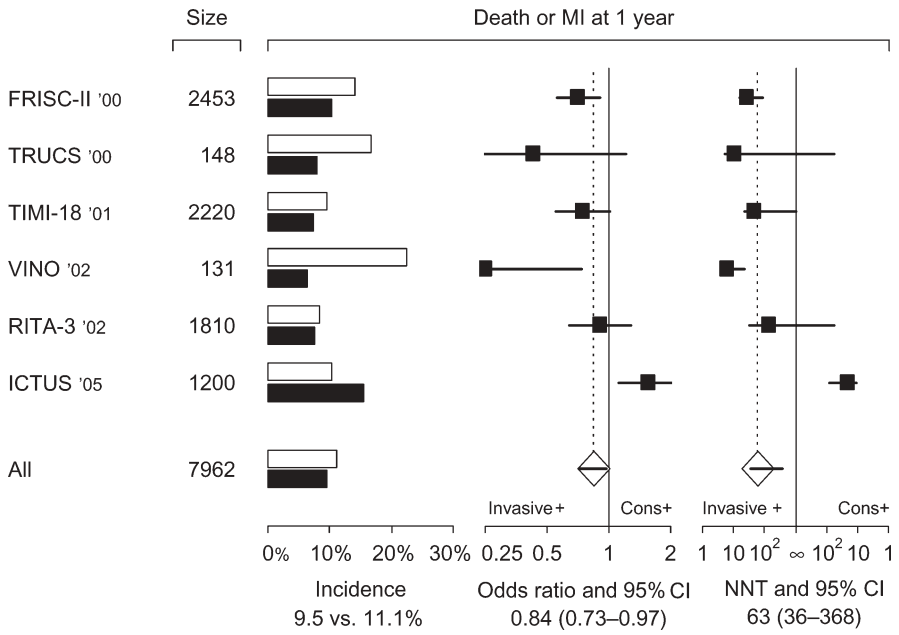

Figure 8 Death or myocardial infarction in six contemporary randomized trials comparing early invasive (filled bars) vs. conservative strategy (open bars). NNT = number of patients who needed to be treated to avoid one event.

confirmed in the follow-up of RITA-3 at 5 years[310] and FRISC-2 at 2 and 5 years.[122,308] Many of the trials analysed in the meta-analysis by Mehta *et al.*[306] were not contemporary. In four of the trials, namely TIMI-3B, VANQWISH, MATE, and FRISC-2, the use of stents and GP IIb/IIIa inhibitors was low or non-existent.[293,311,312] More recently, a review of the most contemporary trials by the Cochrane collaboration confirmed the initial observations reported by Mehta *et al.* This meta-analysis confirmed the existence of a trend towards an early excess of mortality with an invasive strategy (RR 1.59, 95% CI 0.96–2.54), but with a significant long-term benefit in terms of death (RR 0.75, 95% CI 0.62–0.92) or MI (RR 0.75, 95% CI 0.62–0.91) with invasive vs. conservative at 2–5-year follow-up.[313] The recently published ICTUS trial was not included in this meta-analysis, although its results challenge the paradigm of superior outcome with routine invasive strategy.[314] In this trial, 1200 patients were randomized to an early invasive strategy vs. a more conservative (selective) approach. There was no difference in the incidence of the primary composite endpoint of death, MI, or rehospitalization for angina within 1 year (22.7 vs. 21.2%, RR 1.07, 95% CI 0.87–1.33, $P = 0.33$) with early vs. selective invasive strategy. These results were maintained at 3-year follow-up[315] In keeping with previous studies, routine intervention was associated with a significant early hazard. MI was significantly more frequent in the early invasive group (15.0 vs. 10.0%, RR 1.5, 95% CI 1.10–2.04, $P = 0.005$). The majority (67%) of MI [defined as $\geq$1–3 times the upper limits of normal (ULN) CK-MB] was indeed associated with revascularization procedures. The discrepancy between this and previous trials could be attributed in part to the small difference in revascularization rates between the two study groups and the high overall rate of revascularization before discharge (76% in the routine invasive and 40% in the selective group). In addition, the criterion for diagnosis of MI (any CK-MB elevation above ULN as opposed to more than three times ULN) differs between studies. Furthermore, the selection of patients may have been biased, as some studies included all consecutive patients admitted while others did not enter severely unstable patients.

In all randomized trials, a large proportion of patients in the conservative arm eventually underwent revascularization ('crossover') such that the true benefit of revascularization is underestimated.[316] When comparing the relative mortality benefit between routine and selective revascularization strategies with the actual difference in the revascularization rates between arms, a linear relationship emerges: the greater the difference in the rate of revascularization, the greater the benefit on mortality (*Figure 9*).

Timing of invasiveness

With the exception of indications for emergency angiography and revascularization, controversy remains as to the optimal timing between hospital admission, initiation of medical therapy, and invasive evaluation. In 410 consecutive, high-risk patients with either ST-segment depression (65%) or elevated cTnT (67%) enrolled in the ISAR-COOL trial, deferral of intervention did not improve outcome.[317] On the contrary, patients randomized to immediate PCI (on average 2.4 h after admission) had a lower incidence of death or MI at 30 days than patients randomized to deferred PCI (86 h after admission and medical therapy) (5.9 vs. 11.6%, RR 1.96, 95% CI 1.01–3.82, $P = 0.04$). Likewise, no early hazard was observed in TACTICS-TIMI-18 (mean delay for PCI was 22 h) with upstream treatment with GP IIb/IIIa inhibitors.[73]

At variance with these findings, early routine invasive care in the ICTUS trial within 48 h of randomization in 56% and during initial hospitalization in 76% of cases was associated with an excess of MI (15.0 vs. 10.0%, RR 1.5, 95% CI 1.10–2.04, $P = 0.005$). Expedited catheterization was also associated with worse outcome in FRISC-2 as well as in the GRACE and CRUSADE registry.[318–320]

Accordingly, currently available evidence does not mandate a systematic approach of immediate angiography

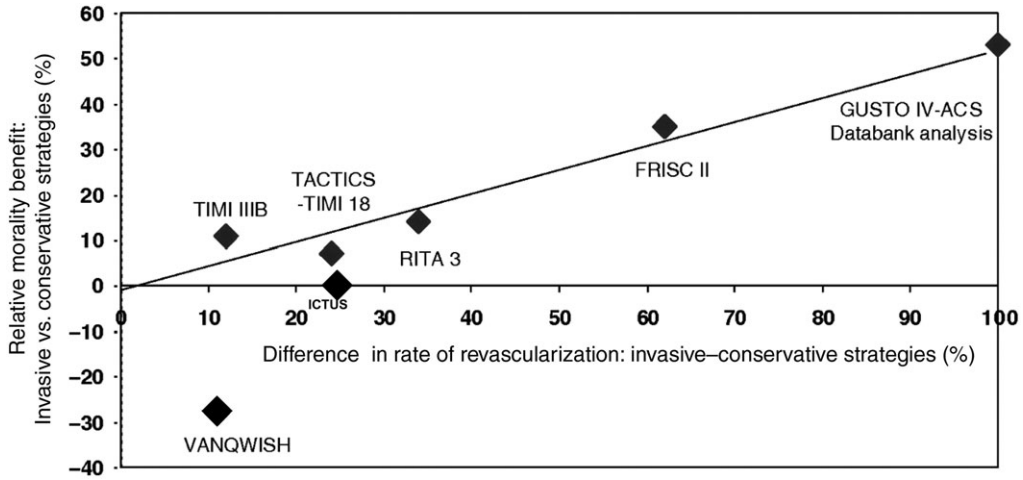

Figure 9 The ability to demonstrate relative mortality benefit with the revascularization strategy depends on the gradient in rates of revascularization between both randomization arms. Modified after Cannon *et al.*[316]

in NSTE-ACS patients stabilized with a contemporary pharmacological approach. Likewise, routine practice of immediate transfer of stabilized patients admitted in hospitals without onsite catheterization facilities is not mandatory, but should be organized within 72 h.

5.4.3 Percutaneous coronary intervention

Outcome after PCI in NSTE-ACS has been markedly improved with the use of intracoronary stenting and contemporary antithrombotic and antiplatelet therapy. The risk of bleeding complications should be balanced against the severity of ischaemia and the patient's risk profile. The choice of access site depends on operator expertise and local preference. Non-pharmacological strategies to reduce access site bleeding complications include the use of closure devices and the radial approach. The femoral approach is preferred in haemodynamically compromised patients to permit the use of intra-aortic balloon counterpulsation. As for all patients undergoing PCI, stent implantation in this setting helps to reduce the threat of abrupt closure and restenosis. The safety and efficacy of DES has not been prospectively tested in this specific population, although patients with NSTE-ACS represent up to 50% of patients included in most PCI trials. The approved DES appear to be equally effective in reducing restenosis in this setting as shown from subgroup analyses of randomized trials and real-world data.[321] Although the incidence of (sub)acute stent thrombosis is higher in NSTE-ACS patients, when compared with stable patients undergoing PCI, the use of DES does not seem to portend a higher risk of (sub)acute stent thrombosis in this specific setting.[287] In view of the potentially severe consequences of acute or subacute stent thrombosis, it is advisable to use a bare metal stent (BMS) in patients scheduled to undergo extra-cardiac interventions or surgery that will require interruption of clopidogrel within the first year after stent implantation.[322,323] This strategy should also be considered in patients requiring long-term VKA treatment. In addition, doubts have been cast on the risk of stent thrombosis and long-term safety of DES in terms of risk of death and MI, particularly when used off-label in complex situations.[324] Recent data suggest that dual antiplatelet therapy should be maintained for 1 year in the case of DES implantation irrespective of the active drug (sirolimus or paclitaxel).[325,326] As long as the concerns have not been addressed and the situation has not been completely clarified, the choice between the use of BMS or DES should be based on an individual assessment of benefit vs. potential risk.[325,326]

The main issue with PCI for NSTE-ACS remains the relatively high incidence of peri-procedural MI, up to 10% in the ICTUS trial.[314] The use of antiplatelet therapy has significantly reduced the incidence of peri-procedural MI.[327] However, embolization of debris or plaque fragments cannot be entirely prevented by state-of-the-art antithrombotic and antiplatelet adjunctive therapy.[328] A wide variety of filter and/or distal protection devices have been tested but failed to improve clinical outcome, with the exception of the subset of saphenous vein graft interventions.[329]

Currently, there are no outcome data supporting routine PCI in non-significant culprit or non-culprit coronary obstructions, as perceived by angiography, even with the use of DES ('plaque sealing').[301]

5.4.4 Coronary artery bypass graft

The proportion of patients with NSTE-ACS undergoing bypass surgery during initial hospitalization is about 10%.[314] It is important to consider the risk of bleeding complications in patients who undergo bypass surgery, although initially treated with aggressive antiplatelet treatment.[330,331] Overall, pre-treatment with a triple or even dual antiplatelet regimen should be considered as only a relative contraindication to early bypass surgery but does require specific surgical measures to minimize bleeding and platelet transfusions (see sections 5.3.3 Glycoprotein IIb/IIIa receptor inhibitors and 6.2 Thrombocytopenia).

5.4.5 Respective indications for percutaneous coronary intervention or coronary artery bypass graft

With the exception of an urgent procedure, the choice of revascularization technique in NSTE-ACS is the same as for elective revascularization procedures. From the randomized controlled trials comparing multivessel-stented PCI with bypass surgery, there was no interaction between the presence of NSTE-ACS, treatment strategy, and outcome.[331,332]

In patients with multivessel disease, all significant stenoses can be treated at once. A staged procedure may be considered, with immediate PCI of the culprit lesion and subsequent reassessment of the need for treatment of other lesions.

Recommendations for invasive evaluation and revascularization (see also section 8 Management strategies).

- **Urgent coronary angiography is recommended in patients with refractory or recurrent angina associated with dynamic ST-deviation, heart failure, life-threatening arrhythmias, or haemodynamic instability (I-C).**
- **Early (<72 h) coronary angiography followed by revascularization (PCI or CABG) in patients with intermediate to high-risk features is recommended (I-A).**
- **Routine invasive evaluation of patients without intermediate to high-risk features is not recommended (III-C), but non-invasive assessment of inducible ischaemia is advised (I-C).**
- **PCI of non-significant lesions is not recommended (III-C).**
- **After critical evaluation of the risk–benefit ratio, and depending on known co-morbidities and potential need for non-cardiac surgery in the short/medium term (e.g. planned intervention or other conditions) requiring temporary withdrawal of dual antiplatelet therapy, consideration should be given to the type of stent to be implanted (BMS or DES) (I-C).**

5.5 Long-term management

Patients with NSTE-ACS after the initial phase carry a high risk of recurrence of ischaemic events. Therefore, active secondary prevention is an essential element of long-term management. Several measures and therapies have been proven to be effective in reducing the risk of recurrence of events after NSTE-ACS either in clinical randomized trials or in observational studies and registries. However, several registries have shown that these lifestyle measures and drug therapies are underused. The role of the physician is to make sure that NSTE-ACS patients receive the appropriate therapy and lifestyle counselling in order to improve long-term outcome. It is beyond the scope of this document to review in detail all the measures and treatments that should be implemented for secondary prevention, but emphasis will be placed on those of paramount importance. Detailed recommendations on secondary prevention have been extensively described in other guidelines.[333–335]

5.5.1 Lifestyle

Several lifestyle interventions, described extensively in other reports, have been proven effective in reducing long-term risk of recurrence of events in patients with CAD, including NSTE-ACS.[333–336]

Smoking cessation is difficult to achieve in the long-term. Smoking resumption is frequent. Active counselling, in addition to adjunctive drug interventions, such as nicotine replacement and bupropione, is necessary.[333–335]

Regular physical activity must be encouraged. Thirty minutes of moderate intensity aerobic activity, if possible every day, or at least five times per week, is recommended. A medically supervised programme for high-risk patients may be necessary.[333–335]

Healthy diet based on low salt intake with reduced intake of saturated fats is essential. Encourage regular intake of fruit and vegetables. Moderate alcohol consumption may be beneficial.[337]

5.5.2 Weight reduction

Weight reduction in obese and overweight patients has to be encouraged. Return to physical activity can help to facilitate weight loss. Significant weight reduction is difficult to achieve, and, to date, no pharmacotherapy can firmly be recommended, although some specific drugs interacting with the endocannabinoid system have been shown to lead to sustained weight loss with minimal side effects.[338,339] Weight reduction has a favourable impact on lipid profile and glycaemic control. The theoretical goal is to achieve a body mass index (BMI) <25 kg/m^2 or a waist circumference <102 cm in men and <88 cm in women. Whereas these are the long-term goals, an initial weight loss of 10% from baseline is a first step. Further weight reduction can be attempted if the initial 10% weight loss is successfully achieved and maintained.

5.5.3 Blood pressure control

The goal is to achieve blood pressure $<140/90$ mmHg in non-diabetic patients and $<130/80$ mmHg in patients with diabetes or chronic renal dysfunction. Lifestyle interventions are an important means of achieving blood pressure control, particularly physical activity, in addition to weight loss and pharmacotherapy.[333–335]

5.5.4 Management of diabetes

Glycaemic balance abnormalities (impaired fasting glucose level, impaired glucose tolerance, or abnormal fasting glucose level) should be actively searched for in every patient with proven NSTE-ACS. In patients with established diabetes, the aim is to achieve HbA1c levels $\leq$6.5%. Counselling with endocrinologists is advisable. Lifestyle measures, in addition to weight loss in obese patients, and adapted pharmacotherapy are of great importance. In patients with impaired fasting glucose level or impaired glucose tolerance, no specific treatment is so far recommended except for lifestyle changes.[340]

5.5.5 Interventions on lipid profile

Interventions on low-density lipoprotein (LDLc) and high-density lipoprotein (HDLc) cholesterol as well as triglycerides are an important component of long-term management of NSTE-ACS. Most of the evidence has been obtained in the field of LDLc reduction, which is best achieved with statins or with a combination of statins and other lipid-lowering agents. Other interventions to correct low HDLc or high triglycerides might be necessary in some patients, although the impact of these measures on long-term outcome is less well established.

Statins

Long-term statin therapy improves outcome for all forms of CAD, after NSTE-ACS or in patients with chronic manifestations of CAD.[341–344] This beneficial effect was shown in all subgroups, including men and women, the elderly, smokers,

diabetic patients, hypertensive patients, or patients with chronic kidney disease (CKD). The recent guidelines recommend combining dietary interventions with pharmacotherapy by statins, or a combination of statins with other lipid-lowering agents, to reduce LDLc to <100 mg/dL (<2.6 mmol/L). However, two aspects of LDLc reduction have to be discussed specifically, namely early prescription of statins at the acute phase of NSTE-ACS and the impact of aggressive lipid-lowering therapy, to achieve LDLc levels <70 mg/dL (<1.81 mmol/L).[333–335]

The rationale behind the prompt initiation of statin therapy after NSTE-ACS includes the possibility of plaque stabilization, anti-inflammatory effects, and restoration of endothelial function. Moreover, an NSTE-ACS may serve as an impetus for the initiation and maintenance of long-term therapy, whereas in the chronic phase, treatment may be received and pursued less vigilantly.

So far little or no benefit of statins initiated soon after the acute phase has been reported in trials, registries, meta-analyses, and *post hoc* analyses of NSTE-ACS studies.[14,345–349] More recent randomized trials specifically addressing this issue have shown that early aggressive lipid-lowering therapy led to a swift and important drop in LDLc, but apparently without major impact on short-term outcome.[350–352] A more recent meta-analysis including 13 trials and 17 963 patients revealed that early initiation of statin therapy was safe and had a positive impact on outcome, with beneficial effects on the rate of death and cardiovascular events over 2 years of follow-up (HR 0.81, 95% CI, 0.77–0.87, $P < 0.001$). Survival benefit was apparent only after 4 months, achieving statistical significance by 12 months.[353]

The potential benefit of aggressive when compared with moderate lipid-lowering therapy among a wide spectrum of NSTE-ACS patients was assessed in PROVE-IT.[354] This trial enrolled STE-ACS and NSTE-ACS patients with a total cholesterol level <240 mg/dL (6.2 mmol/L). Treatment with pravastatin 40 mg or atorvastatin 80 mg was initiated within 10 days of admission, and follow-up was continued over 18–36 months. By the end of the study, the levels of LDLc were reduced by 21% in the pravastatin arm [to a median level of 95 mg/dL (2.46 mmol/L)], when compared with a 49% reduction in the atorvastatin arm [to a median level of 62 mg/dL (1.6 mmol/L)], with most of the treatment effect achieved within 30 days. The primary composite endpoint (death, MI, unstable angina requiring rehospitalization, revascularization, or stroke) was reduced by 16% in the intensive compared with the non-intensive therapy arm. The difference in outcomes was already apparent within 30 days of randomization. Patients who achieved levels of LDLc <70 mg/dL (1.81 mmolL) had lower event rates than those with higher levels. A similar difference was observed between those who achieved hsCRP levels <2 mg/L after statin therapy when compared with those with levels >2 mg/L. Thus, intensive lipid-lowering therapy, associated with reductions in the levels of LDLc or hsCRP to values of <70 mg/dL (1.81 mmol/L) or <2 mg/L, respectively, leads to improved outcome after ACS.

Other lipid-lowering agents

Limited data are available about the benefit of fibrates, nicotinic acid, and ezetimibe in the setting of NSTE-ACS. A combination of statin and ezetimibe has shown considerable capacity to reduce LDLc and is being tested vs. conventional statin therapy in a large clinical trial in ACS patients (IMPROVE-IT). Low HDLc has been shown to be a risk factor for CAD and death from CAD. Epidemiological studies suggest also that raising HDLc levels may prevent the development of CAD. Each increase in baseline HDLc of 1 mg/dL (0.03 mmol/L) is associated with a 6% decrease in the risk of death from CAD or MI.[355,356] Nicotinic acid has been shown to be able to raise HDLc levels significantly. Evidence from old or small-size studies suggests that raising HDLc may lead to a significant risk reduction for coronary events.[357] A large clinical trial exploring this therapeutic possibility is ongoing. It will assess the potential of an association of statin plus nicotinic acid (niacin) to reduce the rate of cardiovascular events when compared with statin alone in a population of patients with established atherosclerotic disease and atherogenic lipid profile (AIM-HIGH study). Other therapeutic approaches aiming at raising HDLc have failed.[358]

In addition, chronic aerobic exercise was shown to increase HDLc and should be advocated whenever possible[359] (see section 5.6 Rehabilitation and return to physical activity).

Recommendations for lipid-lowering therapy

- **Statins are recommended for all NSTE-ACS patients (in the absence of contraindications), irrespective of cholesterol levels, initiated early (within 1—4 days) after admission, with the aim of achieving LDLc levels <100 mg/dL (<2.6 mmol/L) (I-B).**
- **Intensive lipid-lowering therapy with target LDLc levels <70 mg/dL (<1.81 mmol/L) initiated within 10 days after admission is advisable (IIa-B).**

5.5.6 Antiplatelet agents and anticoagulants

See sections 5.2 Anticoagulants and 5.3 Antiplatelet agents.

5.5.7 Beta-blockers

Beta-blocker therapy should be initiated in all patients and maintained indefinitely in the case of reduced LV function, with or without symptoms of heart failure, unless formal contraindications exist. In other patients, beta-blockers may be useful, but evidence of their long-term benefit is not established. Meta-analysis and registry data have shown that long-term treatment with beta-blockers in patients suffering from NSTE-ACS may lead to a significant risk reduction for death.[360]

Recommendations for use of beta-blockers

- **Beta-blockers should be given to all patients with reduced LV function (I-A).**

5.5.8 Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors (ACE inhibitors) are beneficial in reducing remodelling and improving survival in patients with reduced LV systolic function (with or without clinical heart failure) after MI.[361–363] Therefore, their initial use in the context of ACS was limited to patients with reduced LV systolic function. Subsequently, several trials suggested an anti-atherogenic effect of ACE inhibitors in patients with risk factors for atherosclerosis or

established atherosclerotic disease, irrespective of LV function and beyond their effect on blood pressure.[268,364,365] Meta-analyses of major trials carried out with the main objective of demonstrating the anti-atherogenic effect of ACE inhibitors have shown a 14% risk reduction for death at 4 years with ACE inhibitors in this setting.[366–368] To date, only ramipril and perindopril have shown efficacy. Prescription of ACE inhibitors in this indication should be restricted to agents and doses of proven efficacy.[369] The applicability of these findings, although documented in the context of stable CAD, has been extended to all patients with NSTE-ACS. For patients with reduced LV systolic function, the use of an oral ACE inhibitor should be initiated within the first day after admission, in the absence of contraindications. For other patients, treatment should be initiated during the course of hospitalization.

Recommendations for the use of ACE inhibitors

- **ACE inhibitors are indicated long-term in all patients with LVEF ≤40% and in patients with diabetes, hypertension, or CKD, unless contraindicated (I-A).**
- **ACE inhibitors should be considered for all other patients to prevent recurrence of ischaemic events (IIa-B). Agents and doses of proven efficacy are recommended (IIa-C).**

5.5.9 Angiotensin-2 receptor blockers

Recent trials have clearly documented that angiotensin-2 receptor blockers (ARBs) may be used in acute MI patients with reduced LV systolic function.[370,371] They can be used instead of ACE inhibitors or in combination with ACE inhibitors. In contrast to ACE inhibitors, there are no firm data regarding their use as anti-atherogenic agents. For patients with reduced LV systolic function, their use should be initiated within the first day after admission, in the absence of contraindications.

Recommendations for the use of angiotensin receptor blockers

- **ARBs should be considered in patients who are intolerant to ACE inhibitors and/or who have heart failure or MI with LVEF <40% (I-B).**

5.5.10 Aldosterone receptor antagonists

Spironolactone has been shown to be beneficial in the treatment of patients with LV systolic dysfunction and chronic, severe heart failure (NYHA classes III and IV).[372] During chronic use of spironolactone, a minority of patients develop gynaecomastia related to binding of the drug to progesterone receptors. Eplerenone is a new aldosterone receptor antagonist with 1000-fold less affinity for the progesterone receptor than spironolactone. Eplerenone has been evaluated in a randomized, placebo-controlled trial of patients after MI (with or without ST-elevation) and LV systolic dysfunction with either symptomatic heart failure or diabetes mellitus.[373] The acute use of oral eplerenone, in addition to optimal medical and invasive therapy, was associated with improved outcome (morbidity and mortality). Aldosterone receptor antagonists should not be used in the case of severe renal failure [serum creatinine >2.5 mg/dL (221 μmol/L) for men and >2.0 mg/dL (177 μmol/L) for women], hyperkalaemia, or inability to perform serial examinations to monitor potassium levels.

Recommendations for aldosterone receptor antagonists

- **Aldosterone blockade should be considered in patients after MI who are already treated with ACE inhibitors and beta-blockers and who have an LVEF <40% and either diabetes or heart failure, without significant renal dysfunction or hyperkalaemia (I-B).**

5.6 Rehabilitation and return to physical activity

After NSTE-ACS, an assessment of functional capacity and the ability to carry out daily activities or work is needed. This ability is influenced, among other factors, by cardiac function, extent of CAD, the presence and magnitude of residual ischaemia, and the propensity for cardiac arrhythmias. Every patient after NSTE-ACS should undergo an ECG-guided exercise test (or another non-invasive test if exercise cannot be performed or if the ECG is difficult to interpret) within 4–7 weeks after discharge.[374–376] As a rule of thumb, physical activity that includes leisure, professional, and sexual activities should be resumed at 50% of the maximal exercise capacity, expressed as metabolic equivalents (METS), and gradually increased over time. A patient with preserved LV systolic function (EF > 0.40) and without inducible ischaemia or arrhythmias in a stress test can return to work. If the work is in an office environment, an 8 h day can be resumed. If the work is manual, the workload should not exceed 50% of the maximal exercise capacity assessed in the stress test. The workday should not exceed 4 h in the first month, with monthly 2 h increments thereafter. A patient with moderate LV systolic dysfunction (EF between 0.30 and 0.40) or with mild ischaemia in a stress test can resume office work, but should be limited to static manual work. A patient with severe LV systolic dysfunction (EF < 0.30) or significant ischaemia in a stress test can perform office work, provided exercise capacity is >5 METS without symptoms. Otherwise, the patient should refrain from working. As for other physical activities, including sexual activity, the non-invasive test can also guide the physician's advice. In general, a patient with an exercise capacity >5 METS can engage in routine sexual activity. The physician should inform the patient about the timing of resumption of physical and sexual activity, taking into account the above-mentioned cardiac parameters as well as other factors such as the status of the arterial puncture site in a patient after cardiac catheterization. In all cases, close collaboration between the cardiologist and the primary physician is necessary.

Recommendations for rehabilitation and return to physical activity

- **After NSTE-ACS, assessment of functional capacity is recommended (I-C).**
- **Every patient after NSTE-ACS should undergo an ECG-guided exercise test (if technically feasible) or an equivalent non-invasive test for ischaemia, within 4–7 weeks after discharge (IIa-C).**
- **On the basis of cardiovascular status and the results of functional physical capacity assessment, patients should be informed about the timing of resumption and the recommended level of physical activity, including leisure, work, and sexual activities (I-C).**

6. Complications and their management

6.1 Bleeding complications

Bleeding complications are the most frequent non-ischaemic complications observed in the management of NSTE-ACS. Several definitions, including clinical aspects of bleeding (location and impact on haemodynamics) and/or need for blood transfusion as well as magnitude of haemoglobin drop, are used to grade bleeding severity (*Table 7*).[377] Bleeding is graded as severe, life threatening, major, or minor. However, the same term may represent a different bleeding severity depending on the definition used. This implies that different bleeding complication rates may be observed within the same study population depending on whether different definitions are used to grade severity of bleeding. This also implies that the frequency of bleeding may be difficult to compare across studies.

Taking into account all these limitations about bleeding definition, it is estimated that the frequency of major bleeding ranges from 2 to 8% across the spectrum of NSTE-ACS and depends greatly on the type of treatment used, particularly the type and dose of antithrombotic and antiplatelet therapies, invasive procedures, and other factors (*Table 8*).[377,378] In randomized trials, the reported frequency ranges from <2% in OASIS-2, PRISM, and PURSUIT to >8% in SYNERGY.[164,178,236] Figures from registries are generally higher than those in clinical trials. In the CRUSADE registry, blood transfusion used as a surrogate marker of major bleeding was used in more than 15% of patients,[252] possibly reflecting a higher rate of invasive strategy used in the USA. In the GRACE registry, data from 24 045 patients revealed that the overall incidence of major bleeding was 3.9% in patients with STE-ACS and 4.7% in patients with NSTE-ACS, and 2.3% in patients with unstable angina.[379]

6.1.1 Predictors of bleeding risk

The independent predictors of major bleeding in the GRACE registry were advanced age (OR 1.22 per 10-year increase, $P = 0.0002$), female sex (OR 1.36, $P = 0.0116$), history of bleeding (OR 2.18, $P = 0.014$), use of PCI (OR 1.63, $P = 0.0005$), history of renal insufficiency (OR 1.53, $P = 0.0062$), and use of GP IIb/IIIa inhibitors (OR 1.86, $P = 0.0001$), among others (*Table 8*).[379] Excessive doses of drugs, especially in women, elderly patients, or those with renal failure, also increase the risk of bleeding.[168] Renal dysfunction plays a critical role. Bleeding risk exponentially increases with decreasing CrCl.[176,382] A steep increase in bleeding risk is already observed for CrCl levels below 60 mL/min. Better definition of the appropriate dose of antithrombotic agents to be given according to the level of renal dysfunction is needed.

In addition, the same baseline characteristics, namely age, gender, and renal dysfunction, influence the risk of both death and bleeding. In the GRACE registry, the increase in the risk of bleeding with declining renal function parallels the increase in the risk of death as shown in *Figure 10*. This implies that caution has to be exerted with high-risk patients when deciding on aggressive invasive and/or anticoagulant/antiplatelet treatments. Particular attention has to be paid to the selection of the doses of anticoagulants in CKD patients.

According to recent reports, baseline haemoglobin/haematocrit has also been shown to be an independent predictor of bleeding complications, both procedure-related and non-procedure-related bleeds.[383]

Table 7 Elements of the TIMI[380] and GUSTO[381] bleeding definitions

TIMI bleeding classification[380]	
Major	Intracranial haemorrhage or clinically overt bleeding (including imaging) ≥5 g/dL decrease in the haemoglobin concentration
Minor	Clinically overt bleeding (including imaging) with 3 to <5 g/dL decrease in the haemoglobin concentration
Minimal	Clinically overt bleeding (including imaging) with a <3 g/dL decrease in the haemoglobin concentration
GUSTO bleeding classification[381]	
Severe or life threatening	Either intracranial haemorrhage or bleeding that causes haemodynamic compromise and requires intervention
Moderate	Bleeding that requires blood transfusion but does not result in haemodynamic compromise
Mild	Bleeding that does not meet criteria for either severe or moderate bleeding

All TIMI definitions take into account blood transfusions, such that haemoglobin values are adjusted by 1 g/dL for each unit of packed red blood transfused.

Table 8 Multivariate model for major bleeding in patients with non-ST-elevation myocardial infarction[379]

Variable	Adjusted OR	95% CI	*P*-value
Age (per 10-year increase)	1.22	1.10–1.35	0.0002
Female sex	1.36	1.07–1.73	0.0116
History of renal insufficiency	1.53	1.13–2.08	0.0062
History of bleeding	2.18	1.14–4.08	0.014
Mean arterial pressure (per 20 mmHg decrease)	1.14	1.02–1.27	0.019
Diuretics	1.91	1.46–2.49	<0.0001
LMWH only	0.68	0.50–0.92	0.012
LMWH and UFH[a]	0.72	0.52–0.98	0.035
GP IIb/IIIa inhibitors only	1.86	1.43–2.43	<0.0001
Thrombolytics and GP IIb/IIIa inhibitors	4.19	1.68–10.4	0.002
IV inotropic agents	1.88	1.35–2.62	0.0002
Right-heart catheterization	2.01	1.38–2.91	0.0003

[a]Referent groups: male gender; UFH for LMWH only, both LMWH and UFH, and neither LMWH nor UFH; neither thrombolytics nor GP IIb/IIIa inhibitors for thrombolytics only, GP IIb/IIIa inhibitors only, and both thrombolytics and GP IIb/IIIa inhibitors; no for other variables. Hosmer–Lemeshow goodness-of-fit test $P = 0.70$; *C*-statistic = 0.73.

6.1.2 Impact of bleeding on prognosis

Bleeding has a strong impact on prognosis. Major bleeding in the GRACE registry was associated with an increased risk of hospital death (OR 1.64, 95% CI 1.18–2.28, $P < 0.001$).[379] According to several reports including a large meta-analysis

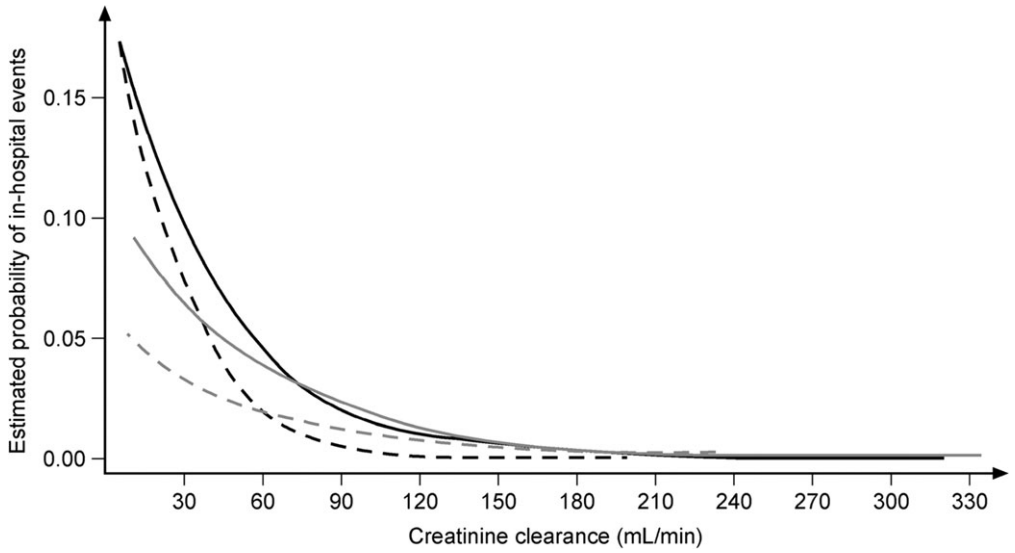

Figure 10 Kernel curves of in-hospital mortality (black) or bleeding (grey) according to the level of creatinine clearance in patients treated with unfractionated heparin (plain curves) and low molecular weight heparin (dashed curves). Reproduced with permission from Collet *et al.*[382]

of registries and trials, including more than 30 000 patients, major bleeding was shown to be associated with a four-fold increase in the risk of death, a five-fold increase in risk of recurrent MI, and a three-fold increase in risk of stroke at 30 days.[377–379,384] Pooled data from four multicentre randomized clinical trials of patients with ACS, totalling 26 452 patients, documented a stepwise increase in the risk of death at 30 days and 6 months, according to the severity of bleeding. At 1 month, the hazard ratios for death were 1.6, 2.7, and 10.6 for mild, moderate, and severe bleeding, respectively (GUSTO definition), and at 6 months, the hazard ratios were 1.4, 2.1, and 7.5, respectively.[384] The same impact on prognosis has been shown to exist for both procedure-related and non-procedure-related bleeding, as well as in other settings, such as PCI.[384] In the OASIS-5 trial, at 30 days, the risk of ischaemic events was strongly influenced by the occurrence of major bleeding. The rate of death was 12.9 vs. 2.8%, the risk of MI 13.9 vs. 3.6%, and the risk of stroke 3.6 vs. 0.8% for patients who suffered a major bleeding vs. no bleeding, respectively. The same is also true for minor bleeding, although the increase in risk is of lesser magnitude.[176] Beyond 30 days, the risk is lower, but still present, as modern treatment of NSTE-ACS includes the use of dual antiplatelet therapy for 12 months, which has been shown to result in a higher long-term risk of bleeding.[378,385]

Several factors contribute to the worse outcome associated with bleeding. Renal failure, as well as haemodynamic consequences of the bleed, and potential deleterious effects of transfusions may account for the higher risk. In addition, bleeding triggers a pro-thrombotic and pro-inflammatory state. The main component of the risk is probably the need to discontinue antiplatelet and antithrombotic drugs, which can lead to an increased risk of events through a rebound phenomenon. However, as the risk factors for both bleeding and ischaemic events are mostly the same, the higher risk patients are exposed to both risks, and also submitted to the most aggressive drug and procedure strategies. Hence, occurrence of bleeding may simply be a precipitating factor for worse outcome in a frail population.

6.1.3 Management of bleeding complications

Prevention of bleeding has become a target as important as the prevention of ischaemic events. In the OASIS-5 trial, the difference in mortality between the two groups was almost entirely associated with the reduction in bleeding in the fondaparinux group. Therefore, risk assessment in patients with NSTE-ACS needs to address the risk of both thrombotic and bleeding complications. Prevention of bleeding encompasses the choice of safer drugs, appropriate dosage (taking into account age, gender, and CrCl), reduced duration of antithrombotic treatment, use of combination of antithrombotic and antiplatelet agents according to proven indications, as well as the choice of radial over femoral approach if angiography or PCI is being considered. In addition, if an invasive procedure is planned, unnecessary delays should be avoided, as this prolongs the duration during which the patient is at risk for bleeding.

Minor bleeding, unless persistent, does not require the interruption of active treatments. Major bleeding such as gastrointestinal, retro-peritoneal bleeding, intracranial haemorrhage, or severe blood loss requires the interruption and neutralization of both antiplatelet and antithrombotic treatment if bleeding cannot be controlled by appropriate interventions. It might not be necessary to interrupt antithrombotic/antiplatelet agents if complete control of the haemorrhage can be obtained with local treatment.[386] In clinical practice, the risk of interrupting antithrombotic and antiplatelet agents must be weighed against the risk of a thrombotic event, particularly if the patient has been submitted to revascularization and stent implantation. The risk of acute thrombotic events after interruption of antithrombotic/antiplatelet agents is maximum after 4–5 days, but persists for up to 30 days.[378]

UFH can be inhibited by an equimolar concentration of protamine sulfate, which neutralizes the factor-IIa activity. However, protamine sulfate has less or no impact on neutralization of factor-Xa activity achieved with LMWH or fondaparinux. In this situation, recombinant factor-VII has been recommended.[387] However, there is no firm evidence that this can control bleeding, and recent data show that the

use of recombinant factor-VIIa is associated with an increased risk of thrombotic complications.[387]

Antiplatelet activity is also difficult to reverse. Aspirin and clopidogrel are irreversible platelet inhibitors. Their action is slowly reversed by the continuous generation of new platelets (around 10–20% per day), so antiplatelet effects persist for 5–10 days after cessation of treatment. No compound was found to reverse significantly the pharmacological activity of clopidogrel. If prompt correction of prolonged bleeding time is required, platelet transfusion is the only possibility to reverse the effects of clopidogrel/aspirin. The recommended minimum dose in adults is $0.5–0.7 \times 10^{11}$ platelets per 7 kg of bodyweight. This is not based on firm evidence, but only on expert consensus.[388]

GP IIb/IIIa inhibitors have different pharmacological properties that are important to consider when evaluating the modalities for reversal. Because little free abciximab circulates in plasma, an infusion of platelets replenishes the number of viable GP IIb/IIIa receptors, and thus allows a return to normal haemostasis. However, although platelet administration may be beneficial in patients experiencing major bleeding with abciximab, no recommendations exist regarding the quantity required to reverse its antiplatelet effect. The situation is different with tirofiban or eptifibatide. As these drugs undergo significant renal elimination, the baseline platelet function of patients with normal renal function can be expected to return to normal within 4–8 h after infusion interruption. If immediate reversal of platelet inhibition is needed, platelet infusion alone may be insufficient because of the large amount of freely circulating molecules. Fibrinogen-containing plasma supplementation may help to restore platelet aggregation.[254,389]

Antiplatelet and/or antithrombotic agents cannot be re-introduced until strict control of the haemorrhage has been obtained for at least 24 h. In the case of peptic ulcer, re-introduction of antiplatelet therapy—whatever the drug or combination of drugs used—needs to be associated with proton pump inhibitors.

6.1.4 Impact of blood transfusion

Blood transfusion can be required to control anaemia and haemodynamic compromise. However, there is ongoing controversy about its real efficacy and safety in the context of NSTE-ACS. Blood transfusion has been shown to improve prognosis in elderly patients suffering from acute MI with haematocrit levels $<30\%$ and may possibly be useful for haematocrit levels in the range of 30–33%.[390] The utility of blood transfusion for higher values of haematocrit is not proven. In another report, blood transfusion improved 1-month outcome in STEMI patients, if given for baseline haemoglobin <12 g/dL.[391] However, in the same report, transfusion was associated with an increased risk of death, MI, and refractory ischaemia in NSTE-ACS. Similarly, blood transfusion was associated with poorer outcome, even after adjustment for baseline characteristics and in-hospital procedures, in a meta-analysis involving more than 24 000 ACS patients.[383] In a more recent meta-analysis, a 20% increase in mortality was reported in patients who received transfusions.[392]

Some small size randomized trials have tested the efficacy of transfusion in critically ill patients, vascular surgery, or patients with recent trauma, and showed that blood transfusion may have no effect on mortality, or even be associated with lower survival.[393–396] In two clinical trials, a restrictive blood transfusion strategy led to better results than a liberal one in terms of mortality and organ failure at 30 days in critically ill patients suffering from acute (including cardiac) conditions and treated in intensive care units. However, no significant difference in 30-day outcome was observed in cardiac patients. In these trials, blood transfusion was given for haemoglobin levels <7 g/dL, aiming at haemoglobin levels between 7 and 9 g/dL in the restrictive and between 10 and 12 g/dL in the liberal strategy.[394,395] Nonetheless, despite several studies, the correct haematocrit or haemoglobin levels to achieve after blood transfusion in patients with anaemia (with or without cardiovascular disease) have not yet been adequately defined.

It is not clearly understood why transfusion may be associated with adverse outcome. Alterations in erythrocyte, nitric oxide biology in stored blood, and high haemoglobin oxygen affinity due to a low rate of 2,3-diphosphoglyceric acid, leading to decreased oxygen delivery to tissues, have been put forward, as well as increases in inflammatory mediators.[397–399]

All in all, the information about the efficacy of and the indications for blood transfusion needs to be critically considered. In mild to moderate anaemia (haematocrit $>25\%$ or haemoglobin levels >8 g/dL), blood transfusion may be associated with increased risk of death at 30 days and should be avoided if anaemia is haemodynamically well tolerated. Below these haematocrit/haemoglobin levels, blood transfusion should be given.[383]

Recommendations for bleeding complications

- **Assessment of bleeding risk is an important component of the decision-making process. Bleeding risk is increased with higher or excessive doses of antithrombotic agents, length of treatment, combinations of several antithrombotic drugs, switch between different anticoagulant drugs, as well as with older age, reduced renal function, low body weight, female gender, baseline haemoglobin, and invasive procedures (I-B).**
- **Bleeding risk should be taken into account when deciding on a treatment strategy. Drugs, combination of drugs, and non-pharmacological procedures (vascular access) known to carry a reduced risk of bleeding should be preferred in patients at high risk of bleeding (I-B).**
- **Minor bleeding should preferably be managed without interruption of active treatments (I-C).**
- **Major bleeding requires interruption and/or neutralization of both anticoagulant and antiplatelet therapy, unless bleeding can be adequately controlled by specific haemostatic intervention (I-C).**
- **Blood transfusion may have deleterious effects on outcome and should therefore be considered individually, but withheld in haemodynamically stable patients with haematocrit >25% or haemoglobin level >8 g/L (I-C).**

6.2 Thrombocytopenia

Thrombocytopenia is defined as a decrease in platelet count to $<100\,000\ \mu L^{-1}$ or a drop of $>50\%$ from baseline platelet count. Thrombocytopenia is considered to be moderate if the platelet count is between 20 000 and 50 000 μL^{-1} and severe if it is less than 10 000 μL^{-1}.

6.2.1 Heparin-induced thrombocytopenia

Thrombocytopenia can occur during UFH or LMWH treatment, but has a different significance and potential for complications depending on whether or not it is immune-mediated.

Mild and transient decline in platelet count occurring 1–4 days after initiation of therapy is common and observed in up to 15% of UFH-treated patients. It is not immune-mediated and rarely leads to a severe reduction in platelet levels. It resolves spontaneously, despite continuation of UFH. Pseudo-thrombocytopenia is a laboratory artefact due to platelet clumping in EDTA-containing tubes and can be avoided by the use of citrate instead of EDTA for blood sampling.

The immune-mediated form of HIT is a serious complication that often leads to severe thrombo-embolic events. It is not dose-dependent, usually causes a severe drop in platelet levels (at least 50%), and typically appears 5–14 days after the start of UFH treatment,[400] but much earlier in patients with recent (within 3 months) UFH exposure.[401] Delayed-onset HIT occurring several days or weeks after the cessation of UFH treatment has also been described.[402] It is beyond the scope of this document to discuss the mechanisms and causes of HIT. When HIT is suspected, laboratory confirmation can be obtained with various tests, but treatment of HIT must be undertaken as soon as the diagnosis is suspected, without waiting for laboratory confirmation.

HIT must be suspected when there is a drop of $>$50% in platelet count or a decrease in platelet count to $<100\,000\ \mu L^{-1}$. Immediate interruption of UFH or LMWH is mandatory, as soon as HIT is suspected. Alternative antithrombotic therapy must be introduced, even in the absence of thrombotic complications. Heparinoids such as danaparoid sodium (Orgaran) may be used, although *in vitro* cross-reactions with UFH or LMWH have been observed, but apparently without causing thrombosis. The alternative is to use DTIs, such as argatroban, or hirudin or derivatives, which do not carry any risk of thrombocytopenia, and make it possible to have sustained and controllable antithrombotic activity, easily monitored by aPTT.[403] Fondaparinux (pentasaccharide) also has the potential to be used in this type of situation, since it has a potent antithrombotic effect, without any cross-reaction with platelets,[404] but is not approved in this indication.

6.2.2 Glycoprotein IIb/inhibitor-induced thrombocytopenia

Thrombocytopenia has been reported to occur at rates ranging from 0.5 to 5.6% in clinical trials of parenteral GP IIb/IIIa inhibitors, a rate comparable with that observed with UFH alone.[244,405–407] Abciximab more than doubles the incidence of severe thrombocytopenia in comparison with placebo. The risk is lower with eptifibatide (0.2% severe thrombocytopenia in PURSUIT)[235] or tirofiban. In the TARGET study, thrombocytopenia developed in 2.4% of the patients treated with abciximab and 0.5% of those treated with tirofiban ($P < 0.001$).[408] Again, it is beyond the scope of this document to discuss the mechanisms and causes of GP IIb/IIIa inhibitor-induced thrombocytopenia.

Severe and profound thrombocytopenia due to GP IIb/IIIa inhibitors may remain asymptomatic with only minor bleeding at the access site and minor oozing. Major bleeds are rare, but may be life threatening. It is recommended that all patients treated with GP IIb/IIIa inhibitors undergo platelet counts within 8 h of onset of drug infusion or in the case of bleeding. In the case of acute profound thrombocytopenia ($<10\,000\ \mu L^{-1}$), discontinuation of GP IIb/IIIa inhibitors as well as UFH or LMWH is recommended. Platelet transfusions are indicated in the case of bleeding. Fibrinogen supplementation with fresh–frozen plasma or cryoprecipitate either alone or in combination with platelet transfusion has also been advocated.[254]

After drug discontinuation, tirofiban-induced thrombocytopenia resolves after a mean of 2.1 days (range 1–6 days), whereas abciximab-induced thrombocytopenia resolves after a mean of 4.5 days (range 1–24 days). Thrombocytopenia induced by GP IIb/IIIa inhibitors is associated with worse outcome, including increased 30-day rates of bleeding, recurrent ischaemia, urgent revascularization, and death.[408]

Recommendations for thrombocyopenia

- **Significant thrombocytopenia ($<100\,000\ \mu L^{-1}$ or >50% drop in platelet count) occurring during treatment with GP IIb/IIIa inhibitors and/or heparin (LMWH or UFH) requires the immediate interruption of these drugs (I-C).**
- **Severe thrombocytopenia ($<10\,000\ \mu L^{-1}$) induced by GP IIb/IIIa inhibitors requires platelet transfusion with or without fibrinogen supplementation with fresh–frozen plasma or cryoprecipitate in the case of bleeding (I-C).**
- **Interruption of heparin (UFH or LMWH) is warranted in the case of documented or suspected HIT. In the case of thrombotic complications, anticoagulation can be achieved with a DTI (I-C).**
- **Prevention of HIT can be achieved with the use of anticoagulants devoid of risk of HIT, such as fondaparinux or bivalirudin, or by brief prescription of heparin (UFH or LMWH) in cases where these compounds are chosen as anticoagulant (I-B).**

7. Special populations and conditions

Some special populations deserve additional considerations for the management of NSTE-ACS. The following groups of patients are at substantial risk of adverse cardiac events or merit alternative therapeutic strategies. Although discussed separately, there is great overlap between the subgroups, i.e. many elderly patients are women and/or have renal dysfunction, diabetes, or anaemia. In this section, some considerations for these populations will be provided. Comprehensive reviews can be found elsewhere.[391,409–412]

7.1 The elderly

There is a substantial increase of elderly patients with CAD worldwide. Although there is no common definition of what represents elderly, either age $>$65 or $>$75 years are the two most common definitions. Although such dichotomous cut-offs are in general helpful, it should be recognized that the risk for mortality increases in a continuous curvilinear manner with each decade after age 50. Thus, the risk of cardiac adverse events such as death, stroke, MI, and heart failure is substantial among patients over the age of 75 with CAD. In the USA, persons over the age of

75 represent only 6% of the population, but account for 37% of all admissions for acute MI and 60% of all MI-related deaths.[413]

In Europe, the rate of patients >75 years old in registries of NSTE-ACS varies from 27 to 34.1%.[414,415] In patients >75 years old, the death rate is at least twice as high as in patients aged <75.[415] Despite the high proportion of elderly patients in registries, the elderly (>75 years) represent less than 10% of all patients in recent trials.[416] Furthermore, it has recently been shown that the elderly enrolled into NSTE-ACS trials also had substantially fewer co-morbid illnesses, particularly renal and heart failure, compared with the general population of elderly patients at the same institutions.[417] Thus, the applicability of findings from the trials that enrolled predominantly younger patients to an older and generally sicker population is questionable. On the basis of these observations, the risk–benefit ratio with any therapeutic strategy should be determined in the elderly, with special consideration for estimated life expectancy, patient wishes, and co-morbidities before invasive strategies and therapy that increase bleeding risk and/or risk of renal failure are applied.

7.1.1 Early diagnostic evaluation in the elderly

The clinical presentation of NSTE-ACS in the elderly can sometimes be difficult. The elderly are more likely to have mild symptoms and frequently have atypical symptoms or no chest pain. Common symptoms in the elderly are shortness of breath (49%), diaphoresis (26%), nausea–vomiting (24%), and syncope (19%).[48,49] The ECG among elderly patients with MI is also more likely to be non-diagnostic, without either ST-elevation or ST-depression in as many as 43%. Presentation with overt heart failure is also common, with up to 41% having symptoms of heart failure on admission to hospital.[418] Thus, among elderly patients presenting with non-specific symptoms, a high level of suspicion for NSTE-ACS should be entertained, even among patients with non-specific ECG findings.

7.1.2 Therapeutic considerations

The bleeding risk linked to LMWH is higher in elderly patients.[379,419] Although there has been a suggestion of a greater therapeutic effect with LMWH compared with UFH, this has not held up after multivariable modelling has adjusted for important baseline characteristics in the elderly vs. younger patients.[419] In OASIS-5, patients over 65 years of age suffered a higher rate of bleeding complications than younger patients, but with a significantly lower risk of bleeding with fondaparinux than with enoxaparin.[176] The meta-analysis of all trials with GP IIb/IIIa inhibitors showed that the therapeutic benefit appears to be less for older patients (OR 0.86 in <60 years vs. 0.96 in >70 years, *P*-value for interaction 0.10), while major bleeding also appeared to be about 60% higher.[229] However, the CURE trial documented a more consistent benefit: about 2% absolute reduction of death, MI, and stroke among elderly patients (>65 years) receiving clopidogrel and aspirin vs. aspirin alone.[167] Attention to the risk–benefit ratio of these therapies needs to be individualized in the elderly patient depending on the treatment and co-morbid illness profiles. Attention has to be paid to the dosage of antithrombotic agents, since in the CRUSADE registry, it was shown that excessive dosing was frequently observed in elderly patients and led to a significantly higher rate of bleeding.[168]

Elderly patients are substantially less likely to receive an invasive strategy after NSTE-ACS, and adjusted observational analysis has failed to show any early survival benefit compared with younger patients.[252] However, a subgroup analysis of one of the largest randomized trials of invasive vs. conservative strategies, using current interventional strategies (stents and GP IIb/IIIa inhibitors), showed a substantial treatment effect in favour of an invasive strategy[420] (*Figure 11*). Among patients >75 years old, there was a 56% relative reduction in death and non-fatal MI. This was offset by a three-fold higher risk of in-hospital major bleeding. Although the FRISC-2 trial did not enrol patients over the age of 75, the greatest reduction in death and non-fatal MI was observed among patients over the age of 65 during a 5-year follow-up [24.4 vs. 31.5% (OR 0.77, CI 0.64–0.93) invasive vs. non-invasive strategy].[122] Taken together, these findings suggest that the invasive strategy is associated with an overall better long-term outcome. However, the risk–benefit ratio needs to be carefully evaluated in elderly patients considered for routine invasive care. It becomes increasingly important with advancing age when evaluating elderly patients to select strategies and/or drugs to minimize the risk of bleeding and adverse outcome. CrCl should always be calculated in elderly patients in order to adapt dosage of drugs with exclusive or substantial renal elimination (see section 7.4 Chronic kidney disease).

Recommendations for the elderly

- **Elderly patients (>75 years old) often have atypical symptoms. Active screening for NSTE-ACS should be initiated at lower levels of suspicion than among younger (<75 years old) patients (I-C).**
- **Treatment decisions in the elderly should be tailored according to estimated life expectancy, patient wishes, and co-morbidities to minimize risk and improve morbidity and mortality outcomes in this frail but high-risk population (I-C).**
- **Elderly patients should be considered for routine early invasive strategy, after careful evaluation of their inherent raised risk of procedure-related complications, especially during CABG (I-B).**

7.2 Gender

In general, women have their first cardiovascular event an average of 10 years later in life compared with men. Thus, in NSTE-ACS, they tend to be older and therefore have more co-morbid illnesses, including renal impairment and heart failure. In registries in Europe, the average age of women with NSTE-ACS was 6 years higher than in men (71 vs. 65 years). On average, 45% of females and 20.5% of males were aged >75. Diabetes was more frequent in females than in males (26 vs. 22%). However, other risk factors were equally distributed in men and women.[421] In a registry of 201 114 patients with a first MI, multivariable analysis showed that younger women had a 25% higher 30-day mortality compared with men. However, gender was not an independent predictor of 1-year survival. Interactions between age and gender observed in short-term case fatality can be explained by increased pre-hospital

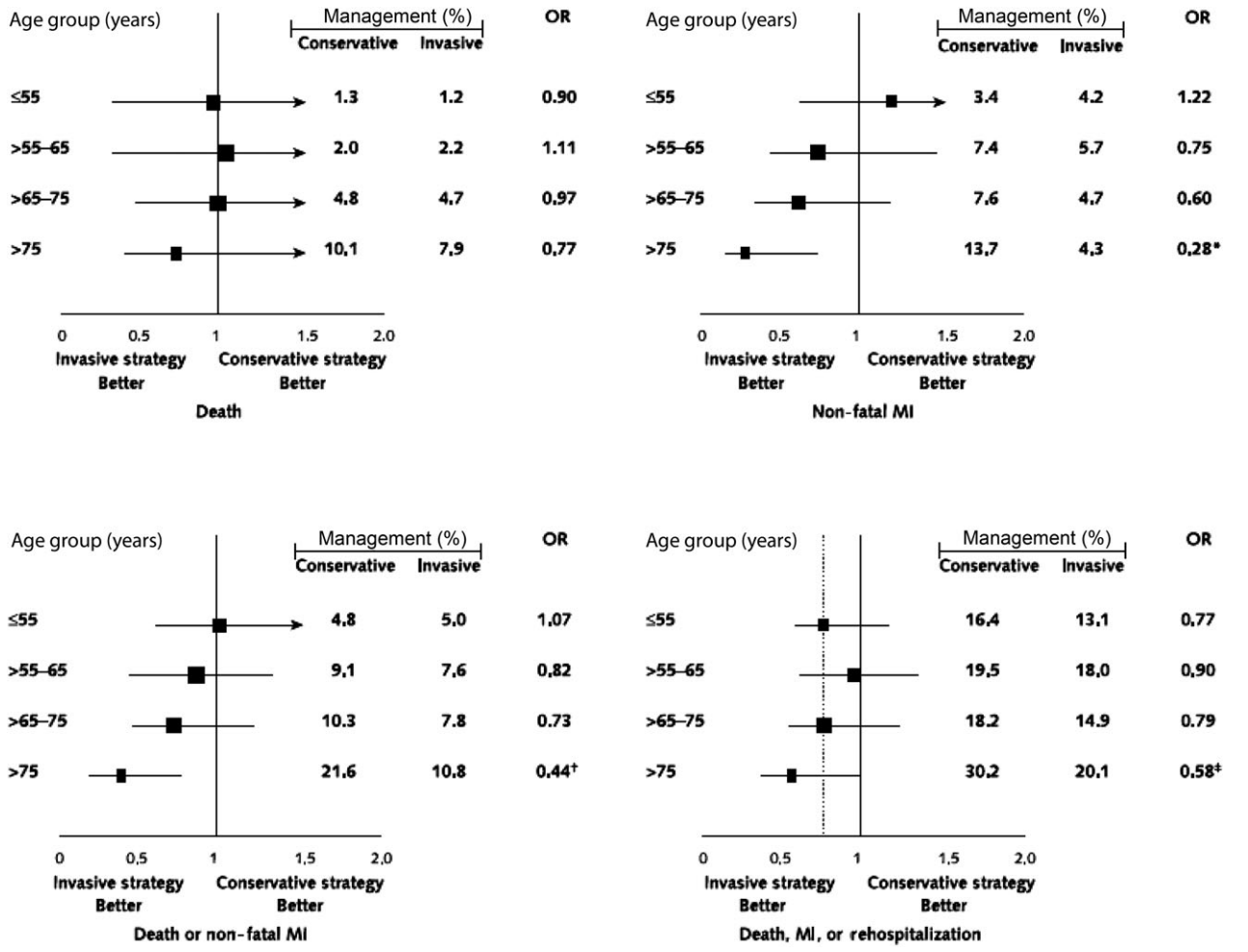

Figure 11 Clinical outcomes for patients stratified by age (invasive vs. conservative strategies) from the TACTICS–TIMI-18 trial.[420] Reproduced with permission. Odds ratios for death; non-fatal myocardial infarction; death or non-fatal myocardial infarction; and death, myocardial infarction, or rehospitalization for acute coronary syndrome at 6 months in patients with unstable angina and non-ST-elevation myocardial infarction. Data are stratified by age group: ≤55 years ($n = 716$), >55–65 years ($n = 614$), >65–75 years ($n = 612$), and >75 years ($n = 278$). The dotted line indicates the point estimate for the primary endpoint among all patients. *$P = 0.010$, †$P = 0.016$, ‡$P = 0.05$.

mortality in men.[422] However, among older women and men, the mortality rates were similar after adjustments for co-morbid illnesses. In the analysis from the GUSTO-2B trial, women with NSTE-ACS had a significantly higher mortality rate at 30 days than did men and similar rates of re-infarctions. In a subgroup with unstable angina, female sex was associated with an independent protective effect.[423]

Females in general are less likely to receive evidence-based therapies including diagnostic procedures in NSTE-ACS.[424] In European registries, women were under-treated when compared with men, especially in terms of PCI (24.4% for men vs. 22.9% for women), prescription of clopidogrel (49% for men vs. 39% for women), and prescription of GP IIb/IIIa inhibitors (24.8% for men vs. vs 23.8% for women). Referral for revascularization, percutaneous or surgical, was significantly lower for women.[253,331,421–426] For most treatments, there has not been any gender differential treatment effect with new therapeutic agents. However, with GP IIb/IIIa inhibitors and early revascularization (by either PCI or CABG), several trials have reported more adverse events in women, especially in those at lower risk. Registry data do not suggest that gender is an independent adverse risk of outcome. Therefore, it is recommended that women be evaluated and treated similarly to men, with special attention to co-morbid risk factors in NSTE-ACS.

7.2.1 Glycoprotein IIb/IIIa inhibitors in women

A meta-analysis of major clinical trials with GP IIb/IIIa inhibitors in NSTE-ACS showed a lack of treatment effect in women, with a significant interaction between sex and allocated treatment, with a treatment benefit in men. There was also a significant treatment interaction in favour of troponin-positive patients.[229] In a pooled analysis of trials with abciximab, no gender difference in the protection from major adverse outcomes was demonstrated. Women had higher rates of bleeding.[427,428] It was suggested that women were more likely to have non-obstructive CAD, in which therapeutic advantage of agents that act on the atherothrombotic process may be minimal.[429] It is recommended that GP IIb/IIIa inhibitors in NSTE-ACS should be used primarily among women with troponin elevation and a high likelihood of CAD.

7.2.2 Revascularization and early invasive strategy among women

In the contemporary practice of PCI with stents and GP IIb/IIIa inhibitors, a meta-analysis of randomized trials of an invasive approach (with revascularization using PCI or CABG) has shown a 23% risk reduction in 2-year mortality (RR 0.77, 95% CI 0.60–0.99). However, when the outcomes of men and women were examined, the treatment benefit was restricted to men (RR 0.68, 95% CI 0.57–0.81), whereas in women there appeared to be no benefit at 6 months to 1 year of follow-up (RR 1.07, 95% CI 0.82–1.41).[430] Both the RITA-3 and the FRISC-2 trials showed a higher rate of death and non-fatal MI among women.[431,432] In the TACTICS-TIMI-18 trial, no gender difference was observed with an invasive strategy. Revascularization compared with a conservative strategy improved the prognosis in women (OR 0.72; 95% CI 0.47–1.11), in the same range as in men (OR, 0.64; 95% CI, 0.47–0.88; $P = 0.60$ for sex interaction). The benefit of invasive therapy was enhanced in women with elevated troponin T levels (OR, 0.47; 95% CI 0.26–0.83).[433] Better long-term outcomes have been demonstrated in unselected women with an early invasive strategy when compared with men.[434] However, in the 5-year follow-up of the FRISC-2 trial, an invasive strategy was not shown to improve outcome in women [21.9 vs. 19.6% rate of death or MI invasive vs. conservative strategy (RR 1.12, 95% CI 0.83–1.50)], whereas a significant improvement was observed in men [19.0 vs. 26.8% rate of death or MI for invasive vs. conservative strategy (RR 0.70, 95% CI 0.59–0.86)], with significant interaction between women and men ($P = 0.01$).[122] Lastly, in a more recent meta-analysis by the Cochrane collaboration, women were shown to derive significantly better long-term benefit than men in terms of death or MI (RR 0.73 95% CI 0.59–0.91) for invasive vs. conservative strategy, but with early hazard.[313] These conflicting results suggest that further randomized trials are required among women to establish whether a routine invasive strategy is of benefit. In the meantime, it is recommended that a routine early invasive strategy should primarily be considered among women who have high-risk criteria such as ongoing ischaemia and troponin elevation, taking into account the existing co-morbid illnesses.

Recommendations for women

- **Women should be evaluated and treated in the same way as men, with special attention to co-morbidities (I-B).**

7.3 Diabetes mellitus

The presence of diabetes mellitus is an independent predictor of higher mortality among patients with NSTE-ACS, and is associated with a two-fold higher risk of death when compared with non-diabetic patients,[435] placing diabetic patients in a high-risk category. Diabetic patients have more co-morbid illnesses, including impaired renal function, heart failure, stroke, and general vascular disease.[436] Overall, ~20–30% of all patients with NSTE-ACS have diabetes and the vast majority has type 2 with insulin resistance. Data from recent registries carried out in the USA and Europe have shown that the rate of diabetes mellitus is increasing among patients with NSTE-ACS and ranges between 29 and 35% in Europe. Diabetes is more frequently observed in women than in men (41.6 vs. 30.7%). Diabetic patients are more often hypertensive (81 vs. 66% in non-diabetic patients) and obese (BMI > 30 is more frequent in diabetic patients than among non-diabetic patients, 28.5 vs. 18.6%), and suffer more frequently from renal failure (7.2 vs. 2.4% among non-diabetic patients).[437,438] When an established diagnosis of diabetes, impaired glucose tolerance, or impaired fasting glycaemia is considered, two-thirds of all patients suffering from either acute or chronic CAD have glucose regulation abnormalities.[439] Patients with impaired glucose tolerance or impaired fasting glycaemia also have a worse prognosis than patients with no glucose regulation abnormalities, but a slightly better prognosis than patients with confirmed diabetes.

As patients with diabetes are at a higher risk for adverse events, a more comprehensive approach to primary and secondary prevention is recommended. Tight glycaemic control using intravenous insulin and glucose was shown in DIGAMI to reduce the 1-year mortality by 30% in STEMI patients.[440] This early benefit was extended up to 39 months.[441] These observations were not confirmed in DIGAMI-2 which, however, showed that glucose level is a strong, independent predictor of long-term mortality following MI in patients with type 2 diabetes, with a 20% increase in long-term mortality for an increase of 3 mmol/L in plasma glucose.[442] Current knowledge indicates that insulin infusion is needed in diabetic patients with high blood glucose levels at admission in order to reach normoglycaemia as soon as possible. Moderate or minor elevation of blood glucose levels at admission may be handled with oral glucose-lowering agents. In the follow-up, strict glucose control is beneficial. Appropriate diet, lifestyle changes, oral agents, and insulin may be needed to achieve this goal. More detailed information on this issue can be found in the specific guidelines describing the management of diabetes and cardiovascular disease.[340]

In the case of angiography and/or angioplasty, the use of contrast medium raises the risk of contrast-induced nephropathy (CIN). Metformin should be interrupted ideally 24 h before the examination or at the latest on the day of the procedure. The risk of lactic acidosis is very low, but is increased in the case of renal failure. Metformin can be re-introduced 48 h after the use of contrast medium, if renal failure has not developed.

Similarly, an invasive treatment and potent antithrombotic therapeutic strategies are recommended. Both FRISC-2 and the TACTICS-TIMI-18 trials showed a 22–27% reduction in death and non-fatal MI in diabetic patients randomized to the early invasive strategy when compared with conservative strategy. Thus, the early invasive strategy is recommended for diabetic patients with NSTE-ACS. As many diabetic patients have multivessel CAD, CABG is frequently recommended based on the BARI trial.[443] We await current trials that are examining the relative merits of the most appropriate invasive strategy for diabetic patients using either DES or CABG.

In the BARI trial (which was not specifically directed at NSTE-ACS), there was a survival advantage for patients with multivessel CAD who were randomized to CABG rather than PCI.[410,444] It has to be stressed that in the BARI trial, old technology was used, and it was more a comparison of PCI (without stents) and surgery. The use of modern technology in the PCI arm may produce different results. However, this was not observed in the most recent

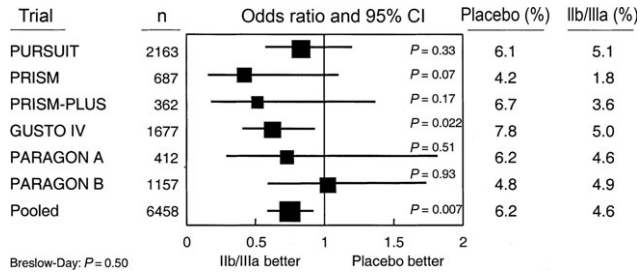

Figure 12 Treatment effect on 30-day mortality among diabetic patients with non-ST-elevation acute coronary syndrome from six randomized clinical trials.[233] Reproduced with permission. Odds ratio with 95% confidence interval and corresponding *P*-values for treatment effect on 30-day mortality among diabetic patients with acute coronary syndrome. Values to the left of 1.0 indicate a survival benefit of platelet glycoprotein IIb/IIIa inhibition.

trial of CABG vs. PCI in the diabetic population with medical refractory unstable angina where the 3-year survival was not statistically different between CABG (72%) and PCI (81%).[445] This trial differs from previous trials of PCI vs. CABG as it enrolled only medical refractory patients. Contemporary therapies with intracoronary stents and GP IIb/IIIa inhibitors were used extensively, but it was not powered enough to show statistical differences. Registry data show that an early invasive approach with a contemporary pharmacological environment and extensive use of stents significantly reduces in-hospital mortality when compared with a conservative approach.[252] The medical management with GP IIb/IIIa inhibitors in diabetic patients has also been examined in a meta-analysis.[233] In 6458 diabetic patients enrolled in the six large NSTE-ACS trials of GP IIb/IIIa inhibitors, there was a 26% reduction in 30-day mortality (6.2% vs. 4.6%, OR 0.74; 95% CI 0.59–0.92; $P = 0.007$) as shown in *Figure 12*. Hence, diabetic patients with NSTE-ACS should receive intravenous GP IIb/IIIa inhibitors as part of the initial medical management that should be continued through the completion of PCI. It is worth mentioning that more recent data obtained in the setting of PCI do not confirm the meta-analysis data, since in elective PCI as well as in high-risk NSTE-ACS patients, abciximab was not shown to lead to higher benefit in diabetic patients.[188,446]

Despite the evidence, it would appear that diabetic patients still remain undertreated when compared with their non-diabetic counterparts. In the European registries, revascularization (any form), thienopyridines, and GP IIb/IIIa inhibitors were prescribed less frequently among diabetic patients than among non-diabetic patients, with a clear impact on in-hospital and long-term mortality (5.9 vs. 3.2% mortality at 1 month and 15.2 vs. 7.6% at 1 year). In addition, registry data show that the presence of diabetes does not influence the choice of revascularization strategy.[447] For a comprehensive review of the management of diabetes in cardiovascular disease, readers are referred to existing guidelines on this topic.[340]

Recommendations for diabetes

- **Tight glycaemic control to achieve normoglycaemia as soon as possible is recommended in all diabetic patients with NSTE-ACS in the acute phase (I-C).**
- **Insulin infusion may be needed to achieve normoglycaemia in selected NSTE-ACS patients with high blood glucose levels at admission (IIa-C).**
- **An early invasive strategy is recommended for diabetic patients with NSTE-ACS (I-A).**
- **Diabetic patients with NSTE-ACS should receive intravenous GP IIb/IIIa inhibitors as part of the initial medical management which should be continued through the completion of PCI (IIa-B).**

7.4 Chronic kidney disease

CKD is classified into five different stages (*Table 9*).[448] Kidney function is best assessed with GFR according to the MDRD equation, which includes ethnicity and sex in its calculation. It should be assessed in all patients with or at increased risk of CAD.[449] However, in daily clinical practice, CrCl is used instead of GFR. Cystatin C was shown to be a good surrogate marker of renal dysfunction.[93,94]

7.4.1 Chronic kidney disease as a marker of risk of coronary artery disease

According to a large US registry, renal dysfunction has been shown to be quite common among the general population and is associated with a higher risk of cardiovascular and all-cause mortality, which increases exponentially with progressive decrease of GFR, with a swift increase in events for GFR <60 mL/min/1.73 m^2.[450] The risk of death from any cause, including cardiovascular disease, rises from an adjusted HR 1.2–5.1 from the least altered to the most severe levels of renal dysfunction, taking GFR >60 mL/min/1.73 m^2 as a reference. The adjusted HRs for occurrence of any cardiovascular disease were 1.4 and 3.4, respectively.[450] Similar observations were made in other reports,[451] some of which confirm that the prevalence of CAD is high at every stage of renal disease, including stage I, and results in a high rate of complications and in a two-fold increase in early mortality when compared with patients without renal dysfunction.[412,451–453] The high prevalence of CAD in CKD patients is due to a high incidence of traditional and also non-traditional risk factors such a intense pro-inflammatory state, hyperhomocysteinaemia, and pro-thrombotic state.[454] Diabetes, which accounts for about 50% of all cases of end-stage renal dysfunction, is an aggravating factor.[455]

Renal dysfunction is frequently observed in NSTE-ACS as in other forms of CAD. It is associated with worse prognosis in patients with overt clinical manifestations of atherosclerosis, including NSTE-ACS, STE-ACS, and PCI, as well as in diabetic patients.[11,456–461] In addition, renal dysfunction is a

Table 9 Stages of chronic kidney disease, according to the National Kidney Foundation[448]

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with mild decrease in GFR	60–89
3	Moderate decrease in GFR	30–59
4	Severe decrease in GFR	15–29
5	Kidney failure	<15 (or dialysis)

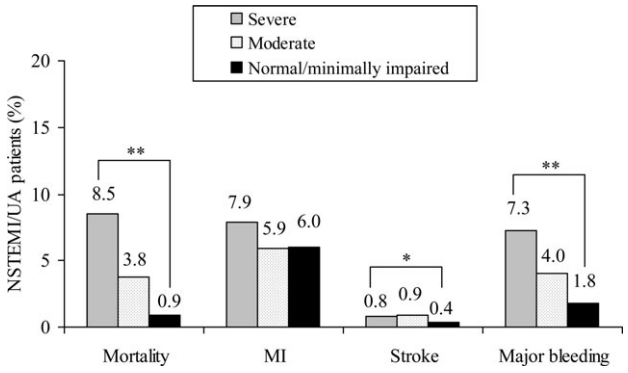

Figure 13 Hospital outcomes according to degree of renal function impairment for the subgroup of patients with non-ST-elevation myocardial infarction/unstable angina from the GRACE registry.[460] *Heart* 2003;**89**:1003–1008, reproduced with permission from the BMJ Publishing Group. $*P < 0.05$ across all categories of renal function within the non-ST-elevation myocardial infarction/unstable angina subgroup. $**P < 0.0001$ across all categories of renal function within the non-ST-elevation myocardial infarction/unstable angina subgroup.

potent independent predictor of bleeding risk in patients with ACS; the more severe the dysfunction, the higher the bleeding risk (*Figure 13*) (see section 6.1 Bleeding complications).

The presence of renal dysfunction complicates the management of patients suffering from NSTE-ACS. In case of severe renal failure (CrCl <30 mL/min), many drugs with exclusive or substantial renal elimination need to be down-titrated or might even be contraindicated, particularly LMWH, fondaparinux, bivalirudin and GP IIb/IIIa inhibitors. In this situation, UFH does not protect against bleeding complications, since in the GRACE registry, a gradual increase in the risk of bleeding with declining renal function was observed with UFH, similar to that observed with LMWH.[382] Since a much lower risk of bleeding complications was observed in OASIS-5 with fondaparinux compared to enoxaparin, even in patients with severe renal failure, fondaparinux has the potential to be used in this situation. Recent data confirm with eptifibatide that dose reduction may reduce bleeding risk[462] (*Table 10*).

7.4.2 Contrast-induced nephropathy

Baseline renal dysfunction may increase the risk of CIN in the case of angiography/angioplasty.[463] Risk of CIN is particularly high in patients with older age, diabetes, dehydration, high volume contrast medium injection, and the use of high-osmolar, as opposed to non-ionic, low osmolar contrast medium. Hydration prior to and following angiography and/or angioplasty is the strategy that has been shown to have the greatest impact in reducing the risk of CIN.[464–468] Patients who need to undergo coronary angiography and/or angioplasty must receive special care in order to reduce or avoid CIN. Current protocols recommend hydration with 250–500 mL of sodium chloride 0.9% before and after the procedure, being cautious in those patients with a history of heart failure. The amount of contrast medium should be limited to a maximum of 50 mL for a diagnostic procedure. Assessment of creatinine level up to day 3 after contrast injection is necessary to detect CIN.

Table 10 Recommendations for the use of drugs in the case of chronic kidney disease

Drug	Recommendations in the case of CKD
Simvastatin[a]	Low renal elimination. In patients with severe renal failure (CrCl <30 mL/min), careful with doses >10 mg
Ramipril[a]	Dose adaptation required if CrCl <30 mL/min (initial dose 1.25 mg daily). Dose must not exceed 5 mg/day
Losartan[a]	Recommended for the treatment of hypertension or renal failure in type 2 diabetes with microalbuminuria 50–100 mg/day. Regular monitoring of electrolyte balance and serum creatinine is recommended
Clopidogrel	No information in patients with renal failure
Enoxaparin[a]	In case of severe renal failure (CrCl <30 mL/min), either contraindicated or dose adjustment required, according to country-specific labelling.
Fondaparinux	Contraindicated in severe renal failure (CrCl <30 mL/min). However, as much lower risk of bleeding complications were observed in OASIS-5 with fondaparinux when compared with enoxaparin, even in patients with severe renal failure, this drug might be the anticoagulant of choice in this situation
Bivalirudin	If the CrCl <30 mL/min, reduction of the infusion rate to 1.0 mg/kg/h should be considered. If a patient is on haemodialysis, the infusion should be reduced to 0.25 mg/kg/h. No reduction in the bolus dose is needed
Tirofiban	Dose adaptation required in patients with renal failure. Fifty per cent of the dose only if CrCl <30 mL/min
Eptifibatide	As 50% of eptifibatide is cleared through the kidney in patients with renal failure, precautions must be taken in patients with impaired renal function (CrCl <50 mL/min). The infusion dose should be reduced to 1 μg/kg/min in such patients. The dose of the bolus remains unchanged at 180 μg/ kg. Eptifibatide is contraindicated in patients with CrCl <30 mL/min
Abciximab	No specific recommendations for the use of abciximab or for dose adjustment in the case of renal failure. Careful evaluation of haemorrhagic risk is needed before using the drug in the case of renal failure
Atenolol	Half dose recommended for patients with CrCl between 15 and 35 mL/min (50 mg/day). Quarter dose (25 mg/day) recommended if CrCl <15 mL/min

[a]Recommendations are indicated where applicable. It is assumed that the same recommendations are valid for other drugs of the same pharmacological class, but this needs to be assessed on a case by case basis (other LMWH, other statins, ACE inhibitors, and angiotensin receptor inhibitors), since, within the same pharmacological class, the route of elimination may vary. Recommendations for the use of drugs listed in this table may vary depending on the exact labelling of each drug in the country where it is used. Some differences in labelling can appear between countries.

In patients with serious renal dysfunction, immediate angiography and/or revascularization may be postponed, unless clinically indicated, in order to reduce the risk of acute renal failure post-intervention. If PCI is required, consideration should be given to deferring it by several days after angiography, if clinically possible. In the case of multivessel PCI, staged procedures may be considered. CABG is associated with a raised risk of renal dysfunction so the risk–benefit ratio should be considered carefully.

7.4.3 Management of chronic kidney disease in patients with coronary artery disease

ACE inhibitors and ARBs have both been shown to reduce microalbuminuria and progression towards end-stage renal dysfunction. ACE inhibitors must be administered under strict monitoring of serum creatinine, which may initially increase when ACE inhibitors are introduced, and thereafter return to baseline in most patients. Their use is contraindicated in patients with renal artery stenosis. ARBs can be used as an alternative to ACE inhibitors. Only ACE inhibitors and statins have been shown to reduce the risk of cardiovascular events in patients with renal dysfunction and should therefore be used as for any other patient suffering from NSTE-ACS. Data on the impact of revascularization on outcome in patients with CKD are sparse, since in most trials, renal dysfunction was an exclusion criterion so that patients with CKD are under-represented.[469] Revascularization was shown in a large registry as well as in substudies of trials in the setting of NSTE-ACS to improve outcome of CKD patients, not only at the stage of end-stage renal failure but also at the stage of moderate renal dysfunction.[458,470,471] In the same registry, as in others, it was shown that patients with renal dysfunction are often treated suboptimally and do not receive guideline-recommended therapy.[458]

7.4.4 Biomarkers in chronic kidney disease

Troponin elevations are sometimes found in asymptomatic patients with renal dysfunction, particularly those under haemodialysis, without clear evidence of ongoing NSTE-ACS. These troponin elevations may render the diagnosis of NSTE-ACS difficult in this setting. However, the prognosis of patients with CKD is impaired in the case of troponin elevation independent of the anginal status.[77,78,472–474]

Recommendations for patients with CKD

- **CrCl and/or GFR should be calculated for every patient hospitalized for NSTE-ACS (I-B). Elderly people, women, and low body weight patients merit special attention as near normal serum creatinine levels may be associated with lower than expected CrCl and GFR levels (I-B).**
- **Patients with CKD should receive the same first-line treatment as any other patient, in the absence of contraindications (I-B).**
- **In patients with CrCl <30 mL/min or GFR <30 mL/min/1.73 m^2, a careful approach to the use of anticoagulants is recommended, since dose adjustment is necessary with some, while others are contraindicated (I-C).**
- **UFH infusion adjusted according to aPTT is recommended when CrCl <30 mL/min or GFR <30 mL/min/1.73 m^2 (I-C).**
- **GP IIb/IIIa inhibitors can be used in the case of renal failure. Dose adaptation is needed with eptifibatide and tirofiban. Careful evaluation of the bleeding risk is recommended for abciximab (I-B).**
- **Patients with CKD with CrCl <60 mL/min are at high risk of further ischaemic events and therefore should be submitted to invasive evaluation and revascularization whenever possible (IIa-B).**
- **Appropriate measures are advised in order to reduce the risk of CIN (I-B).**

7.5 Anaemia

Anaemia has been shown to be associated with worse prognosis, and particularly higher mortality in various conditions, including heart failure, renal failure, various types of surgery, and malignancy,[475–481] but also across the whole spectrum of CAD, including STEMI, NSTE-ACS, PCI, and CABG.[391,482,483]

According to the World Health Organization criteria (haematocrit $<$39% or haemoglobin levels $<$13 g/dL in men and $<$12 g/dL in women),[484] anaemia may be present in 5–10% of patients with NSTE-ACS.[383] Figures as high as 43% were observed among elderly patients with acute MI, but only 4.2% had haematocrit levels $<$30%.[390] In a more recent report, anaemia was observed in 30.6% of cases of ACS, but only 5.4% had haemoglobin $<$10 g/dL.[391]

Anaemia in NSTE-ACS is associated with worse prognosis. A recent meta-analysis involving nearly 40 000 patients with both NSTE-ACS and STEMI showed that outcome at 30 days is significantly influenced by admission haemoglobin levels. The probability of cardiovascular death, MI, or recurrent ischaemia increases as haemoglobin falls below 11 g/dL, with an OR of 1.45 per 1 g/dL decrement in haemoglobin, taking those with a haemoglobin level of 15–16 g/dL as the reference group. The rate of cardiovascular events also increases with haemoglobin levels higher than 16 g/dL.[391] The same reverse J-shaped relationship between mortality and haemoglobin levels was observed in a cohort of 5888 elderly patients followed up for 11 years in the Cardiovascular Health Study.[485] Other reports in different contexts, such as STEMI, PCI, and CABG, have also identified anaemia as a marker of worse prognosis.[390,483,486] Anaemia is associated with more co-morbidities, such as older age, presence of diabetes, and renal failure[482,483] but also non-cardiovascular conditions (haemorrhagic diathesis or malignancy), which may partly account for the adverse prognosis. However, after adjustment on a broad array of baseline characteristics, a dose–response relationship across the spectrum of ACS was observed; the more profound the baseline haemoglobin, the worse the prognosis.[391,485] There seems to be a causal link between anaemia and risk of cardiovascular death. Indeed, anaemia increases heart rate and cardiac output, leading to development of LV hypertrophy, and an imbalance between oxygen demand and supply to the myocardium. These mechanisms, in addition to compromised oxygen supply to infarcted or ischaemic myocardium, can lead to increased infarct size, development of arrhythmias, and may also aggravate hypotension, and eventually worsen prognosis.

Baseline haemoglobin was also shown to be an independent predictor of the risk of bleeding; the lower the baseline haemoglobin, the higher the risk, for both procedure-related and non-procedure-related bleeding.[383,487] Therefore, as modern

treatment of NSTE-ACS may lead to a worsening of anaemia, because of increased risk of bleeding, special attention has to be paid to baseline haemoglobin level when deciding upon the therapeutic approach[179,488,489] (see section 6.1 Bleeding complications).

Recommendations for anaemia

- **Low baseline haemoglobin is an independent marker of the risk of ischaemic and bleeding events at 30 days. It should be taken into consideration in assessing initial risk (I-B).**
- **All necessary measures should be taken during the course of initial management to avoid worsening of anaemia by bleeding (I-B) (see section 6.1 Bleeding complications).**
- **Well-tolerated anaemia at baseline in patients with NSTE-ACS should not lead to systematic blood transfusion which should be considered only in the case of compromised haemodynamic status (I-C) (see section 6.1 Bleeding complications).**

7.6 Normal coronary arteries

A sizeable proportion of patients with NSTE-ACS have normal coronary arteries or only minor abnormalities. The pathophysiology of NSTE-ACS is not homogeneous and possible mechanisms include: (i) a coronary artery spasm (Prinzmetal's angina); (ii) an intramural plaque complicated by acute thrombosis with subsequent recanalization; (iii) coronary emboli; and (iv) syndrome X.

In patients admitted with suspected NSTE-ACS, the demonstration of normal or nearly normal coronary arteries at angiography challenges the diagnosis. However, ST-segment changes and release of biomarkers in patients with typical chest pain and patent coronary arteries without significant stenotic lesions may be due to true necrosis rather than false-positive results. About 15% of patients with proven NSTE-ACS actually have normal or nearly normal coronary arteries. This tends to be more common in women. Important atherosclerotic burden may be present even in the absence of angiographically significant stenoses because it may occur in a diffuse manner and lead to arterial wall remodelling in which the wall thickens and expands outwards without encroaching on the lumen.[490] The prognosis of these patients is similar to that of patients with NSTE-ACS and significant coronary atherosclerosis, and they therefore merit optimal antithrombotic therapy and secondary prevention with antiplatelet agents and statins.[41]

Prinzmetal's variant angina refers to an unusual syndrome of cardiac pain secondary to myocardial ischaemia that is not precipitated by physical exertion or emotional stress, and is associated with transient ST-segment elevation.[491] The original hypothesis that it is the result of a coronary vasospasm has been convincingly demonstrated by coronary arteriography. The vasospasm causes a transient, abrupt, marked decrease in the diameter of epicardial coronary arteries, thus leading to severe myocardial ischaemia. Vasospasm may occur at sites of severe focal stenoses, but often in patients with an apparently normal vessel at angiography. Patients with variant angina tend to be younger than those with conventional NSTE-ACS and are often heavy smokers. The symptom is often severe and may be accompanied by syncope. Attacks of Prinzmetal's angina tend to be clustered between midnight and eight o'clock in the morning.[491,492] Spasm of epicardial coronary artery, leading to transmural ischaemia, is the diagnostic hallmark of Prinzmetal's angina. The spasm may be spontaneous or provoked by an acetylcholine or ergonovine test or hyperventilation. The mainstay therapy for Prinzmetal's angina is the administration of calcium antagonists, shown to be effective in preventing coronary spasm, alone or in combination with nitrates. They should be prescribed at maximally tolerated doses on a long-term basis.[492]

In rare cases, NSTE-ACS with normal or near-normal coronary arteriogram is linked to coronary embolism, due to atrial fibrillation or atrial flutter. As atrial fibrillation is often clinically unrecognized, the frequency of this mechanism of NSTE-ACS may be underestimated.[493]

The term 'syndrome X' is used to describe patients with angina precipitated by exercise, ST-segment depression on stress test, and a non-obstructed coronary artery at angiography. The chest pain may increase in frequency or intensity, or occur at rest. The patients may present with typical features of unstable angina.[494,495] The prognosis is usually excellent. The real cause of the syndrome has not been established, but it is most frequently associated with impaired endothelial-dependent arterial vasodilatation, decreased nitric oxide production, and increased sensitivity to sympathetic stimulation. There is growing evidence that such patients often have an increased response to pain. Because the prognosis is excellent, the most important therapy is reassurance and symptom relief, for which nitrates, beta-blockers, and calcium antagonists have been found to be effective.

Apical ballooning, recently described, may present clinically as NSTE-ACS and is characterized by normal coronary arteries at angiography accompanied by apical and sometimes medioventricular akinesis unrelated to the distribution of a coronary artery. This is typically fully reversible within weeks. The exact mechanism of this syndrome is presently unknown.[496,497]

8. Management strategies

NSTE-ACS encompasses a heterogeneous spectrum of patients with different levels of risk in terms of death, MI, or recurrence of MI. In the following paragraphs, a stepwise strategy is outlined which is based on the above detailed analysis of the available scientific data and which should be applicable to most patients admitted with suspected NSTE-ACS. It must be appreciated, however, that specific findings in individual patients may result in appropriate deviations from the proposed strategy. For every patient, the physician must make an individual decision taking into account the patient's history (co-morbid illnesses, age, etc.), his/her clinical condition, findings during the initial assessment on first contact, and the available pharmacological and non-pharmacological treatment options.

8.1 First step: initial evaluation

Chest pain or discomfort will be the symptom that leads to the patient seeking medical attention or hospitalization.

A patient with suspected NSTE-ACS must be evaluated in a hospital and immediately seen by a qualified physician. Specialized chest pain units provide the best and most expeditious care.[498]

The initial step is to assign the patient without delay to a working diagnosis on which the treatment strategy will be based. The criteria are the following:

- quality of chest pain and a symptom-oriented physical examination;
- assessment of the likelihood of CAD (e.g. age, risk factors, previous MI, CABG, PCI);
- ECG (ST-deviation or other ECG abnormalities).

On the basis of these findings which should be available within 10 min after first medical contact, the patient can be assigned to one of the three major working diagnoses:

- STEMI requiring immediate reperfusion;
- NSTE-ACS;
- ACS (highly) unlikely.

The treatment of patients with STEMI is covered in the respective guidelines.[2] The assignment to the category 'unlikely' must be done with caution and only when another explanation is obvious (e.g. trauma). Additional ECG leads (V_3R and V_4R, V_7–V_9) should be recorded, especially in patients with persisting chest pain.

Blood is drawn on arrival of the patient in hospital and the result should be available within 60 min to be used in the second strategy step. Initial blood tests must at least include: troponin T or troponin I, CK (-MB), creatinine, haemoglobin, and leukocyte count.

The assignment to the category NSTE-ACS will result in the second strategy step.

Table 11 Primary therapeutic measures

Oxygen	Insufflation (4–8 L/min) if oxygen saturation is $<$90%
Nitrates	Sublingually or intravenously (caution if systolic blood pressure $<$90 mmHg)
Aspirin	Initial dose of 160–325 mg non-enteric formulation followed by 75–100 mg/day (intravenous administration is acceptable)
Clopidogrel	Loading dose of 300 mg (or 600 mg for rapid onset of action) followed by 75 mg daily
Anticoagulation	Choice between different options depends on strategy: • UFH intravenous bolus 60–70 IU/kg (maximum 5000 IU) followed by infusion of 12–15 IU/kg/h (maximum 1000 IU/h) titrated to aPTT 1.5–2.5 times control • Fondaparinux 2.5 mg/daily subcutaneously • Enoxaparin 1 mg/kg twice daily subcutaneously • Dalteparin 120 IU/kg twice daily subcutaneously • Nadroparin 86 IU/kg twice daily subcutaneously • Bivalirudin 0.1 mg/kg bolus followed by 0.25 mg/kg/h
Morphine	3–5 mg intravenously or subcutaneously, depending on pain severity
Oral beta-blocker	Particularly if tachycardia or hypertension without sign of heart failure
Atropine	0.5–1 mg intravenously if bradycardia or vagal reaction

8.2 Second step: diagnosis validation and risk assessment

8.2.1 Diagnosis validation

After the patient is assigned to the group NSTE-ACS, intravenous and oral treatments will be started according to *Table 11*.

The first-line treatment should be made up of at least nitrates, beta-blockers, aspirin, clopidogrel, and anticoagulation, the type depending on the management strategy, i.e. urgent invasive, early invasive, or conservative (see Third step).

The further management will be based on additional information/data:

- routine clinical chemistry, particularly troponins (on presentation and after 6–12 h) and other markers according to working diagnoses (e.g. D-dimers, BNP, NT-proBNP);
- repeat, preferably continuous, ST-segment monitoring (when available);
- Echocardiogram, MRI, CT, or nuclear imaging for differential diagnoses (e.g. aortic dissection, pulmonary embolism);
- responsiveness to antianginal treatment;
- risk score assessment;
- bleeding risk assessment.

During this step, other diagnoses may be confirmed or excluded, such as acute anaemia, pulmonary embolism, and aortic aneurysm (see *Table 4*; section 4.3 Differential diagnoses).

8.2.2 Risk assessment

The treatment of the individual patient is tailored according to the risk for subsequent events which should be assessed early at the initial presentation as well as repeatedly thereafter in the light of continuing or repetitive symptoms and additional information from clinical chemistry or imaging modalities.

Risk assessment is an important component of the decision-making process and is subject to constant re-evaluation. It encompasses assessment of both ischaemic and bleeding risk. The risk factors for bleeding and ischaemic events overlap considerably, with the result that patients at high risk of ischaemic events are also at high risk of bleeding complications. Therefore, the choice of the pharmacological environment (dual or triple antiplatelet therapy, anticoagulants) has become critical, as has the dosage of the drugs. In addition, in cases where invasive strategy is needed, the choice of the vascular approach is very important, since the radial approach has been shown to reduce the risk of bleeding when compared with the femoral approach. In this context, particular attention has to be paid to renal dysfunction, shown to be particularly frequent in elderly patients and among diabetics.

During this step, the decision has to be made whether the patient should go on to cardiac catheterization or not.

8.3 Third step: invasive strategy

Cardiac catheterization is advised to prevent early complications and/or to improve long-term outcome (*Figure 14*). Accordingly, the need for and timing of an invasive strategy has to be tailored according to the acuteness of risk into three categories: conservative, early invasive, or urgent invasive.

8.3.1 Conservative strategy

Patients that fulfil all the below criteria may be regarded as low risk and should not be submitted to early invasive evaluation:

- no recurrence of chest pain;
- no signs of heart failure;
- no abnormalities in the initial ECG or a second ECG (6–12 h);
- no elevation of troponins (arrival and at 6–12 h);

Low risk as assessed by a risk score (see section 4.4 Risk stratification) can support the decision-making process for a conservative strategy. The further management in these patients is according to the evaluation of stable CAD.[499] Before discharge, a stress test for inducible ischaemia is useful for further decision-making.

Patients who cannot be excluded by the above criteria should go on to cardiac catheterization.

8.3.2 Urgent invasive strategy

Urgent invasive strategy should be undertaken for patients who are early in the process of developing major myocardial necrosis escaping the ECG (e.g. occlusion of the circumflex artery) or are estimated to be at high risk of rapid progression to vessel occlusion.

These patients are characterized by:

- refractory angina (e.g. evolving MI without ST-abnormalities);
- recurrent angina despite intense antianginal treatment associated with ST-depression ($\geq$2 mm) or deep negative T-waves;
- clinical symptoms of heart failure or haemodynamic instability ('shock');
- life-threatening arrhythmias (ventricular fibrillation or ventricular tachycardia).

In addition to the medication shown in *Table 11*, a GP IIb/IIIa inhibitor (tirofiban, eptifibatide) should be added in symptomatic patients bridging the time to catheterization.

8.3.3 Early invasive strategy

Most patients initially respond to the antianginal treatment, but are at increased risk and need early angiography. The timing depends on the local circumstances, but it should be performed within 72 h.

The following features indicate patients who should undergo routine early angiography:

- elevated troponin levels;
- dynamic ST or T-wave changes (symptomatic or silent) ($\geq$0.5 mm);
- diabetes mellitus;
- reduced renal function (GFR$<$60 mL/min/1.73 m^2);
- depressed LVEF$<$40%;
- early post-MI angina;
- PCI within 6 months;
- previous CABG;
- intermediate to high risk according to a risk score (*Table 5*).

A GP IIb/IIIa inhibitor (tirofiban, eptifibatide) should be added to the standard treatment prior to catheterization in the case of elevated troponins, dynamic ST/T changes, or diabetes provided there is no overt excessive bleeding risk.

The decision about the timing of catheterization must continuously be re-evaluated and modified according to clinical evolution and occurrence of new clinical findings.

8.4 Fourth step: revascularization modalities

If the angiogram shows no critical coronary lesions, patients will be referred for medical therapy. The diagnosis of NSTE-ACS may be reconsidered and particular attention should be paid to other possible reasons for symptoms at presentation before the patient is discharged. However, the absence of critical coronary lesions does not rule out the diagnosis if clinical presentation was suggestive of ischaemic chest pain and if biomarkers were positive. In this situation, patients should receive treatment according to recommendations in NSTE-ACS.

Recommendations for the choice of a revascularization modality in NSTE-ACS are similar to those for elective revascularization procedures. In patients with single-vessel disease, PCI with stenting of the culprit lesion is the first choice. In patients with multivessel disease, the decision for PCI or CABG must be made individually. A sequential approach with treating the culprit lesion by PCI followed by elective CABG may be advantageous in some patients.

The anticoagulant should not be changed for PCI. In patients pre-treated with fondaparinux, UFH must be added before PCI. In patients pre-treated with tirofiban or eptifibatide, the infusion should be maintained throughout the intervention. Patients untreated with GP IIb/IIIA inhibitors should preferably receive abciximab before PCI. There is less evidence for the use of eptifibatide or tirofiban in this setting.

If CABG is planned, clopidogrel should be stopped and surgery deferred for 5 days, if the clinical condition and the angiographic findings permit this.

If angiography shows no options for revascularization, owing to the extent of the lesions and/or poor distal run-off, freedom from angina at rest should be achieved by intensified medical therapy, and secondary preventive measures should be instituted.

8.5 Fifth step: discharge and post-discharge management

Although in NSTE-ACS most adverse events occur in the early phase, the risk for MI or death remains elevated over several months. Patients treated with early revascularization are at

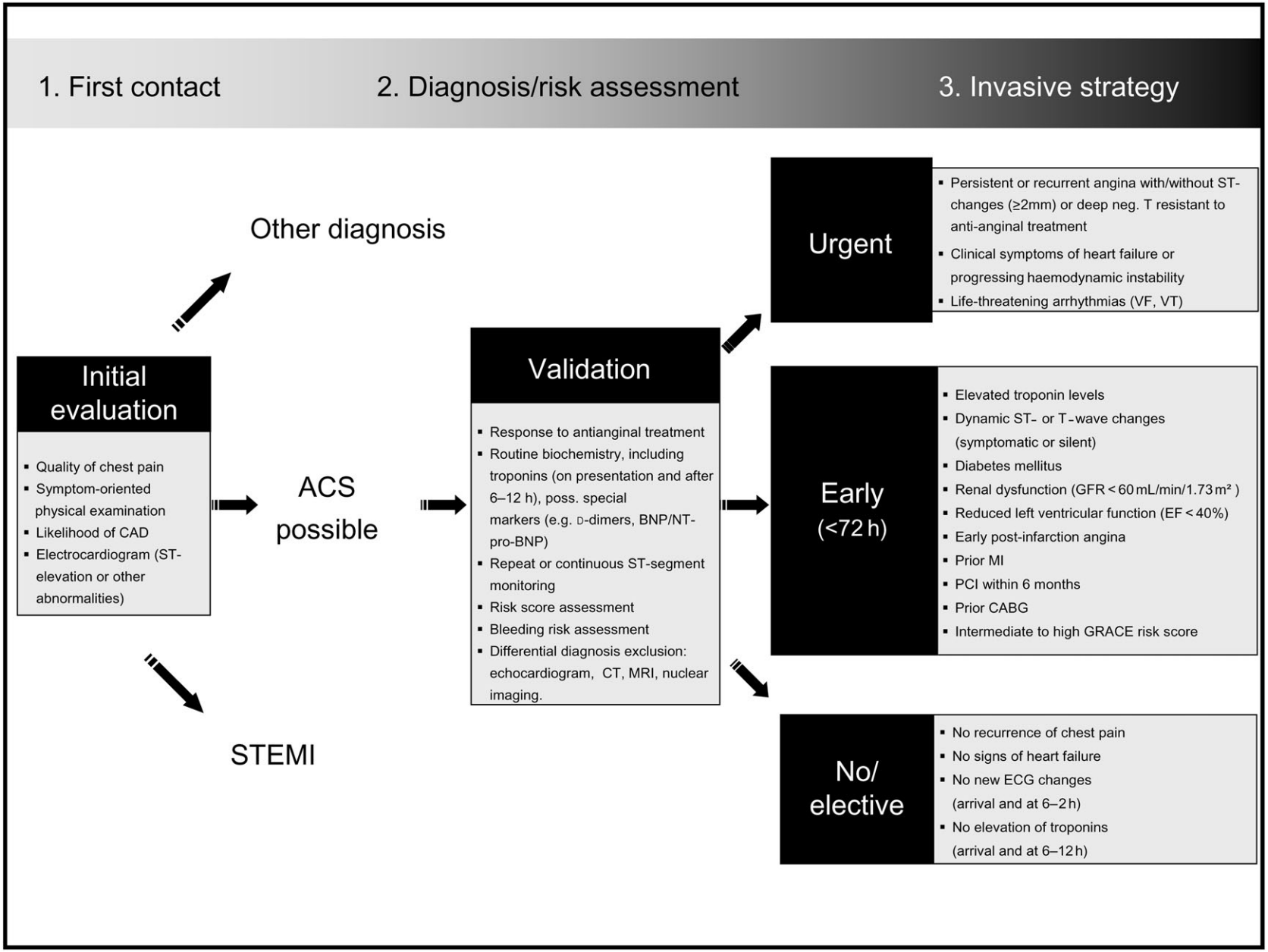

Figure 14 Decision-making algorithm for the management of patients with non-ST-elevation acute coronary syndrome.

low (~2.5%) risk for developing life-threatening arrhythmias, with 80% occurring during the first 12 h after onset of symptoms.[500] Accordingly, monitoring of the patients beyond 24–48 h is not warranted.

Discharge from hospital depends on clinical and angiographic findings. Patients with NSTE-ACS should be hospitalized for at least 24 h after successful stenting of the culprit lesion.

Intense risk factor modification is warranted in all patients following the diagnosis of NSTE-ACS (see section 5.5 Long-term management).

9. Performance measures

Despite the presence of consistent European and national guidelines, substantial variations exist in adherence to guidelines both within and between countries. There are large variations in the use of diagnostic procedures and in the application of risk stratification. Similarly, there are great variations in the use of medical and interventional treatments and variations in the selection of patients for specific therapeutic strategies.[10,11,252,501–503] Such variations in the application of evidence-based strategies, within and between countries, are associated with differences in outcome. Registry studies have examined the relationship between the use of evidence-based treatment strategies and event rates, and they provide clear support that improving guideline adherence will improve patient outcomes.[14,15,504–508] Thus, priority needs to be given to improving the uptake of evidence-based guidelines.

Publication of guidelines may have a very limited impact on quality of care unless national and local audits and performance measures are adopted. A systematic, multidisciplinary approach is required combining education, and the identification, and resolution of logistic problems. A well-structured treatment process associated with continuous monitoring of performance indicators can improve outcomes.[7,509–514]

Quality is a relative concept that requires comparison either with the performances of others or with the previous standards. The standard of care in a unit is a consequence of a large number of individual decisions and actions, by several care providers, for each patient. Estimates of quality need to be based on indicators of care that are measurable and relevant for the health-care provider and the patient. To permit temporal comparisons within a centre, and across centres, performance indicators need to be well defined and standardized.[510] The measurements need to be performed in similar patient populations, and with risk adjustment. This requires measurement of individual patient's risk characteristics, an adequate sample size, and robust statistical comparisons. In general, estimates of quality of care in individual units need to assess process of care (e.g. rates of usage of medications and interventions with Class I-A recommendations) rather than infrequent outcome events (mortality or MI). Reliable estimates of rates of death or MI require large populations and prolonged observation periods.

Estimates of quality can be applied to individual units, hospitals, regions, or nations. However, for performance indicators to change the process of care, they have to be applied consistently, locally, and based on current rather than historical performance. Thus, this necessitates repeated or continuous measurements and feedback of performance to individual care centres.[7,252,503,508,509,511–514]

For patients with ACS, the CARDS data set (available from http//:www.escardio.org) is an appropriate and standardized ESC- and EU-recommended database for quality development.[510] The CARDS data set, or similar national data sets with continuous monitoring of the standards of treatment of ACS patients, has been implemented in a number of European countries.[7,508] These data sets have revealed almost as large variation within a country[508] as between countries.[11,508] Nevertheless, such continuous registry programmes have contributed to impressive improvements in the standards of care and in outcomes.[14,15,504–508]

Currently, the most useful performance indicators in individual centres for monitoring and improving the standards of care in non-STEMI ACS include the following.

- Class I-recommended antiplatelet and anticoagulation: use of aspirin, clopidogrel, and UFH/LMWH (enoxaparin)/fondaparinux/bivalirudin; use of GP IIb/IIIa inhibitors before and/or during early PCI procedures.
- Class I-recommended interventional therapy: use of early invasive procedures in intermediate–high risk patients.
- Risk stratification: use of the above treatment measures in target populations in accordance with risk stratification (using risk scores), in the absence of contraindications.
- Class I-recommended secondary prevention therapy: statins, beta-blockade in patients with reduced LV function, ACE inhibition, smoking cessation, glycaemic control, lifestyle changes.

Regional, national, and international audit programmes that include thousands rather than hundreds of patients can measure outcome events (i.e. recurrent MI and mortality) and can be used to evaluate the impact of improved adherence to guidelines on clinical outcomes.[14,15,504–508] However, such large-scale programmes also require action at a local level. In each hospital, continuous monitoring of performance indicators is strongly encouraged to enhance the quality of treatment and to minimize unwarranted variations in evidence-based care. Consistent application of therapies based on robust evidence (e.g. Class I recommendation) may have larger effects on real-life cardiovascular health than those seen in selected trial populations, especially with the combined implementation of several effective treatment modalities. Such programmes have been successfully implemented in several countries including Sweden (RIKS-HIA Registry), the UK (MINAP Registry), Germany, Italy, and Israel on a regional basis, or in intermittent programmes in many other countries. These performance measure programmes are also proposed and developed by the ESC through the continuous ACS Registry within the Euro Heart Survey Programme.

Recommendations for performance measures

- **Development of regional and/or national programmes to measure performance indicators systematically and provide feedback to individual hospitals is strongly encouraged (I-C).**

10. Abbreviations

- ACC (American College of Cardiology)
- ACE inhibitors (Angiotensin-converting enzyme inhibitors)
- ACS (Acute coronary syndrome)
- ACT (Activated clotting time)
- ADP (Adenosine diphosphate)
- AHA (American Heart Association)
- aPTT (Activated partial thromboplastin time)
- ARB (Angiotensin receptor blocker)
- A-V (Atrioventricular)
- BMS Bare metal stent
- BNP (Brain natriuretic peptide)
- CABG (Coronary bypass graft surgery)
- CAD (Coronary artery disease)
- CARDS (Cardiology Audit and Registration Data Standards)
- CCS (Canadian Cardiovascular Society)
- CI (Confidence interval)
- CIN (Contrast-induced nephropathy)
- CK (Creatinine kinase)
- CKD (Chronic kidney disease)
- CK-MB (Creatinine kinase myocardial band)
- COX (Cyclo-oxygenase)
- CPG (Committee for Practice Guidelines)
- CrCl (Creatinine clearance)
- CT (Computed tomography)
- cTnT or cTnI (Cardiac troponin T or cardiac troponin I)
- DES (Drug-eluting stent)
- dL (decilitre)
- DPG (Diphosphoglyceric)
- DTI (Direct thrombin inhibitor)
- DVT (Deep vein thrombosis)
- e.g. (for example)
- ECG (Electrocardiogram)
- EDTA (Ethylenediamine triacetic acid)
- EF (Ejection fraction)
- ESC (European Society of Cardiology)
- EU (European Union)
- Factor-Xa (Activated factor-X)
- GFR (Glomerular filtration rate)
- GPIIb/IIIa inhibitors (Glypoprotein IIb/IIIa inhibitors)
- Hct (Haematocrit)
- HDL (High-density lipoprotein)
- HIT (Heparin-induced thrombocytopenia)
- HR (Hazard ratio)
- hsCRP (High-sensitive C-reactive protein)
- i.e. (that is)
- INR (International normalized ratio)
- IU (International units)
- kg (kilogram)
- LBBB (Left-bundle branch block)
- LDL (Low-density lipoprotein)
- LMWH (Low molecular weight heparin)
- LV (Left ventricular)
- LVEF (Left ventricular ejection fraction)
- MB (Myocardial band)
- MDRD (Modification of Diet in Renal Disease)
- METS (Metabolic equivalents)
- mg (milligram)
- MI (Myocardial infarction)
- mL (millilitre)
- mm (millimetre)
- MPO (Myeloperoxidase)
- MRI (Magnetic resonance imaging)
- mV (millivolt)
- NNT (Numbers needed to treat)
- NSAID (Non-steroidal anti-inflammatory drug)
- NSTE-ACS (Non-ST-elevation acute coronary syndromes)
- NSTEMI (Non-ST elevation myocardial infarction)
- NT-proBNP (N-terminal pro-hormone brain natriuretic peptide)
- OR (Odds ratio)
- PCI (Percutaneous coronary intervention)
- PDA (Personal digital assistant)
- PF4 (Platelet factor 4)
- RR (Risk ratio)
- STE-ACS (ST-elevation-acute coronary syndrome)
- STEMI (ST-elevation myocardial infarction)
- t-PA (Tissue plasminogen activator)
- TVR (Target vessel revascularization)
- UFH (Unfractionated heparin)
- ULN (Upper limits of normal)
- VKA (Vitamin K antagonist)
- VF (Ventricular fibrillation)
- VT (Ventricular tachycardia)
- VTE (Venous thrombo-embolism)

11. Trial acronyms

- ACUITY (Acute Catheterization and Urgent Intervention Triage strategy)
- ACUTE-2 (Antithrombotic Combination Using Tirofiban and Enoxaparin)
- ASPIRE (Arixtra Study in Percutaneous Coronary Interventions)
- BARI (Bypass Angioplasty Revascularisation Investigation)
- CAPRIE (Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events)
- CAPTURE (Chimeric 7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment)
- CARDS (Collaborative Atorvastatin Diabetes Study)
- CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance)
- CRUSADE (Can Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines)
- CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events)
- DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction)
- EARLY-ACS (Early Glycoprotein IIb/IIIa Inhibition in patients with Non-ST-segment Elevation Acute Coronary Syndromes)
- ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy)
- ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events)
- FRISC (Fast Revascularisation during InStability in Coronary artery disease)
- FRISC-2 (Fragmin and Fast Revascularisation during InStability in Coronary artery disease II)
- GRACE (Global Registry of Acute Coronary Events)
- GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries)

- GUSTO-2 (Global Use of Strategies To open Occluded coronary arteries II)
- GUSTO-4 (Global Utilization of Strategies To open Occluded coronary arteries IV)
- GUSTO-4-ACS (Global Utilization of Strategies To open Occluded coronary arteries trial IV in Acute Coronary Syndromes)
- HINT (Holland Interuniversity Nifedipine/metopropol Trial)
- HOPE (Heart Outcomes Prevention Evaluation study)
- ICTUS (Invasive versus Conservative Treatment in Unstable Coronary Syndrome)
- IMPACT-2 (Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis II)
- INTERACT (Integrilin and Enoxoparin Randomized Assessment on Acute Coronary Syndrome Treatment)
- IONA (Impact of Nicorandil in Angina)
- ISAR (Intracoronary Stenting and Antithrombotic Regimen)
- ISAR-COOL (Intracoronary Stenting With Antithrombotic Regimen Cooling-Off)
- ISAR-REACT-2 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2)
- MATE (Medicine vs. Angiography in Thrombolytic Exclusion)
- MINAP (National Audit of Myocardial Infarction Project)
- OASIS (Organization to Assess Strategies for Ischaemic Syndromes pilot study)
- OASIS-5 (Organization to Assess Strategies in Acute Ischemic Syndromes 5)
- OASIS-6 (Organization for the Assessment of Strategies for Ischemic Syndromes 6)
- PRISM (Platelet Receptor Inhibition in Ischaemic Syndrome Management)
- PRISM-PLUS (Platelet Receptor Inhibition in Ischaemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms)
- PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy trial)
- PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina; Receptor Suppression Using Integrilin Therapy)
- RESTORE (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis)
- RITA-3 (Randomized Intervention Trial of unstable Angina 3)
- STEEPLE (The Safety and Efficacy of Enoxaparin In PCI Patients In International Randomized Evaluation)
- SYNERGY (Superior Yield of the New strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa inhibitors)
- TACTICS–TIMI-18 (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)
- TARGET (Tirofiban and Reopro Give Similar Efficacy Outcomes)
- TENACITY (Tirofiban Novel Dosing vs. Abciximab with Evaluation of Clopidogrel and Inhibition of Thrombin Study)
- TIMI (Thrombolysis in Myocardial Infarction)
- TIMI-11A (Thrombolysis in Myocardial Infarction Phase 11A)
- TIMI-11B (Thrombolysis in Myocardial Infarction Phase 11B)
- TIMI-3B (Thrombolysis in Myocardial Ischaemia Phase III)
- VANQWISH (Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital)

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References

1. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 1997;**349**:1498–1504.
2. Van de Werf F, Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KA, Julian D, Lengyel M, Neumann FJ, Ruzyllo W, Thygesen C, Underwood SR, Vahanian A, Verheugt FW, Wijns W. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2003;**24**:28–66.
3. Bertrand ME, Simoons ML, Fox KA, Wallentin LC, Hamm CW, McFadden E, De Feyter PJ, Specchia G, Ruzyllo W. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2002;**23**:1809–1840.
4. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995;**310**:452–454.
5. Alpert JS, Thygesen K, Antman EM, Bassand JP. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J* 2000;**21**:1502–1513.
6. GRACE Investigators. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) project: a multinational registry of patients hospitalized with acute coronary syndromes. *Am Heart J* 2001;**141**:190–199.
7. Birkhead JS, Walker L, Pearson M, Weston C, Cunningham AD, Rickards AF. Improving care for patients with acute coronary syndromes: initial results from the National Audit of Myocardial Infarction Project (MINAP). *Heart* 2004;**90**:1004–1009.
8. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KA. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004;**291**:2727–2733.
9. Fox KA, Goodman SG, Klein W, Brieger D, Steg PG, Dabbous O, Avezum A. Management of acute coronary syndromes. Variations in practice and outcome; findings from the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2002;**23**:1177–1189.
10. Hasdai D, Behar S, Boyko V, Danchin N, Bassand JP, Battler A. Cardiac biomarkers and acute coronary syndromes—the Euro Heart Survey of Acute Coronary Syndromes Experience. *Eur Heart J* 2003;**24**:1189–1194.

11. Hasdai D, Behar S, Wallentin L, Danchin N, Gitt AK, Boersma E, Fioretti PM, Simoons ML, Battler A. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin; the Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). *Eur Heart J* 2002; **23**:1190–1201.
12. Hoekstra JW, Pollack CV Jr, Roe MT, Peterson ED, Brindis R, Harrington RA, Christenson RH, Smith SC, Ohman EM, Gibler WB. Improving the care of patients with non-ST-elevation acute coronary syndromes in the emergency department: the CRUSADE initiative. *Acad Emerg Med* 2002;**9**:1146–1155.
13. Lev EI, Battler A, Behar S, Porter A, Haim M, Boyko V, Hasdai D. Frequency, characteristics, and outcome of patients hospitalized with acute coronary syndromes with undetermined electrocardiographic patterns. *Am J Cardiol* 2003;**91**:224–227.
14. Stenestrand U, Wallentin L. Early statin treatment following acute myocardial infarction and 1-year survival. *JAMA* 2001;**285**:430–436.
15. Stenestrand U, Wallentin L. Early revascularisation and 1-year survival in 14-day survivors of acute myocardial infarction: a prospective cohort study. *Lancet* 2002;**359**:1805–1811.
16. Goldberg RJ, Gore JM, Alpert JS, Dalen JE. Recent changes in attack and survival rates of acute myocardial infarction (1975 through 1981). The Worcester Heart Attack Study. *JAMA* 1986;**255**:2774–2779.
17. Bata IR, Gregor RD, Eastwood BJ, Wolf HK. Trends in the incidence of acute myocardial infarction between 1984 and 1993—The Halifax County MONICA Project. *Can J Cardiol* 2000;**16**:589–595.
18. Fox KA, Cokkinos DV, Deckers J, Keil U, Maggioni A, Steg G. The ENACT study: a pan-European survey of acute coronary syndromes. European Network for Acute Coronary Treatment. *Eur Heart J* 2000;**21**: 1440–1449.
19. Furman MI, Dauerman HL, Goldberg RJ, Yarzebski J, Lessard D, Gore JM. Twenty-two year (1975 to 1997) trends in the incidence, in-hospital and long-term case fatality rates from initial Q-wave and non-Q-wave myocardial infarction: a multi-hospital, community-wide perspective. *J Am Coll Cardiol* 2001;**37**:1571–1580.
20. van der Pal-de Bruin KM, Verkleij H, Jansen J, Bartelds A, Kromhout D. The incidence of suspected myocardial infarction in Dutch general practice in the period 1978–1994. *Eur Heart J* 1998;**19**:429–434.
21. Savonitto S, Ardissino D, Granger CB, Morando G, Prando MD, Mafrici A, Cavallini C, Melandri G, Thompson TD, Vahanian A, Ohman EM, Califf RM, Van de Werf F, Topol EJ. Prognostic value of the admission electrocardiogram in acute coronary syndromes. *JAMA* 1999;**281**: 707–713.
22. Volmink JA, Newton JN, Hicks NR, Sleight P, Fowler GH, Neil HA. Coronary event and case fatality rates in an English population: results of the Oxford myocardial infarction incidence study. The Oxford Myocardial Infarction Incidence Study Group. *Heart* 1998;**80**:40–44.
23. Terkelsen CJ, Lassen JF, Norgaard BL, Gerdes JC, Jensen T, Gotzsche LB, Nielsen TT, Andersen HR. Mortality rates in patients with ST-elevation vs. non-ST-elevation acute myocardial infarction: observations from an unselected cohort. *Eur Heart J* 2005;**26**:18–26.
24. Bahit MC, Granger CB, Wallentin L. Persistence of the prothrombotic state after acute coronary syndromes: implications for treatment. *Am Heart J* 2002;**143**:205–216.
25. Bogaty P, Poirier P, Simard S, Boyer L, Solymoss S, Dagenais GR. Biological profiles in subjects with recurrent acute coronary events compared with subjects with long-standing stable angina. *Circulation* 2001;**103**: 3062–3068.
26. Hamm C, Heeschen C, Falk E, Fox KAA. Acute coronary syndromes: pathophysiology, diagnosis and risk stratification. In: Camm AJ, Luescher TF, Serruys PW, ed. *The ESC Textbook of Cardiovascular Medicine*. Oxford: UK, Blackwell Publishing; 2006. p333–366.
27. Davies MJ. The pathophysiology of acute coronary syndromes. *Heart* 2000;**83**:361–366.
28. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. *Circulation* 2001;**104**:365–372.
29. Libby P. Inflammation in atherosclerosis. *Nature* 2002;**420**:868–874.
30. Hansson GK, Libby P, Schonbeck U, Yan ZQ. Innate and adaptive immunity in the pathogenesis of atherosclerosis. *Circ Res* 2002;**91**:281–291.
31. Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death. Autopsy evidence of recurrent mural thrombosis with peripheral embolization culminating in total vascular occlusion. *Circulation* 1985;**71**:699–708.
32. Davies MJ, Thomas AC, Knapman PA, Hangartner JR. Intramyocardial platelet aggregation in patients with unstable angina suffering sudden ischemic cardiac death. *Circulation* 1986;**73**:418–427.
33. Mizuno K, Satomura K, Miyamoto A, Arakawa K, Shibuya T, Arai T, Kurita A, Nakamura H, Ambrose JA. Angioscopic evaluation of coronary-artery thrombi in acute coronary syndromes. *N Engl J Med* 1992;**326**:287–291.
34. Fitzgerald DJ, Roy L, Catella F, FitzGerald GA. Platelet activation in unstable coronary disease. *N Engl J Med* 1986;**315**:983–989.
35. Ardissino D, Merlini PA, Ariens R, Coppola R, Bramucci E, Mannucci PM. Tissue-factor antigen and activity in human coronary atherosclerotic plaques. *Lancet* 1997;**349**:769–771.
36. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. *N Engl J Med* 2000;**343**: 1139–1147.
37. Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, Maseri A. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. *N Engl J Med* 1994;**331**: 417–424.
38. Rioufol G, Finet G, Ginon I, Andre-Fouet X, Rossi R, Vialle E, Desjoyaux E, Convert G, Huret JF, Tabib A. Multiple atherosclerotic plaque rupture in acute coronary syndrome: a three-vessel intravascular ultrasound study. *Circulation* 2002;**106**:804–808.
39. Fichtlscherer S, Breuer S, Zeiher AM. Prognostic value of systemic endothelial dysfunction in patients with acute coronary syndromes: further evidence for the existence of the 'vulnerable' patient. *Circulation* 2004;**110**:1926–1932.
40. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000;**101**:1899–1906.
41. Bugiardini R, Bairey Merz CN. Angina with 'normal' coronary arteries: a changing philosophy. *JAMA* 2005;**293**:477–484.
42. Kaski JC, Chester MR, Chen L, Katritsis D. Rapid angiographic progression of coronary artery disease in patients with angina pectoris. The role of complex stenosis morphology. *Circulation* 1995;**92**: 2058–2065.
43. Tofler GH, Muller JE. Triggering of acute cardiovascular disease and potential preventive strategies. *Circulation* 2006;**114**:1863–1872.
44. Skyschally A, Leineweber K, Gres P, Haude M, Erbel R, Heusch G. Coronary microembolization. *Basic Res Cardiol* 2006;**101**:373–382.
45. Campeau L. Letter: Grading of angina pectoris. *Circulation* 1976;**54**: 522–523.
46. van Domburg RT, van Miltenburg-van Zijl AJ, Veerhoek RJ, Simoons ML. Unstable angina: good long-term outcome after a complicated early course. *J Am Coll Cardiol* 1998;**31**:1534–1539.
47. Canto JG, Fincher C, Kiefe CI, Allison JJ, Li Q, Funkhouser E, Centor RM, Selker HP, Weissman NW. Atypical presentations among Medicare beneficiaries with unstable angina pectoris. *Am J Cardiol* 2002;**90**:248–253.
48. Culic V, Eterovic D, Miric D, Silic N. Symptom presentation of acute myocardial infarction: influence of sex, age, and risk factors. *Am Heart J* 2002;**144**:1012–1017.
49. Brieger D, Eagle KA, Goodman SG, Steg PG, Budaj A, White K, Montalescot G. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. *Chest* 2004;**126**:461–469.
50. Braunwald E. Unstable angina. A classification. *Circulation* 1989;**80**: 410–414.
51. van Miltenburg-van Zijl AJ, Simoons ML, Veerhoek RJ, Bossuyt PM. Incidence and follow-up of Braunwald subgroups in unstable angina pectoris. *J Am Coll Cardiol* 1995;**25**:1286–1292.
52. Hamm CW, Braunwald E. A classification of unstable angina revisited. *Circulation* 2000;**102**:118–122.
53. Diercks DB, Peacock WF, Hiestand BC, Chen AY, Pollack CV Jr, Kirk JD, Smith SC Jr, Gibler WB, Ohman EM, Blomkalns AL, Newby LK, Hochman JS, Peterson ED, Roe MT. Frequency and consequences of recording an electrocardiogram $>$ 10 min after arrival in an emergency room in non-ST-segment elevation acute coronary syndromes (from the CRUSADE Initiative). *Am J Cardiol* 2006;**97**:437–442.
54. Cannon CP, McCabe CH, Stone PH, Rogers WJ, Schactman M, Thompson BW, Pearce DJ, Diver DJ, Kells C, Feldman T, Williams M, Gibson RS, Kronenberg MW, Ganz LI, Anderson HV, Braunwald E. The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q wave myocardial infarction: results of the TIMI III Registry ECG Ancillary Study. Thrombolysis in Myocardial Ischemia. *J Am Coll Cardiol* 1997;**30**:133–140.
55. Holmvang L, Clemmensen P, Lindahl B, Lagerqvist B, Venge P, Wagner G, Wallentin L, Grande P. Quantitative analysis of the admission

electrocardiogram identifies patients with unstable coronary artery disease who benefit the most from early invasive treatment. *J Am Coll Cardiol* 2003;**41**:905–915.
56. Hyde TA, French JK, Wong CK, Straznicky IT, Whitlock RM, White HD. Four-year survival of patients with acute coronary syndromes without ST-segment elevation and prognostic significance of 0.5-mm ST-segment depression. *Am J Cardiol* 1999;**84**:379–385.
57. Kaul P, Fu Y, Chang WC, Harrington RA, Wagner GS, Goodman SG, Granger CB, Moliterno DJ, Van de Werf F, Califf RM, Topol EJ, Armstrong PW. Prognostic value of ST segment depression in acute coronary syndromes: insights from PARAGON-A applied to GUSTO-IIb. PARAGON-A and GUSTO IIb Investigators. Platelet IIb/IIIa Antagonism for the Reduction of Acute Global Organization Network. *J Am Coll Cardiol* 2001;**38**:64–71.
58. Nyman I, Areskog M, Areskog NH, Swahn E, Wallentin L. Very early risk stratification by electrocardiogram at rest in men with suspected unstable coronary heart disease. The RISC Study Group. *J Intern Med* 1993;**234**:293–301.
59. de Zwaan C, Bar FW, Janssen JH, Cheriex EC, Dassen WR, Brugada P, Penn OC, Wellens HJ. Angiographic and clinical characteristics of patients with unstable angina showing an ECG pattern indicating critical narrowing of the proximal LAD coronary artery. *Am Heart J* 1989;**117**: 657–665.
60. McCarthy BD, Wong JB, Selker HP. Detecting acute cardiac ischemia in the emergency department: a review of the literature. *J Gen Intern Med* 1990;**5**:365–373.
61. Rouan GW, Lee TH, Cook EF, Brand DA, Weisberg MC, Goldman L. Clinical characteristics and outcome of acute myocardial infarction in patients with initially normal or nonspecific electrocardiograms (a report from the Multicenter Chest Pain Study). *Am J Cardiol* 1989;**64**:1087–1092.
62. Akkerhuis KM, Klootwijk PA, Lindeboom W, Umans VA, Meij S, Kint PP, Simoons ML. Recurrent ischaemia during continuous multilead ST-segment monitoring identifies patients with acute coronary syndromes at high risk of adverse cardiac events; meta-analysis of three studies involving 995 patients. *Eur Heart J* 2001;**22**:1997–2006.
63. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia as a marker for early unfavorable outcomes in patients with unstable angina. *N Engl J Med* 1986;**314**:1214–1219.
64. Jernberg T, Lindahl B, Wallentin L. The combination of a continuous 12-lead ECG and troponin T; a valuable tool for risk stratification during the first 6 h in patients with chest pain and a non-diagnostic ECG. *Eur Heart J* 2000;**21**:1464–1472.
65. Patel DJ, Holdright DR, Knight CJ, Mulcahy D, Thakrar B, Wright C, Sparrow J, Wicks M, Hubbard W, Thomas R, Sutton GC, Hendry G, Purcell H, Fox K. Early continuous ST segment monitoring in unstable angina: prognostic value additional to the clinical characteristics and the admission electrocardiogram. *Heart* 1996;**75**:222–228.
66. Nyman I, Wallentin L, Areskog M, Areskog NH, Swahn E. Risk stratification by early exercise testing after an episode of unstable coronary artery disease. The RISC Study Group. *Int J Cardiol* 1993;**39**:131–142.
67. Eggers KM, Oldgren J, Nordenskjold A, Lindahl B. Diagnostic value of serial measurement of cardiac markers in patients with chest pain: limited value of adding myoglobin to troponin I for exclusion of myocardial infarction. *Am Heart J* 2004;**148**:574–581.
68. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Personal Communication*.
69. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, Fischer GA, Fung AY, Thompson C, Wybenga D, Braunwald E. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996;**335**:1342–1349.
70. Hamm CW, Ravkilde J, Gerhardt W, Jorgensen P, Peheim E, Ljungdahl L, Goldmann B, Katus HA. The prognostic value of serum troponin T in unstable angina. *N Engl J Med* 1992;**327**:146–150.
71. James SK, Lindahl B, Siegbahn A, Stridsberg M, Venge P, Armstrong P, Barnathan ES, Califf R, Topol EJ, Simoons ML, Wallentin L. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. *Circulation* 2003;**108**: 275–281.
72. Lindahl B, Diderholm E, Lagerqvist B, Venge P, Wallentin L. Mechanisms behind the prognostic value of troponin T in unstable coronary artery disease: a FRISC II substudy. *J Am Coll Cardiol* 2001;**38**:979–986.
73. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann FJ, Robertson DH, DeLucca PT, DiBattiste PM, Gibson CM, Braunwald E. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;**344**:1879–1887.
74. Hamm CW, Heeschen C, Goldmann B, Vahanian A, Adgey J, Miguel CM, Rutsch W, Berger J, Kootstra J, Simoons ML. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators. *N Engl J Med* 1999;**340**:1623–1629.
75. Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. PRISM Study Investigators. Platelet Receptor Inhibition in Ischemic Syndrome Management. *Lancet* 1999;**354**:1757–1762.
76. Hamm CW, Goldmann BU, Heeschen C, Kreymann G, Berger J, Meinertz T. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. *N Engl J Med* 1997;**337**:1648–1653.
77. Apple FS, Murakami MM, Pearce LA, Herzog CA. Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. *Circulation* 2002;**106**:2941–2945.
78. Aviles RJ, Askari AT, Lindahl B, Wallentin L, Jia G, Ohman EM, Mahaffey KW, Newby LK, Califf RM, Simoons ML, Topol EJ, Berger P, Lauer MS. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med* 2002;**346**:2047–2052.
79. Heeschen C, Hamm CW, Bruemmer J, Simoons ML. Predictive value of C-reactive protein and troponin T in patients with unstable angina: a comparative analysis. CAPTURE Investigators. Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment trial. *J Am Coll Cardiol* 2000;**35**:1535–1542.
80. Morrow DA, Rifai N, Antman EM, Weiner DL, McCabe CH, Cannon CP, Braunwald E. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in myocardial infarction. *J Am Coll Cardiol* 1998;**31**:1460–1465.
81. de Winter RJ, Koch KT, van Straalen JP, Heyde G, Bax M, Schotborgh CE, Mulder KJ, Sanders GT, Fischer J, Tijssen JG, Piek JJ. C-reactive protein and coronary events following percutaneous coronary angioplasty. *Am J Med* 2003;**115**:85–90.
82. de Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, McCabe CH, Hall C, Cannon CP, Braunwald E. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med* 2001;**345**:1014–1021.
83. Jernberg T, Stridsberg M, Venge P, Lindahl B. N-terminal pro brain natriuretic peptide on admission for early risk stratification of patients with chest pain and no ST-segment elevation. *J Am Coll Cardiol* 2002; **40**:437–445.
84. Heeschen C, Hamm CW, Mitrovic V, Lantelme NH, White HD. N-terminal pro-B-type natriuretic peptide levels for dynamic risk stratification of patients with acute coronary syndromes. *Circulation* 2004;**110**: 3206–3212.
85. Weber M, Kleine C, Keil E, Rau M, Berkowitsch A, Elsaesser A, Mitrovic V, Hamm C. Release pattern of N-terminal pro B-type natriuretic peptide (NT-proBNP) in acute coronary syndromes. *Clin Res Cardiol* 2006;**95**: 270–280.
86. Mueller C, Laule-Kilian K, Schindler C, Klima T, Frana B, Rodriguez D, Scholer A, Christ M, Perruchoud AP. Cost-effectiveness of B-type natriuretic peptide testing in patients with acute dyspnea. *Arch Intern Med* 2006;**166**:1081–1087.
87. Al Suwaidi J, Reddan DN, Williams K, Pieper KS, Harrington RA, Califf RM, Granger CB, Ohman EM, Holmes DR Jr. Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. *Circulation* 2002;**106**:974–980.
88. Masoudi FA, Plomondon ME, Magid DJ, Sales A, Rumsfeld JS. Renal insufficiency and mortality from acute coronary syndromes. *Am Heart J* 2004; **147**:623–629.
89. Weber JA, van Zanten AP. Interferences in current methods for measurements of creatinine. *Clin Chem* 1991;**37**:695–700.
90. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;**16**:31–41.
91. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;**130**:461–470.
92. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, Murphy SA, Budaj A, Varshavsky S, Wolff AA, Skene A, McCabe CH, Braunwald E; MERLIN-TIMI 36 Trial Investigators. Effects of ranolazine on recurrent cardiovascular

events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. *JAMA* 2007;**297**:1775–1783.
93. Coll E, Botey A, Alvarez L, Poch E, Quinto L, Saurina A, Vera M, Piera C, Darnell A. Serum cystatin C as a new marker for noninvasive estimation of glomerular filtration rate and as a marker for early renal impairment. *Am J Kidney Dis* 2000;**36**:29–34.
94. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, Siscovick DS, Stehman-Breen C. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med* 2005;**352**: 2049–2060.
95. Jernberg T, Lindahl B, James S, Larsson A, Hansson LO, Wallentin L. Cystatin C: a novel predictor of outcome in suspected or confirmed non-ST-elevation acute coronary syndrome. *Circulation* 2004;**110**: 2342–2348.
96. Baldus S, Heeschen C, Meinertz T, Zeiher AM, Eiserich JP, Munzel T, Simoons ML, Hamm CW. Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. *Circulation* 2003;**108**: 1440–1445.
97. Brennan ML, Penn MS, Van Lente F, Nambi V, Shishehbor MH, Aviles RJ, Goormastic M, Pepoy ML, McErlean ES, Topol EJ, Nissen SE, Hazen SL. Prognostic value of myeloperoxidase in patients with chest pain. *N Engl J Med* 2003;**349**:1595–1604.
98. Heeschen C, Dimmeler S, Hamm CW, van den Brand MJ, Boersma E, Zeiher AM, Simoons ML. Soluble CD40 ligand in acute coronary syndromes. *N Engl J Med* 2003;**348**:1104–1111.
99. Varo N, de Lemos JA, Libby P, Morrow DA, Murphy SA, Nuzzo R, Gibson CM, Cannon CP, Braunwald E, Schonbeck U. Soluble CD40L: risk prediction after acute coronary syndromes. *Circulation* 2003;**108**: 1049–1052.
100. Antman EM, Grudzien C, Sacks DB. Evaluation of a rapid bedside assay for detection of serum cardiac troponin T. *JAMA* 1995;**273**:1279–1282.
101. Ohman EM, Armstrong PW, White HD, Granger CB, Wilcox RG, Weaver WD, Gibler WB, Stebbins AL, Cianciolo C, Califf RM, Topol EJ. Risk stratification with a point-of-care cardiac troponin T test in acute myocardial infarction. GUSTOIII Investigators. Global Use of Strategies To Open Occluded Coronary Arteries. *Am J Cardiol* 1999;**84**: 1281–1286.
102. Wu AH, Apple FS, Gibler WB, Jesse RL, Warshaw MM, Valdes R Jr. National Academy of Clinical Biochemistry Standards of Laboratory Practice: recommendations for the use of cardiac markers in coronary artery diseases. *Clin Chem* 1999;**45**:1104–1121.
103. Sylven C, Lindahl S, Hellkvist K, Nyquist O, Rasmanis G. Excellent reliability of nurse-based bedside diagnosis of acute myocardial infarction by rapid dry-strip creatine kinase MB, myoglobin, and troponin T. *Am Heart J* 1998;**135**:677–683.
104. Muller-Bardorff M, Rauscher T, Kampmann M, Schoolmann S, Laufenberg F, Mangold D, Zerback R, Remppis A, Katus HA. Quantitative bedside assay for cardiac troponin T: a complementary method to centralized laboratory testing. *Clin Chem* 1999;**45**:1002–1008.
105. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, Douglas PS, Faxon DP, Gillam LD, Kimball TR, Kussmaul WG, Pearlman AS, Philbrick JT, Rakowski H, Thys DM, Antman EM, Smith SC Jr, Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). *Circulation* 2003;**108**:1146–1162.
106. Amanullah AM, Lindvall K. Predischarge exercise echocardiography in patients with unstable angina who respond to medical treatment. *Clin Cardiol* 1992;**15**:417–423.
107. Amanullah AM, Lindvall K, Bevegard S. Prognostic significance of exercise thallium-201 myocardial perfusion imaging compared to stress echocardiography and clinical variables in patients with unstable angina who respond to medical treatment. *Int J Cardiol* 1993;**39**:71–78.
108. Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging in patients with unstable angina who respond to medical treatment. *J Am Coll Cardiol* 1991;**17**:1053–1057.
109. Kwong RY, Schussheim AE, Rekhraj S, Aletras AH, Geller N, Davis J, Christian TF, Balaban RS, Arai AE. Detecting acute coronary syndrome in the emergency department with cardiac magnetic resonance imaging. *Circulation* 2003;**107**:531–537.
110. Udelson JE, Beshansky JR, Ballin DS, Feldman JA, Griffith JL, Handler J, Heller GV, Hendel RC, Pope JH, Ruthazer R, Spiegler EJ, Woolard RH, Selker HP. Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: a randomized controlled trial. *JAMA* 2002;**288**:2693–2700.
111. Luchi RJ, Scott SM, Deupree RH. Comparison of medical and surgical treatment for unstable angina pectoris. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1987;**316**:977–984.
112. Dirksen MS, Jukema JW, Bax JJ, Lamb HJ, Boersma E, Tuinenburg JC, Geleijns J, van der Wall EE, de Roos A. Cardiac multidetector-row computed tomography in patients with unstable angina. *Am J Cardiol* 2005; **95**:457–461.
113. Hasdai D, Lev EI, Behar S, Boyko V, Danchin N, Vahanian A, Battler A. Acute coronary syndromes in patients with pre-existing moderate to severe valvular disease of the heart: lessons from the Euro-Heart Survey of acute coronary syndromes. *Eur Heart J* 2003;**24**:623–629.
114. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med* 2004;**351**:2611–2618.
115. Fedullo PF, Tapson VF. Clinical practice. The evaluation of suspected pulmonary embolism. *N Engl J Med* 2003;**349**:1247–1256.
116. James P, Ellis CJ, Whitlock RM, McNeil AR, Henley J, Anderson NE. Relation between troponin T concentration and mortality in patients presenting with an acute stroke: observational study. *BMJ* 2000;**320**: 1502–1504.
117. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, de Werf FV, Avezum A, Goodman SG, Flather MD, Anderson FA Jr, Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 2006;**333**:1091.
118. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003;**163**:2345–2353.
119. de Araujo Goncalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. *Eur Heart J* 2005;**26**: 865–872.
120. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;**284**:835–842.
121. Lagerqvist B, Diderholm E, Lindahl B, Husted S, Kontny F, Stahle E, Swahn E, Venge P, Siegbahn A, Wallentin L. FRISC score for selection of patients for an early invasive treatment strategy in unstable coronary artery disease. *Heart* 2005;**91**:1047–1052.
122. Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E, Wallentin L. 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. *Lancet* 2006;**368**:998–1004.
123. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, Akkerhuis KM, Harrington RA, Deckers JW, Armstrong PW, Lincoff AM, Califf RM, Topol EJ, Simoons ML. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation* 2000;**101**:2557–2567.
124. Telford AM, Wilson C. Trial of heparin versus atenolol in prevention of myocardial infarction in intermediate coronary syndrome. *Lancet* 1981;**1**:1225–1228.
125. Lubsen J, Tijssen JG. Efficacy of nifedipine and metoprolol in the early treatment of unstable angina in the coronary care unit: findings from the Holland Interuniversity Nifedipine/metoprolol Trial (HINT). *Am J Cardiol* 1987;**60**:18A–25A.
126. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. *JAMA* 1988;**260**: 2259–2263.
127. The MIAMI Trial Research Group. Metoprolol in acute myocardial infarction (MIAMI). A randomised placebo-controlled international trial. *Eur Heart J* 1985;**6**:199–226.
128. Kaplan K, Davison R, Parker M, Przybylek J, Teagarden JR, Lesch M. Intravenous nitroglycerin for the treatment of angina at rest unresponsive to standard nitrate therapy. *Am J Cardiol* 1983;**51**:694–698.
129. DePace NL, Herling IM, Kotler MN, Hakki AH, Spielman SR, Segal BL. Intravenous nitroglycerin for rest angina. Potential pathophysiologic mechanisms of action. *Arch Intern Med* 1982;**142**:1806–1809.
130. Roubin GS, Harris PJ, Eckhardt I, Hensley W, Kelly DT. Intravenous nitroglycerine in refractory unstable angina pectoris. *Aust N Z J Med* 1982; **12**:598–602.

131. Curfman GD, Heinsimer JA, Lozner EC, Fung HL. Intravenous nitroglycerin in the treatment of spontaneous angina pectoris: a prospective, randomized trial. *Circulation* 1983;**67**:276–282.
132. Dellborg M, Gustafsson G, Swedberg K. Buccal versus intravenous nitroglycerin in unstable angina pectoris. *Eur J Clin Pharmacol* 1991;**41**:5–9.
133. Theroux P, Taeymans Y, Morissette D, Bosch X, Pelletier GB, Waters DD. A randomized study comparing propranolol and diltiazem in the treatment of unstable angina. *J Am Coll Cardiol* 1985;**5**:717–722.
134. Parodi O, Simonetti I, Michelassi C, Carpeggiani C, Biagini A, L'Abbate A, Maseri A. Comparison of verapamil and propranolol therapy for angina pectoris at rest: a randomized, multiple-crossover, controlled trial in the coronary care unit. *Am J Cardiol* 1986;**57**:899–906.
135. Smith NL, Reiber GE, Psaty BM, Heckbert SR, Siscovick DS, Ritchie JL, Every NR, Koepsell TD. Health outcomes associated with beta-blocker and diltiazem treatment of unstable angina. *J Am Coll Cardiol* 1998; **32**:1305–1311.
136. Gibson RS, Young PM, Boden WE, Schechtman K, Roberts R. Prognostic significance and beneficial effect of diltiazem on the incidence of early recurrent ischemia after non-Q-wave myocardial infarction: results from the Multicenter Diltiazem Reinfarction Study. *Am J Cardiol* 1987;**60**:203–209.
137. Held PH, Yusuf S, Furberg CD. Calcium channel blockers in acute myocardial infarction and unstable angina: an overview. *BMJ* 1989;**299**: 1187–1192.
138. Psaty BM, Heckbert SR, Koepsell TD, Siscovick DS, Raghunathan TE, Weiss NS, Rosendaal FR, Lemaitre RN, Smith NL, Wahl PW, Wagner EH, Furberg CD. The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 1995;**274**:620–625.
139. Yusuf S, Held P, Furberg C. Update of effects of calcium antagonists in myocardial infarction or angina in light of the second Danish Verapamil Infarction Trial (DAVIT-II) and other recent studies. *Am J Cardiol* 1991; **67**:1295–1297.
140. Boden WE, van Gilst WH, Scheldewaert RG, Starkey IR, Carlier MF, Julian DG, Whitehead A, Bertrand ME, Col JJ, Pedersen OL, Lie KI, Santoni JP, Fox KM. Diltiazem in acute myocardial infarction treated with thrombolytic agents: a randomised placebo-controlled trial. Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis post-Thrombolysis (INTERCEPT). *Lancet* 2000;**355**: 1751–1756.
141. Borer JS. Therapeutic effects of I(f) blockade: evidence and perspective. *Pharmacol Res* 2006;**53**:440–445.
142. McClellan KJ, Plosker GL. Trimetazidine. A review of its use in stable angina pectoris and other coronary conditions. *Drugs* 1999;**58**:143–157.
143. Chaitman BR. Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. *Circulation* 2006;**113**: 2462–2472.
144. IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet* 2002;**359**:1269–1275.
145. Harrington RA, Becker RC, Ezekowitz M, Meade TW, O'Connor CM, Vorchheimer DA, Guyatt GH. Antithrombotic therapy for coronary artery disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;**126**:513S–548S.
146. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;**126**:188S–203S.
147. Theroux P, Ouimet H, McCans J, Latour JG, Joly P, Levy G, Pelletier E, Juneau M, Stasiak J, deGuise P, Pelletier GB, Rinzler D, Waters DD. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988;**319**:1105–1111.
148. Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet* 2000; **355**:1936–1942.
149. Collins R, MacMahon S, Flather M, Baigent C, Remvig L, Mortensen S, Appleby P, Godwin J, Yusuf S, Peto R. Clinical effects of anticoagulant therapy in suspected acute myocardial infarction: systematic overview of randomised trials. *BMJ* 1996;**313**:652–659.
150. Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *JAMA* 1996;**276**:811–815.
151. Antman EM, McCabe CH, Gurfinkel EP, Turpie AG, Bernink PJ, Salein D, Bayes De Luna A, Fox K, Lablanche JM, Radley D, Premmereur J, Braunwald E. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation* 1999;**100**:1593–1601.
152. Cohen M, Demers C, Gurfinkel EP, Turpie AG, Fromell GJ, Goodman S, Langer A, Califf RM, Fox KA, Premmereur J, Bigonzi F. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med* 1997;**337**: 447–452.
153. Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease Investigators. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;**354**:701–707.
154. Fragmin During Instability in Coronary Artery Disease (FRISC) Study Group. Low-molecular-weight heparin during instability in coronary artery disease. *Lancet* 1996;**347**:561–568.
155. Klein W, Buchwald A, Hillis SE, Monrad S, Sanz G, Turpie AG, van der Meer J, Olaisson E, Undeland S, Ludwig K. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC). *Circulation* 1997;**96**:61–68.
156. TIMI 11A Investigators. Dose-ranging trial of enoxaparin for unstable angina: results of TIMI 11A. The Thrombolysis in Myocardial Infarction (TIMI) 11A Trial Investigators. *J Am Coll Cardiol* 1997;**29**:1474–1482.
157. Fragmin During Instability in Coronary Artery Disease (FRISC) Study Group. Low-molecular-weight heparin during instability in coronary artery disease. *Lancet* 1996;**347**:561–568.
158. Gurfinkel EP, Manos EJ, Mejail RI, Cerda MA, Duronto EA, Garcia CN, Daroca AM, Mautner B. Low molecular weight heparin versus regular heparin or aspirin in the treatment of unstable angina and silent ischemia. *J Am Coll Cardiol* 1995;**26**:313–318.
159. FRAX.I.S. (FRAxiparine in Ischemic Syndromes) Investigators. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q wave myocardial infarction: FRAX.I.S. (Fraxiparine in Ischaemic Syndrome). *Eur Heart J* 1999; **20**:1553–1562.
160. Lindahl B, Venge P, Wallentin L. The FRISC experience with troponin T. Use as decision tool and comparison with other prognostic markers. *Eur Heart J* 1998;**19**(Suppl. N):N51–N58.
161. Blazing MA, de Lemos JA, White HD, Fox KA, Verheugt FW, Ardissino D, DiBattiste PM, Palmisano J, Bilheimer DW, Snapinn SM, Ramsey KE, Gardner LH, Hasselblad V, Pfeffer MA, Lewis EF, Braunwald E, Califf RM. Safety and efficacy of enoxaparin vs. unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes who receive tirofiban and aspirin: a randomized controlled trial. *JAMA* 2004;**292**:55–64.
162. Cohen M, Theroux P, Borzak S, Frey MJ, White HD, Van Mieghem W, Senatore F, Lis J, Mukherjee R, Harris K, Bigonzi F. Randomized double-blind safety study of enoxaparin versus unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes treated with tirofiban and aspirin: the ACUTE II study. The antithrombotic combination using tirofiban and enoxaparin. *Am Heart J* 2002;**144**: 470–477.
163. Goodman SG, Fitchett D, Armstrong PW, Tan M, Langer A. Randomized evaluation of the safety and efficacy of enoxaparin versus unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes receiving the glycoprotein IIb/IIIa inhibitor eptifibatide. *Circulation* 2003;**107**:238–244.
164. Ferguson JJ, Califf RM, Antman EM, Cohen M, Grines CL, Goodman S, Kereiakes DJ, Langer A, Mahaffey KW, Nessel CC, Armstrong PW, Avezum A, Aylward P, Becker RC, Biasucci L, Borzak S, Col J, Frey MJ, Fry E, Gulba DC, Guneri S, Gurfinkel E, Harrington R, Hochman JS, Kleiman NS, Leon MB, Lopez-Sendon JL, Pepine CJ, Ruzyllo W, Steinhubl SR, Teirstein PS, Toro-Figueroa L, White H. Enoxaparin vs. unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. *JAMA* 2004;**292**:45–54.
165. Petersen JL, Mahaffey KW, Hasselblad V, Antman EM, Cohen M, Goodman SG, Langer A, Blazing MA, Le-Moigne-Amrani A, de Lemos JA, Nessel CC, Harrington RA, Ferguson JJ, Braunwald E, Califf RM. Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-segment elevation acute coronary syndromes: a systematic overview. *JAMA* 2004;**292**:89–96.

166. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Granger CB, Budaj A, Peters RJG, Bassand JP, Wallentin L, Joyner C, Fox KAA. Effects of Fondaparinux, a factor Xa inhibitor, on mortality and reinfarction in patients with acute myocardial infarction presenting with ST-segment elevation. Organization to Assess Strategies for Ischemic Syndromes (OASIS)-6 Investigators. *JAMA* 2006;**295**:1519–1530.
167. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494–502.
168. Alexander KP, Chen AY, Roe MT, Newby LK, Gibson CM, Allen-LaPointe NM, Pollack C, Gibler WB, Ohman EM, Peterson ED. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. *JAMA* 2005; **294**:3108–3116.
169. Ferguson JJ, Antman EM, Bates ER, Cohen M, Every NR, Harrington RA, Pepine CJ, Theroux P. Combining enoxaparin and glycoprotein IIb/IIIa antagonists for the treatment of acute coronary syndromes: final results of the National Investigators Collaborating on Enoxaparin-3 (NICE-3) study. *Am Heart J* 2003;**146**:628–634.
170. James S, Armstrong P, Califf R, Husted S, Kontny F, Niemminen M, Pfisterer M, Simoons ML, Wallentin L. Safety and efficacy of abciximab combined with dalteparin in treatment of acute coronary syndromes. *Eur Heart J* 2002;**23**:1538–1545.
171. Mukherjee D, Mahaffey KW, Moliterno DJ, Harrington RA, Yadav JS, Pieper KS, Gallup D, Dyke C, Roe MT, Berdan L, Lauer MS, Manttari M, White HD, Califf RM, Topol EJ. Promise of combined low-molecular-weight heparin and platelet glycoprotein IIb/IIIa inhibition: results from Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organization Network B (PARAGON B). *Am Heart J* 2002;**144**:995–1002.
172. Zeymer U, Gitt A, Junger C, Koeth O, Zahn R, Wienbergen H, Gottwik M, Senges J. Clinical benefit of enoxaparin in patients with high-risk acute coronary syndromes without ST elevations in clinical practice. *Am J Cardiol* 2006;**98**:19–22.
173. Simoons ML, Bobbink IW, Boland J, Gardien M, Klootwijk P, Lensing AW, Ruzyllo W, Umans VA, Vahanian A, Van De Werf F, Zeymer U. A dose-finding study of fondaparinux in patients with non-ST-segment elevation acute coronary syndromes: the Pentasaccharide in Unstable Angina (PENTUA) Study. *J Am Coll Cardiol* 2004;**43**:2183–2190.
174. Mehta SR, Steg PG, Granger CB, Bassand JP, Faxon DP, Weitz JI, Afzal R, Rush B, Peters RJ, Natarajan MK, Velianou JL, Goodhart DM, Labinaz M, Tanguay JF, Fox KA, Yusuf S. Randomized, blinded trial comparing fondaparinux with unfractionated heparin in patients undergoing contemporary percutaneous coronary intervention: Arixtra Study in Percutaneous Coronary Intervention: a Randomized Evaluation (ASPIRE) Pilot Trial. *Circulation* 2005;**111**:1390–1397.
175. MICHELANGELO OASIS 5 Steering Committee; Mehta SR, Yusuf S, Granger CB, Wallentin L, Peters RJ, Bassand JP, Budaj A, Joyner C, Chrolavicus S, Fox KA. Design and rationale of the MICHELANGELO. Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-5 trial program evaluating fondaparinux, a synthetic factor Xa inhibitor, in patients with non-ST-segment elevation acute coronary syndromes. *Am Heart J* 2005;**150**:1107.
176. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Granger CB, Budaj A, Peters RJ, Bassand JP, Wallentin L, Joyner C, Fox KA. Efficacy and safety of fondaparinux compared to enoxaparin in 20,078 patients with acute coronary syndromes without ST segment elevation. The OASIS (Organization to Assess Strategies in Acute Ischemic Syndromes)-5 Investigators. *N Engl J Med* 2006;**354**:1464–1476.
177. Direct Thrombin Inhibitor Trialists' Collaborative Group. Direct thrombin inhibitors in acute coronary syndromes: principal results of a meta-analysis based on individual patients' data. *Lancet* 2002;**359**: 294–302.
178. Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) Investigators. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularisation procedures in patients with acute myocardial ischaemia without ST elevation: a randomised trial. *Lancet* 1999;**353**: 429–438.
179. Bittl JA, Chaitman BR, Feit F, Kimball W, Topol EJ. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: final report reanalysis of the Bivalirudin Angioplasty Study. *Am Heart J* 2001;**142**:952–959.
180. Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Kereiakes DJ, Rutsch W, Wilcox RG, de Feyter PJ, Vahanian A, Topol EJ. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003;**289**:853–863.
181. Lincoff AM, Kleiman NS, Kereiakes DJ, Feit F, Bittl JA, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Rutsch W, Wilcox RG, de Feyter PJ, Vahanian A, Topol EJ. Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs. heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. *JAMA* 2004;**292**:696–703.
182. Silber S, Albertsson P, Aviles FF, Camici PG, Colombo A, Hamm C, Jorgensen E, Marco J, Nordrehaug JE, Ruzyllo W, Urban P, Stone GW, Wijns W. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J* 2005;**26**:804–847.
183. Dang CH, Durkalski VL, Nappi JM. Evaluation of treatment with direct thrombin inhibitors in patients with heparin-induced thrombocytopenia. *Pharmacotherapy* 2006;**26**:461–468.
184. Lubenow N, Greinacher A. Drugs for the prevention and treatment of thrombosis in patients with heparin-induced thrombocytopenia. *Am J Cardiovasc Drugs* 2001;**1**:429–443.
185. Warkentin TE. Management of heparin-induced thrombocytopenia: a critical comparison of lepirudin and argatroban. *Thromb Res* 2003; **110**:73–82.
186. Stone GW, Bertrand M, Colombo A, Dangas G, Farkouh ME, Feit F, Lansky AJ, Lincoff AM, Mehran R, Moses JW, Ohman M, White HD. Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial: study design and rationale. *Am Heart J* 2004;**148**: 764–775.
187. Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, Moses JW, White HD, Pocock SJ, Ware JH, Feit F, Colombo A, Aylward PE, Cequier AR, Darius H, Desmet W, Ebrahimi R, Hamon M, Rasmussen LH, Rupprecht HJ, Hoekstra J, Mehran R, Ohman EM. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; **355**:2203–2216.
188. Kastrati A, Mehilli J, Neumann FJ, Dotzer F, ten Berg J, Bollwein H, Graf I, Ibrahim M, Pache J, Seyfarth M, Schuhlen H, Dirschinger J, Berger PB, Schomig A. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA* 2006; **295**:1531–1538.
189. Brown D, Volkers P, Day S. An introductory note to the CHMP guidelines: choice of the non-inferiority margin and data monitoring committees. *Stat Med* 2006;**25**:1623–1627.
190. Committee for Medicinal Products for Human Use (CHMP). Guideline on the choice of the non-inferiority margin. *Stat Med* 2006;**25**:1628–1638.
191. Andres AM, Tejedor IH. An approximate unconditional test of non-inferiority between two proportions. *Stat Med* 2001;**20**:2206–2208.
192. Brown D, Volkers P, Day S. An introductory note to CHMP guidelines: choice of the non-inferiority margin and data monitoring committees. *Stat Med* 2006;**25**:1623–1627.
193. Chow SC, Shao J. On non-inferiority margin and statistical tests in active control trials. *Stat Med* 2006;**25**:1101–1113.
194. Hung HM, Wang SJ, O'Neill R. A regulatory perspective on choice of margin and statistical inference issue in non-inferiority trials. *Biometrical J* 2005;**47**:28–36; discussion 99–107.
195. Kang SH, Chen JJ. An approximate unconditional test of non-inferiority between two proportions. *Stat Med* 2000;**19**:2089–2100.
196. Sidik K. Exact unconditional tests for testing non-inferiority in matched-pairs design. *Stat Med* 2003;**22**:265–278.
197. Kaul S, Diamond GA. Making sense of noninferiority: a clinical and statistical perspective on its application to cardiovascular clinical trials. *Prog Cardiovasc Dis* 2007;**49**:284–299.
198. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; **126**:204S–233S.
199. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002;**347**: 969–974.
200. Andreotti F, Testa L, Biondi-Zoccai GG, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25 307 patients. *Eur Heart J* 2006;**27**:519–526.

201. Organization to Assess Strategies for Ischemic Syndromes (OASIS) Investigators. Effects of long-term, moderate-intensity oral anticoagulation in addition to aspirin in unstable angina. *J Am Coll Cardiol* 2001;**37**: 475–484.
202. Buresly K, Eisenberg MJ, Zhang X, Pilote L. Bleeding complications associated with combinations of aspirin, thienopyridine derivatives, and warfarin in elderly patients following acute myocardial infarction. *Arch Intern Med* 2005;**165**:784–789.
203. Natarajan MK, Velianou JL, Turpie AG, Mehta SR, Raco D, Goodhart DM, Afzal R, Ginsberg JS. A randomized pilot study of dalteparin versus unfractionated heparin during percutaneous coronary interventions. *Am Heart J* 2006;**151**:175.
204. Popma JJ, Berger P, Ohman EM, Harrington RA, Grines C, Weitz JI. Antithrombotic therapy during percutaneous coronary intervention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;**126**:576S–599S.
205. Montalescot G, White HD, Gallo R, Cohen M, Steg PG, Aylward PE, Bode C, Chiariello M, King SB III, Harrington RA, Desmet WJ, Macaya C, Steinhubl SR. Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention. *N Engl J Med* 2006;**355**: 1006–1017.
206. Majure DT, Aberegg SK. Fondaparinux versus enoxaparin in acute coronary syndromes. *N Engl J Med* 2006;**354**:2829; author reply 2830.
207. Theroux P, Waters D, Qiu S, McCans J, de Guise P, Juneau M. Aspirin versus heparin to prevent myocardial infarction during the acute phase of unstable angina. *Circulation* 1993;**88**:2045–2048.
208. Cairns JA, Singer J, Gent M, Holder DA, Rogers D, Sackett DL, Sealey B, Tanser P, Vandervoort M. One year mortality outcomes of all coronary and intensive care unit patients with acute myocardial infarction, unstable angina or other chest pain in Hamilton, Ontario, a city of 375,000 people. *Can J Cardiol* 1989;**5**:239–246.
209. Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.
210. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;**348**:1329–1339.
211. Silberman S, Neukirch-Stoop C, Steg PG. Rapid desensitization procedure for patients with aspirin hypersensitivity undergoing coronary stenting. *Am J Cardiol* 2005;**95**:509–510.
212. Gollapudi RR, Teirstein PS, Stevenson DD, Simon RA. Aspirin sensitivity: implications for patients with coronary artery disease. *JAMA* 2004;**292**: 3017–3023.
213. Ramanuja S, Breall JA, Kalaria VG. Approach to 'aspirin allergy' in cardiovascular patients. *Circulation* 2004;**110**:e1–e4.
214. Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL, Diaz R, Commerford PJ, Valentin V, Yusuf S. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation* 2003;**108**: 1682–1687.
215. Balsano F, Rizzon P, Violi F, Scrutinio D, Cimminiello C, Aguglia F, Pasotti C, Rudelli G. Antiplatelet treatment with ticlopidine in unstable angina. A controlled multicenter clinical trial. The Studio della Ticlopidina nell'Angina Instabile Group. *Circulation* 1990;**82**:17–26.
216. Budaj A, Yusuf S, Mehta SR, Fox KA, Tognoni G, Zhao F, Chrolavicius S, Hunt D, Keltai M, Franzosi MG. Benefit of clopidogrel in patients with acute coronary syndromes without ST-segment elevation in various risk groups. *Circulation* 2002;**106**:1622–1626.
217. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;**354**: 1706–1717.
218. Chan AW, Moliterno DJ, Berger PB, Stone GW, DiBattiste PM, Yakubov SL, Sapp SK, Wolski K, Bhatt DL, Topol EJ. Triple antiplatelet therapy during percutaneous coronary intervention is associated with improved outcomes including one-year survival: results from the Do Tirofiban and ReoProGive Similar Efficacy Outcome Trial (TARGET). *J Am Coll Cardiol* 2003;**42**:1188–1195.
219. Steinhubl SR, Berger PB, Mann JT III, Fry ET, DeLago A, Wilmer C, Topol EJ. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;**288**:2411–2420.
220. Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, Yusuf S. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. *Circulation* 2004;**110**:1202–1208.
221. Kandzari DE, Berger PB, Kastrati A, Steinhubl SR, Mehilli J, Dotzer F, Ten Berg JM, Neumann FJ, Bollwein H, Dirschinger J, Schomig A. Influence of treatment duration with a 600-mg dose of clopidogrel before percutaneous coronary revascularization. *J Am Coll Cardiol* 2004;**44**: 2133–2136.
222. Montalescot G, Sideris G, Meuleman C, Bal-dit-Sollier C, Lellouche N, Steg PG, Slama M, Milleron O, Collet JP, Henry P, Beygui F, Drouet L. A randomized comparison of high clopidogrel loading doses in patients with non-ST-segment elevation acute coronary syndromes: the ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) trial. *J Am Coll Cardiol* 2006;**48**:931–938.
223. Patti G, Colonna G, Pasceri V, Pepe LL, Montinaro A, Di Sciascio G. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. *Circulation* 2005;**111**:2099–2106.
224. von Beckerath N, Taubert D, Pogatsa-Murray G, Schomig E, Kastrati A, Schomig A. Absorption, metabolization, and antiplatelet effects of 300-, 600-, and 900-mg loading doses of clopidogrel: results of the ISAR-CHOICE (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) Trial. *Circulation* 2005;**112**:2946–2950.
225. Hochholzer W, Trenk D, Bestehorn HP, Fischer B, Valina CM, Ferenc M, Gick M, Caputo A, Buttner HJ, Neumann FJ. Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. *J Am Coll Cardiol* 2006;**48**:1742–1750.
226. Szuk T, Gyongyosi M, Homorodi N, Kristof E, Kiraly C, Edes IF, Facsko A, Pavo N, Sodeck G, Strehblow C, Farhan S, Maurer G, Glogar D, Domanovits H, Huber K, Edes I. Effect of timing of clopidogrel administration on 30-day clinical outcomes: 300-mg loading dose immediately after coronary stenting versus pretreatment 6 to 24 h before stenting in a large unselected patient cohort. *Am Heart J* 2007;**153**:289–295.
227. SYMPHONY Investigators. Comparison of sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial. The SYMPHONY Investigators. Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-acute Coronary Syndromes. *Lancet* 2000;**355**:337–345.
228. Topol EJ, Easton D, Harrington RA, Amarenco P, Califf RM, Graffagnino C, Davis S, Diener HC, Ferguson J, Fitzgerald D, Granett J, Shuaib A, Koudstaal PJ, Theroux P, Van de Werf F, Sigmon K, Pieper K, Vallee M, Willerson JT. Randomized, double-blind, placebo-controlled, international trial of the oral IIb/IIIa antagonist lotrafiban in coronary and cerebrovascular disease. *Circulation* 2003; **108**:399–406.
229. Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, Van de Werf F, de Torbal A, Armstrong PW, Wallentin LC, Wilcox RG, Simes J, Califf RM, Topol EJ, Simoons ML. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 2002;**359**:189–198.
230. Roffi M, Chew DP, Mukherjee D, Bhatt DL, White JA, Moliterno DJ, Heeschen C, Hamm CW, Robbins MA, Kleiman NS, Theroux P, White HD, Topol EJ. Platelet glycoprotein IIb/IIIa inhibition in acute coronary syndromes. Gradient of benefit related to the revascularization strategy. *Eur Heart J* 2002;**23**:1441–1448.
231. Boersma E, Akkerhuis KM, Theroux P, Califf RM, Topol EJ, Simoons ML. Platelet glycoprotein IIb/IIIa receptor inhibition in non-ST-elevation acute coronary syndromes: early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. *Circulation* 1999;**100**:2045–2048.
232. Kong DF, Califf RM, Miller DP, Moliterno DJ, White HD, Harrington RA, Tcheng JE, Lincoff AM, Hasselblad V, Topol EJ. Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. *Circulation* 1998;**98**:2829–2835.
233. Roffi M, Chew DP, Mukherjee D, Bhatt DL, White JA, Heeschen C, Hamm CW, Moliterno DJ, Califf RM, White HD, Kleiman NS, Theroux P, Topol EJ. Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non-ST-segment-elevation acute coronary syndromes. *Circulation* 2001;**104**:2767–2771.

234. Simoons ML. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. *Lancet* 2001;**357**:1915–1924.
235. PURSUIT Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med* 1998; **339**:436–443.
236. PRISM Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. *N Engl J Med* 1998;**338**:1498–1505.
237. PRISM PLUS Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. *N Engl J Med* 1998;**338**:1488–1497.
238. Kong DF, Hasselblad V, Harrington RA, White HD, Tcheng JE, Kandzari DE, Topol EJ, Califf RM. Meta-analysis of survival with platelet glycoprotein IIb/IIIa antagonists for percutaneous coronary interventions. *Am J Cardiol* 2003;**92**:651–655.
239. EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. The EPILOG Investigators. *N Engl J Med* 1997;**336**:1689–1696.
240. EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. The EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet* 1998;**352**:87–92.
241. Lincoff AM, Califf RM, Anderson KM, Weisman HF, Aguirre FV, Kleiman NS, Harrington RA, Topol EJ. Evidence for prevention of death and myocardial infarction with platelet membrane glycoprotein IIb/IIIa receptor blockade by abciximab (c7E3 Fab) among patients with unstable angina undergoing percutaneous coronary revascularization. EPIC Investigators. Evaluation of 7E3 in Preventing Ischemic Complications. *J Am Coll Cardiol* 1997;**30**:149–156.
242. Anderson KM, Califf RM, Stone GW, Neumann FJ, Montalescot G, Miller DP, Ferguson JJ III, Willerson JT, Weisman HF, Topol EJ. Long-term mortality benefit with abciximab in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2001;**37**:2059–2065.
243. CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. *Lancet* 1997;**349**:1429–1435.
244. Topol EJ, Moliterno DJ, Herrmann HC, Powers ER, Grines CL, Cohen DJ, Cohen EA, Bertrand M, Neumann FJ, Stone GW, DiBattiste PM, Demopoulos L. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 2001; **344**:1888–1894.
245. Moliterno DJ, Yakubov SJ, DiBattiste PM, Herrmann HC, Stone GW, Macaya C, Neumann FJ, Ardissino D, Bassand JP, Borzi L, Yeung AC, Harris KA, Demopoulos LA, Topol EJ. Outcomes at 6 months for the direct comparison of tirofiban and abciximab during percutaneous coronary revascularisation with stent placement: the TARGET follow-up study. *Lancet* 2002;**360**:355–360.
246. IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II. *Lancet* 1997;**349**:1422–1428.
247. ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet* 2000;**356**:2037–2044.
248. RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. The RESTORE Investigators. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation* 1997;**96**: 1445–1453.
249. Valgimigli M, Percoco G, Barbieri D, Ferrari F, Guardigli G, Parrinello G, Soukhomovskaia O, Ferrari R. The additive value of tirofiban administered with the high-dose bolus in the prevention of ischemic complications during high-risk coronary angioplasty: the ADVANCE Trial. *J Am Coll Cardiol* 2004;**44**:14–19.
250. Giugliano RP, Newby LK, Harrington RA, Gibson CM, Van de Werf F, Armstrong P, Montalescot G, Gilbert J, Strony JT, Califf RM, Braunwald E. The early glycoprotein IIb/IIIa inhibition in non-ST-segment elevation acute coronary syndrome (EARLY ACS) trial: a randomized placebo-controlled trial evaluating the clinical benefits of early front-loaded eptifibatide in the treatment of patients with non-ST-segment elevation acute coronary syndrome—study design and rationale. *Am Heart J* 2005;**149**:994–1002.
251. Stone GW, Bertrand ME, Moses JW, Ohman EM, Lincoff AM, Ware JH, Pocock SJ, McLaurin BT, Cox DA, Jafar MZ, Chandna H, Hartmann F, Leisch F, Strasser RH, Desaga M, Stuckey TD, Zelman RB, Lieber IH, Cohen DJ, Mehran R, White HD. Routine upstream initiation vs. deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: the ACUITY timing trial. *JAMA* 2007;**297**:591–602.
252. Bhatt DL, Roe MT, Peterson ED, Li Y, Chen AY, Harrington RA, Greenbaum AB, Berger PB, Cannon CP, Cohen DJ, Gibson CM, Saucedo JF, Kleiman NS, Hochman JS, Boden WE, Brindis RG, Peacock WF, Smith SC Jr, Pollack CV Jr, Gibler WB, Ohman EM. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *JAMA* 2004;**292**: 2096–2104.
253. Lenzen MJ, Boersma E, Bertrand ME, Maier W, Moris C, Piscione F, Sechtem U, Stahle E, Widimsky P, de Jaegere P, Scholte op Reimer WJ, Mercado N, Wijns W. Management and outcome of patients with established coronary artery disease: the Euro Heart Survey on coronary revascularization. *Eur Heart J* 2005;**26**:1169–1179.
254. Li YF, Spencer FA, Becker RC. Comparative efficacy of fibrinogen and platelet supplementation on the *in vitro* reversibility of competitive glycoprotein IIb/IIIa receptor-directed platelet inhibition. *Am Heart J* 2002;**143**:725–732.
255. de Lemos JA, Blazing MA, Wiviott SD, Brady WE, White HD, Fox KA, Palmisano J, Ramsey KE, Bilheimer DW, Lewis EF, Pfeffer M, Califf RM, Braunwald E. Enoxaparin versus unfractionated heparin in patients treated with tirofiban, aspirin and an early conservative initial management strategy: results from the A phase of the A-to-Z trial. *Eur Heart J* 2004;**25**:1688–1694.
256. Young JJ, Kereiakes DJ, Grines CL. Low-molecular-weight heparin therapy in percutaneous coronary intervention: the NICE 1 and NICE 4 trials. National Investigators Collaborating on Enoxaparin Investigators. *J Invasive Cardiol* 2000;**12**(Suppl. E):E14–E18.
257. Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, Moses JW, White HD, Pocock SJ, Ware JH, Feit F, Colombo A, Aylward P, Cequier AR, Darius H, Desmet W, Ebrahimi R, Hamon M, Rasmussen LH, Rupprecht HJ, Hoekstra JW, Mehran R, Ohman EM, for the ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;**355**:2203–2216.
258. Patrono C, Coller B, FitzGerald GA, Hirsh J, Roth G. Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;**126**:234S–264S.
259. Patrono C. Aspirin resistance: definition, mechanisms and clinical read-outs. *J Thromb Haemost* 2003;**1**:1710–1713.
260. Berglund U, Wallentin L. Persistent inhibition of platelet function during long-term treatment with 75 mg acetylsalicylic acid daily in men with unstable coronary artery disease. *Eur Heart J* 1991;**12**:428–433.
261. Buchanan MR, Brister SJ. Individual variation in the effects of ASA on platelet function: implications for the use of ASA clinically. *Can J Cardiol* 1995;**11**:221–227.
262. Helgason CM, Bolin KM, Hoff JA, Winkler SR, Mangat A, Tortorice KL, Brace LD. Development of aspirin resistance in persons with previous ischemic stroke. *Stroke* 1994;**25**:2331–2336.
263. Helgason CM, Tortorice KL, Winkler SR, Penney DW, Schuler JJ, McClelland TJ, Brace LD. Aspirin response and failure in cerebral infarction. *Stroke* 1993;**24**:345–350.
264. Helgason CM, Hoff JA, Kondos GT, Brace LD. Platelet aggregation in patients with atrial fibrillation taking aspirin or warfarin. *Stroke* 1993; **24**:1458–1461.
265. Mueller MR, Salat A, Stangl P, Murabito M, Pulaki S, Boehm D, Koppensteiner R, Ergun E, Mittlboeck M, Schreiner W, Losert U, Wolner E. Variable platelet response to low-dose ASA and the risk of limb deterioration in patients submitted to peripheral arterial angioplasty. *Thromb Haemost* 1997;**78**:1003–1007.
266. Weksler BB, Kent JL, Rudolph D, Scherer PB, Levy DE. Effects of low dose aspirin on platelet function in patients with recent cerebral ischemia. *Stroke* 1985;**16**:5–9.
267. Eikelboom JW, Hirsh J, Weitz JI, Johnston M, Yi Q, Yusuf S. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial

infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. *Circulation* 2002;**105**:1650–1655.
268. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;**342**:145–153.
269. Rocca B, Secchiero P, Ciabattoni G, Ranelletti FO, Catani L, Guidotti L, Melloni E, Maggiano N, Zauli G, Patrono C. Cyclooxygenase-2 expression is induced during human megakaryopoiesis and characterizes newly formed platelets. *Proc Natl Acad Sci USA* 2002;**99**:7634–7639.
270. Cipollone F, Ciabattoni G, Patrignani P, Pasquale M, Di Gregorio D, Bucciarelli T, Davi G, Cuccurullo F, Patrono C. Oxidant stress and aspirin-insensitive thromboxane biosynthesis in severe unstable angina. *Circulation* 2000;**102**:1007–1013.
271. Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, Vyas SN, FitzGerald GA. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001;**345**:1809–1817.
272. Kurth T, Glynn RJ, Walker AM, Chan KA, Buring JE, Hennekens CH, Gaziano JM. Inhibition of clinical benefits of aspirin on first myocardial infarction by nonsteroidal antiinflammatory drugs. *Circulation* 2003; **108**:1191–1195.
273. MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet* 2003;**361**:573–574.
274. Gislason GH, Jacobsen S, Rasmussen JN, Rasmussen S, Buch P, Friberg J, Schramm TK, Abildstrom SZ, Kober L, Madsen M, Torp-Pedersen C. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. *Circulation* 2006;**113**: 2906–2913.
275. Nguyen TA, Diodati JG, Pharand C. Resistance to clopidogrel: a review of the evidence. *J Am Coll Cardiol* 2005;**45**:1157–1164.
276. Geisler T, Langer H, Wydymus M, Gohring K, Zurn C, Bigalke B, Stellos K, May AE, Gawaz M. Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation. *Eur Heart J* 2006; **27**:2420–2425.
277. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation* 2003;**107**:2908–2913.
278. Matetzky S, Shenkman B, Guetta V, Shechter M, Bienart R, Goldenberg I, Novikov I, Pres H, Savion N, Varon D, Hod H. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. *Circulation* 2004;**109**: 3171–3175.
279. Saw J, Steinhubl SR, Berger PB, Kereiakes DJ, Serebruany VL, Brennan D, Topol EJ. Lack of adverse clopidogrel–atorvastatin clinical interaction from secondary analysis of a randomized, placebo-controlled clopidogrel trial. *Circulation* 2003;**108**:921–924.
280. Lim MJ, Spencer FA, Gore JM, Dabbous OH, Agnelli G, Kline-Rogers EM, Dibenedetto D, Eagle KA, Mehta RH. Impact of combined pharmacologic treatment with clopidogrel and a statin on outcomes of patients with non-ST-segment elevation acute coronary syndromes: perspectives from a large multinational registry. *Eur Heart J* 2005;**26**:1063–1069.
281. van Hecken A, Depre M, Wynants K, Vanbilloen H, Verbruggen A, Arnout J, Vanhove P, Cariou R, De Schepper PJ. Effect of clopidogrel on naproxen-induced gastrointestinal blood loss in healthy volunteers. *Drug Metab Drug Interact* 1998;**14**:193–205.
282. Collet JP, Montalescot G, Blanchet B, Tanguy ML, Golmard JL, Choussat R, Beygui F, Payot L, Vignolles N, Metzger JP, Thomas D. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. *Circulation* 2004;**110**:2361–2367.
283. Ho PM, Spertus JA, Masoudi FA, Reid KJ, Peterson ED, Magid DJ, Krumholz HM, Rumsfeld JS. Impact of medication therapy discontinuation on mortality after myocardial infarction. *Arch Intern Med* 2006; **166**:1842–1847.
284. Jeremias A, Sylvia B, Bridges J, Kirtane AJ, Bigelow B, Pinto DS, Ho KK, Cohen DJ, Garcia LA, Cutlip DE, Carrozza JP Jr. Stent thrombosis after successful sirolimus-eluting stent implantation. *Circulation* 2004;**109**: 1930–1932.
285. Kaluza GL, Joseph J, Lee JR, Raizner ME, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J Am Coll Cardiol* 2000;**35**:1288–1294.
286. Ong AT, Hoye A, Aoki J, van Mieghem CA, Rodriguez Granillo GA, Sonnenschein K, Regar E, McFadden EP, Sianos G, van der Giessen WJ, de Jaegere PP, de Feyter P, van Domburg RT, Serruys PW. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. *J Am Coll Cardiol* 2005;**45**:947–953.
287. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;**293**:2126–2130.
288. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004; **364**:1519–1521.
289. Wilson SH, Fasseas P, Orford JL, Lennon RJ, Horlocker T, Charnoff NE, Melby S, Berger PB. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. *J Am Coll Cardiol* 2003;**42**:234–240.
290. Albaladejo P, Marret E, Piriou V, Samama CM. Perioperative management of antiplatelet agents in patients with coronary stents: recommendations of a French Task Force. *Br J Anaesth* 2006;**97**:580–582.
291. Grines CL, Bonow RO, Casey DE Jr, Gardner TJ, Lockhart PB, Moliterno DJ, O'Gara P, Whitlow P. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents. A Science Advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with Representation from the American College of Physicians. *Circulation* 2007;**115**:813–818.
292. Bertrand ME, LaBlanche JM, Tilmant PY, Thieuleux FA, Delforge MR, Carre AG, Asseman P, Berzin B, Libersa C, Laurent JM. Frequency of provoked coronary arterial spasm in 1089 consecutive patients undergoing coronary arteriography. *Circulation* 1982;**65**:1299–1306.
293. TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation* 1994;**89**: 1545–1556.
294. FRISC II Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. *Lancet* 1999;**354**:708–715.
295. Rioufol G, Gilard M, Finet G, Ginon I, Boschat J, Andre-Fouet X. Evolution of spontaneous atherosclerotic plaque rupture with medical therapy: long-term follow-up with intravascular ultrasound. *Circulation* 2004;**110**:2875–2880.
296. Avanzas P, Arroyo-Espliguero R, Cosin-Sales J, Aldama G, Pizzi C, Quiles J, Kaski JC. Markers of inflammation and multiple complex stenoses (pancoronary plaque vulnerability) in patients with non-ST segment elevation acute coronary syndromes. *Heart* 2004;**90**:847–852.
297. Rodriguez-Granillo GA, Garcia-Garcia HM, Valgimigli M, Vaina S, van Mieghem C, van Geuns RJ, van der Ent M, Regar E, de Jaegere P, van der Giessen W, de Feyter P, Serruys PW. Global characterization of coronary plaque rupture phenotype using three-vessel intravascular ultrasound radiofrequency data analysis. *Eur Heart J* 2006;**27**:1921–1927.
298. Rodriguez-Granillo GA, McFadden EP, Valgimigli M, van Mieghem CA, Regar E, de Feyter PJ, Serruys PW. Coronary plaque composition of nonculprit lesions, assessed by *in vivo* intracoronary ultrasound radio frequency data analysis, is related to clinical presentation. *Am Heart J* 2006;**151**:1020–1024.
299. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, Fayad Z, Stone PH, Waxman S, Raggi P, Madjid M, Zarrabi A, Burke A, Yuan C, Fitzgerald PJ, Siscovick DS, de Korte CL, Aikawa M, Juhani Airaksinen KE, Assmann G, Becker CR, Chesebro JH, Farb A, Galis ZS, Jackson C, Jang IK, Koenig W, Lodder RA, March K, Demirovic J, Navab M, Priori SG, Rekhter MD, Bahr R, Grundy SM, Mehran R, Colombo A, Boerwinkle E, Ballantyne C, Insull W Jr, Schwartz RS, Vogel R, Serruys PW, Hansson GK, Faxon DP, Kaul S, Drexler H, Greenland P, Muller JE, Virmani R, Ridker PM, Zipes DP, Shah PK, Willerson JT. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: part I. *Circulation* 2003;**108**:1664–1672.
300. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, Fayad Z, Stone PH, Waxman S, Raggi P, Madjid M, Zarrabi A, Burke A, Yuan C, Fitzgerald PJ, Siscovick DS, de Korte CL, Aikawa M, Airaksinen KE, Assmann G, Becker CR, Chesebro JH, Farb A, Galis ZS, Jackson C,

Jang IK, Koenig W, Lodder RA, March K, Demirovic J, Navab M, Priori SG, Rekhter MD, Bahr R, Grundy SM, Mehran R, Colombo A, Boerwinkle E, Ballantyne C, Insull W Jr, Schwartz RS, Vogel R, Serruys PW, Hansson GK, Faxon DP, Kaul S, Drexler H, Greenland P, Muller JE, Virmani R, Ridker PM, Zipes DP, Shah PK, Willerson JT. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: part II. *Circulation* 2003;**108**:1772–1778.

301. Mercado N, Maier W, Boersma E, Bucher C, de Valk V, O'Neill WW, Gersh BJ, Meier B, Serruys PW, Wijns W. Clinical and angiographic outcome of patients with mild coronary lesions treated with balloon angioplasty or coronary stenting. Implications for mechanical plaque sealing. *Eur Heart J* 2003;**24**:541–551.
302. Al-Khatib SM, Granger CB, Huang Y, Lee KL, Califf RM, Simoons ML, Armstrong PW, Van de Werf F, White HD, Simes RJ, Moliterno DJ, Topol EJ, Harrington RA. Sustained ventricular arrhythmias among patients with acute coronary syndromes with no ST-segment elevation: incidence, predictors, and outcomes. *Circulation* 2002;**106**:309–312.
303. Srichai MB, Jaber WA, Prior DL, Marso SP, Houghtaling PL, Menon V, Simoons ML, Harrington RA, Hochman JS. Evaluating the benefits of glycoprotein IIb/IIIa inhibitors in heart failure at baseline in acute coronary syndromes. *Am Heart J* 2004;**147**:84–90.
304. Yan AT, Yan RT, Tan M, Chow CM, Fitchett DH, Georgescu AA, Hassan Q, Luchansky J, Langer A, Goodman SG. ST-segment depression in non-ST elevation acute coronary syndromes: quantitative analysis may not provide incremental prognostic value beyond comprehensive risk stratification. *Am Heart J* 2006;**152**:270–276.
305. Bholasingh R, Cornel JH, Kamp O, van Straalen JP, Sanders GT, Tijssen JG, Umans VA, Visser CA, de Winter RJ. Prognostic value of predischarge dobutamine stress echocardiography in chest pain patients with a negative cardiac troponin T. *J Am Coll Cardiol* 2003;**41**:596–602.
306. Mehta SR, Cannon CP, Fox KA, Wallentin L, Boden WE, Spacek R, Widimsky P, McCullough PA, Hunt D, Braunwald E, Yusuf S. Routine vs. selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA* 2005;**293**:2908–2917.
307. Diderholm E, Andren B, Frostfeldt G, Genberg M, Jernberg T, Lagerqvist B, Lindahl B, Venge P, Wallentin L. The prognostic and therapeutic implications of increased troponin T levels and ST depression in unstable coronary artery disease: the FRISC II invasive troponin T electrocardiogram substudy. *Am Heart J* 2002;**143**:760–767.
308. Lagerqvist B, Husted S, Kontny F, Naslund U, Stahle E, Swahn E, Wallentin L. A long-term perspective on the protective effects of an early invasive strategy in unstable coronary artery disease: two-year follow-up of the FRISC-II invasive study. *J Am Coll Cardiol* 2002;**40**:1902–1914.
309. Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol* 2006;**48**:1319–1325.
310. Fox KA, Poole-Wilson P, Clayton TC, Henderson RA, Shaw TR, Wheatley DJ, Knight R, Pocock SJ. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. *Lancet* 2005;**366**:914–920.
311. Boden WE, O'Rourke RA, Crawford MH, Blaustein AS, Deedwania PC, Zoble RG, Wexler LF, Kleiger RE, Pepine CJ, Ferry DR, Chow BK, Lavori PW. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med* 1998;**338**:1785–1792.
312. McCullough PA, O'Neill WW, Graham M, Stomel RJ, Rogers F, David S, Farhat A, Kazlauskaite R, Al-Zagoum M, Grines CL. A prospective randomized trial of triage angiography in acute coronary syndromes ineligible for thrombolytic therapy. Results of the medicine versus angiography in thrombolytic exclusion (MATE) trial. *J Am Coll Cardiol* 1998;**32**:596–605.
313. Hoenig MR, Doust JA, Aroney CN, Scott IA. Early invasive versus conservative strategies for unstable angina & non-ST-elevation myocardial infarction in the stent era. *Cochrane Database Syst Rev* 2006;**3**:CD004815.
314. de Winter RJ, Windhausen F, Cornel JH, Dunselman PH, Janus CL, Bendermacher PE, Michels HR, Sanders GT, Tijssen JG, Verheugt FW. Early invasive versus selectively invasive management for acute coronary syndromes. *N Engl J Med* 2005;**353**:1095–1104.
315. Hirsch A, Windhausen F, Tijssen JG, Verheugt FW, Cornel JH, de Winter RJ. Long-term outcome after an early invasive versus selective invasive treatment strategy in patients with non-ST-elevation acute coronary syndrome and elevated cardiac troponin T (the ICTUS trial): a follow-up study. *Lancet* 2007;**369**:827–835.
316. Cannon CP. Revascularisation for everyone? *Eur Heart J* 2004;**25**:1471–1472.
317. Neumann FJ, Kastrati A, Pogatsa-Murray G, Mehilli J, Bollwein H, Bestehorn HP, Schmitt C, Seyfarth M, Dirschinger J, Schomig A. Evaluation of prolonged antithrombotic pretreatment ('cooling-off' strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. *JAMA* 2003;**290**:1593–1599.
318. Fox KA, Anderson FA, Dabbous OH, Steg PG, Lopez-Sendon JL, Van de Werf F, Budaj A, Gurfinkel EP, Goodman SG, Brieger D. Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The global registry of acute coronary events (GRACE). *Heart* 2007;**93**:177–182.
319. Mehta RH, Roe MT, Chen AY, Lytle BL, Pollack CV Jr, Brindis RG, Smith SC Jr, Harrington RA, Fintel D, Fraulo ES, Califf RM, Gibler WB, Ohman EM, Peterson ED. Recent trends in the care of patients with non-ST-segment elevation acute coronary syndromes: insights from the CRUSADE initiative. *Arch Intern Med* 2006;**166**:2027–2034.
320. Van de Werf F, Gore JM, Avezum A, Gulba DC, Goodman SG, Budaj A, Brieger D, White K, Fox KA, Eagle KA, Kennelly BM. Access to catheterisation facilities in patients admitted with acute coronary syndrome: multinational registry study. *BMJ* 2005;**330**:441.
321. Lemos PA, Lee CH, Degertekin M, Saia F, Tanabe K, Arampatzis CA, Hoye A, van Duuren M, Sianos G, Smits PC, de Feyter P, van der Giessen WJ, van Domburg RT, Serruys PW. Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes: insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *J Am Coll Cardiol* 2003;**41**:2093–2099.
322. Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, Kramer JM, Harrington RA, Matchar DB, Kandzari DE, Peterson ED, Schulman KA, Califf RM. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA* 2007;**297**:159–168.
323. Fajadet J, Wijns W, Laarman GJ, Kuck KH, Ormiston J, Munzel T, Popma JJ, Fitzgerald PJ, Bonan R, Kuntz RE. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation* 2006;**114**:798–806.
324. Bavry AA, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. *Am J Med* 2006;**119**:1056–1061.
325. Farb A, Boam AB. Stent thrombosis redux—the FDA perspective. *N Engl J Med* 2007;**356**:984–987.
326. Maisel WH. Unanswered questions—drug-eluting stents and the risk of late thrombosis. *N Engl J Med* 2007;**356**:981–984.
327. Pieper KS, Tsiatis AA, Davidian M, Hasselblad V, Kleiman NS, Boersma E, Chang WC, Griffin J, Armstrong PW, Califf RM, Harrington RA. Differential treatment benefit of platelet glycoprotein IIb/IIIa inhibition with percutaneous coronary intervention versus medical therapy for acute coronary syndromes: exploration of methods. *Circulation* 2004;**109**:641–646.
328. Claeys MJ, Van der Planken MG, Bosmans JM, Michiels JJ, Vertessen F, Van Der Goten P, Wuyts FL, Vrints CJ. Does pre-treatment with aspirin and loading dose clopidogrel obviate the need for glycoprotein IIb/IIIa antagonists during elective coronary stenting? A focus on periprocedural myonecrosis. *Eur Heart J* 2005;**26**:567–575.
329. Mauri L, Rogers C, Baim DS. Devices for distal protection during percutaneous coronary revascularization. *Circulation* 2006;**113**:2651–2656.
330. Chu MW, Wilson SR, Novick RJ, Stitt LW, Quantz MA. Does clopidogrel increase blood loss following coronary artery bypass surgery? *Ann Thorac Surg* 2004;**78**:1536–1541.
331. Solodky A, Behar S, Boyko V, Battler A, Hasdai D. The outcome of coronary artery bypass grafting surgery among patients hospitalized with acute coronary syndrome: the Euro Heart Survey of acute coronary syndrome experience. *Cardiology* 2005;**103**:44–47.
332. Mercado N, Wijns W, Serruys PW, Sigwart U, Flather MD, Stables RH, O'Neill WW, Rodriguez A, Lemos PA, Hueb WA, Gersh BJ, Booth J, Boersma E. One-year outcomes of coronary artery bypass graft surgery versus percutaneous coronary intervention with multiple stenting for multisystem disease: a meta-analysis of individual patient data from randomized clinical trials. *J Thorac Cardiovasc Surg* 2005;**130**:512–519.
333. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, Manger

Cats V, Orth-Gomer K, Perk J, Pyorala K, Rodicio JL, Sans S, Sansoy V, Sechtem U, Silber S, Thomsen T, Wood D. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J* 2003;**24**:1601–1610.

334. Smith SC Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, Grundy SM, Hiratzka L, Jones D, Krumholz HM, Mosca L, Pasternak RC, Pearson T, Pfeffer MA, Taubert KA. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation* 2006;**113**:2363–2372.
335. Smith SC Jr, Blair SN, Bonow RO, Brass LM, Cerqueira MD, Dracup K, Fuster V, Gotto A, Grundy SM, Miller NH, Jacobs A, Jones D, Krauss RM, Mosca L, Ockene I, Pasternak RC, Pearson T, Pfeffer MA, Starke RD, Taubert KA. AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update. A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *J Am Coll Cardiol* 2001;**38**:1581–1583.
336. Iestra JA, Kromhout D, van der Schouw YT, Grobbee DE, Boshuizen HC, van Staveren WA. Effect size estimates of lifestyle and dietary changes on all-cause mortality in coronary artery disease patients: a systematic review. *Circulation* 2005;**112**:924–934.
337. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study. *Lancet* 2004;**364**:937–952.
338. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA* 2006;**295**:761–775.
339. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* 2005;**365**:1389–1397.
340. Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, Cosentino F, Jonsson B, Laakso M, Malmberg K, Priori S, Ostergren J, Tuomilehto J, Thrainsdottir I, Vanhorebeek I, Stramba-Badiale M, Lindgren P, Qiao Q, Priori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL, Deckers JW, Bertrand M, Charbonnel B, Erdmann E, Ferrannini E, Flyvbjerg A, Gohlke H, Juanatey JR, Graham I, Monteiro PF, Parhofer K, Pyorala K, Raz I, Schernthaner G, Volpe M, Wood D. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary: The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2007;**28**:88–136.
341. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.
342. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;**352**:1425–1435.
343. Scandinavian Simvastatin Survival Study Investigators. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383–1389.
344. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;**361**:1149–1158.
345. Kayikcioglu M, Can L, Kultursay H, Payzin S, Turkoglu C. Early use of pravastatin in patients with acute myocardial infarction undergoing coronary angioplasty. *Acta Cardiol* 2002;**57**:295–302.
346. SoRelle R. Cardiovascular news. FLORIDA. *Circulation* 2000;**102**:E9050–E9051.
347. Fonarow GC, Wright RS, Spencer FA, Fredrick PD, Dong W, Every N, French WJ. Effect of statin use within the first 24 h of admission for acute myocardial infarction on early morbidity and mortality. *Am J Cardiol* 2005;**96**:611–616.
348. Heeschen C, Hamm CW, Laufs U, Snapinn S, Bohm M, White HD. Withdrawal of statins increases event rates in patients with acute coronary syndromes. *Circulation* 2002;**105**:1446–1452.
349. Spencer FA, Fonarow GC, Frederick PD, Wright RS, Every N, Goldberg RJ, Gore JM, Dong W, Becker RC, French W. Early withdrawal of statin therapy in patients with non-ST-segment elevation myocardial infarction: national registry of myocardial infarction. *Arch Intern Med* 2004;**164**:2162–2168.
350. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;**285**:1711–1718.
351. Thompson PL, Meredith I, Amerena J, Campbell TJ, Sloman JG, Harris PJ. Effect of pravastatin compared with placebo initiated within 24 h of onset of acute myocardial infarction or unstable angina: the Pravastatin in Acute Coronary Treatment (PACT) trial. *Am Heart J* 2004;**148**:e2.
352. de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, Rouleau JL, Pedersen TR, Gardner LH, Mukherjee R, Ramsey KE, Palmisano J, Bilheimer DW, Pfeffer MA, Califf RM, Braunwald E. Early intensive vs. a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004;**292**:1307–1316.
353. Hulten E, Jackson JL, Douglas K, George S, Villines TC. The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2006;**166**:1814–1821.
354. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005;**352**:20–28.
355. Gordon DJ, Knoke J, Probstfield JL, Superko R, Tyroler HA. High-density lipoprotein cholesterol and coronary heart disease in hypercholesterolemic men: the Lipid Research Clinics Coronary Primary Prevention Trial. *Circulation* 1986;**74**:1217–1225.
356. Miller NE, Thelle DS, Forde OH, Mjos OD. The Tromso heart-study. High-density lipoprotein and coronary heart-disease: a prospective case–control study. *Lancet* 1977;**1**:965–968.
357. Chapman MJ, Assmann G, Fruchart JC, Shepherd J, Sirtori C. Raising high-density lipoprotein cholesterol with reduction of cardiovascular risk: the role of nicotinic acid—a position paper developed by the European Consensus Panel on HDL-C. *Curr Med Res Opin* 2004;**20**:1253–1268.
358. Nissen SE, Tardif JC, Nicholls SJ, Revkin JH, Shear CL, Duggan WT, Ruzyllo W, Bachinsky WB, Lasala GP, Tuzcu EM. Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med* 2007;**356**:1304–1316.
359. Kelley GA, Kelley KS, Franklin B. Aerobic exercise and lipids and lipoproteins in patients with cardiovascular disease: a meta-analysis of randomized controlled trials. *J Cardiopulm Rehabil* 2006;**26**:131–139; quiz 140–131, discussion 142–134.
360. Lopez-Sendon J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, Tendera M, Waagstein F, Kjekshus J, Lechat P, Torp-Pedersen C. Expert consensus document on beta-adrenergic receptor blockers. *Eur Heart J* 2004;**25**:1341–1362.
361. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;**342**:821–828.
362. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH, Hawkins CM on behalf of the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;**327**:669–677.
363. Torp-Pedersen C, Kober L. Effect of ACE inhibitor trandolapril on life expectancy of patients with reduced left-ventricular function after acute myocardial infarction. TRACE Study Group. Trandolapril Cardiac Evaluation. *Lancet* 1999;**354**:9–12.
364. Braunwald E, Domanski MJ, Fowler SE, Geller NL, Gersh BJ, Hsia J, Pfeffer MA, Rice MM, Rosenberg YD, Rouleau JL. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;**351**:2058–2068.
365. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised,

double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;**362**:782–788.
366. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet* 2006;**368**:581–588.
367. Danchin N, Cucherat M, Thuillez C, Durand E, Kadri Z, Steg PG. Angiotensin-converting enzyme inhibitors in patients with coronary artery disease and absence of heart failure or left ventricular systolic dysfunction: an overview of long-term randomized controlled trials. *Arch Intern Med* 2006;**166**:787–796.
368. Yusuf S, Pogue J. ACE inhibition in stable coronary artery disease. *N Engl J Med* 2005;**352**:937–939; author reply 937–939.
369. Fox K, Ferrari R, Yusuf S, Borer JS. Should angiotensin-converting enzyme-inhibitors be used to improve outcome in patients with coronary artery disease and 'preserved' left ventricular function? *Eur Heart J* 2006;**27**:2154–2157.
370. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet* 2002;**360**:752–760.
371. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;**349**:1893–1906.
372. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**:709–717.
373. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–1321.
374. 20th Bethesda Conference Insurability and employability of the patient with ischemic heart disease. 3–4 October 1988, Bethesda, Maryland. *J Am Coll Cardiol* 1989;**14**:1003–1044.
375. Boudrez H, De Backer G. Recent findings on return to work after an acute myocardial infarction or coronary artery bypass grafting. *Acta Cardiol* 2000;**55**:341–349.
376. Turkulin K, Cerovec D, Baborski F. Predictive markers of occupational activity in 415 post myocardial infarction patients after one-year follow-up. *Eur Heart J* 1988;**9**(Suppl. L):103–108.
377. Rao SV, Eikelboom JW, Granger CB, Harrington RA, Califf RM, Bassand JP. Bleeding and blood transfusion issues in patients with non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007;**28**:1193–1204.
378. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation* 2006;**114**:774–782.
379. Moscucci M, Fox KA, Cannon CP, Klein W, Lopez-Sendon J, Montalescot G, White K, Goldberg RJ. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2003;**24**:1815–1823.
380. Antman EM, Morrow DA, McCabe CH, Jiang F, White HD, Fox KA, Sharma D, Chew P, Braunwald E. Enoxaparin versus unfractionated heparin as antithrombin therapy in patients receiving fibrinolysis for ST-elevation myocardial infarction. Design and rationale for the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction study 25 (ExTRACT-TIMI 25). *Am Heart J* 2005;**149**:217–226.
381. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;**329**:673–682.
382. Collet JP, Montalescot G, Agnelli G, Van de Werf F, Gurfinkel EP, Lopez-Sendon J, Laufenberg CV, Klutman M, Gowda N, Gulba D. Non-ST-segment elevation acute coronary syndrome in patients with renal dysfunction: benefit of low-molecular-weight heparin alone or with glycoprotein IIb/IIIa inhibitors on outcomes. The Global Registry of Acute Coronary Events. *Eur Heart J* 2005;**26**:2285–2293.
383. Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, Moliterno DJ, Lindblad L, Pieper K, Topol EJ, Stamler JS, Califf RM. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA* 2004;**292**:1555–1562.
384. Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, Van de Werf F, Mahaffey KW, Califf RM, Harrington RA. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. *Am J Cardiol* 2005;**96**:1200–1206.
385. Yusuf S, Mehta SR, Zhao F, Gersh BJ, Commerford PJ, Blumenthal M, Budaj A, Wittlinger T, Fox KA. Early and late effects of clopidogrel in patients with acute coronary syndromes. *Circulation* 2003;**107**: 966–972.
386. Barkun A, Bardou M, Marshall JK. Consensus recommendations for managing patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med* 2003;**139**:843–857.
387. O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 2006;**295**:293–298.
388. Samama CM, Djoudi R, Lecompte T, Nathan-Denizot N, Schved JF. Perioperative platelet transfusion: recommendations of the Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSaPS) 2003. *Can J Anaesth* 2005;**52**:30–37.
389. Schroeder WS, Gandhi PJ. Emergency management of hemorrhagic complications in the era of glycoprotein IIb/IIIa receptor antagonists, clopidogrel, low molecular weight heparin, and third-generation fibrinolytic agents. *Curr Cardiol Rep* 2003;**5**:310–317.
390. Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001;**345**:1230–1236.
391. Sabatine MS, Morrow DA, Giugliano RP, Burton PB, Murphy SA, McCabe CH, Gibson CM, Braunwald E. Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. *Circulation* 2005; **111**:2042–2049.
392. Hill SR, Carless PA, Henry DA, Carson JL, Hebert PC, McClelland DB, Henderson KM. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev* 2002;CD002042.
393. Bush RL, Pevec WC, Holcroft JW. A prospective, randomized trial limiting perioperative red blood cell transfusions in vascular patients. *Am J Surg* 1997;**174**:143–148.
394. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999;**340**:409–417.
395. Hebert PC, Yetisir E, Martin C, Blajchman MA, Wells G, Marshall J, Tweeddale M, Pagliarello G, Schweitzer I. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? *Crit Care Med* 2001;**29**:227–234.
396. Johnson RG, Thurer RL, Kruskall MS, Sirois C, Gervino EV, Critchlow J, Weintraub RM. Comparison of two transfusion strategies after elective operations for myocardial revascularization. *J Thorac Cardiovasc Surg* 1992;**104**:307–314.
397. Welch HG, Meehan KR, Goodnough LT. Prudent strategies for elective red blood cell transfusion. *Ann Intern Med* 1992;**116**:393–402.
398. McMahon TJ, Moon RE, Luschinger BP, Carraway MS, Stone AE, Stolp BW, Gow AJ, Pawloski JR, Watke P, Singel DJ, Piantadosi CA, Stamler JS. Nitric oxide in the human respiratory cycle. *Nat Med* 2002;**8**:711–717.
399. Fransen E, Maessen J, Dentener M, Senden N, Buurman W. Impact of blood transfusions on inflammatory mediator release in patients undergoing cardiac surgery. *Chest* 1999;**116**:1233–1239.
400. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med* 2001;**344**:1286–1292.
401. Lubenow N, Kempf R, Eichner A, Eichler P, Carlsson LE, Greinacher A. Heparin-induced thrombocytopenia: temporal pattern of thrombocytopenia in relation to initial use or reexposure to heparin. *Chest* 2002; **122**:37–42.
402. Rice L, Attisha WK, Drexler A, Francis JL. Delayed-onset heparin-induced thrombocytopenia. *Ann Intern Med* 2002;**136**:210–215.
403. Schiele F, Vuillemenot A, Kramarz P, Kieffer Y, Anguenot T, Bernard Y, Bassand JP. Use of recombinant hirudin as antithrombotic treatment in patients with heparin-induced thrombocytopenia. *Am J Hematol* 1995;**50**:20–25.
404. Savi P, Chong BH, Greinacher A, Gruel Y, Kelton JG, Warkentin TE, Eichler P, Meuleman D, Petitou M, Herault JP, Cariou R, Herbert JM. Effect of fondaparinux on platelet activation in the presence of heparin-dependent antibodies: a blinded comparative multicenter study with unfractionated heparin. *Blood* 2005;**105**:139–144.
405. Dasgupta H, Blankenship JC, Wood GC, Frey CM, Demko SL, Menapace FJ. Thrombocytopenia complicating treatment with intravenous glycoprotein IIb/IIIa receptor inhibitors: a pooled analysis. *Am Heart J* 2000;**140**:206–211.

406. Moliterno DJ, Topol EJ. A direct comparison of tirofiban and abciximab during percutaneous coronary revascularization and stent placement: rationale and design of the TARGET study. *Am Heart J* 2000;**140**: 722–726.
407. Jubelirer SJ, Koenig BA, Bates MC. Acute profound thrombocytopenia following C7E3 Fab (Abciximab) therapy: case reports, review of the literature and implications for therapy. *Am J Hematol* 1999;**61**:205–208.
408. Merlini PA, Rossi M, Menozzi A, Buratti S, Brennan DM, Moliterno DJ, Topol EJ, Ardissino D. Thrombocytopenia caused by abciximab or tirofiban and its association with clinical outcome in patients undergoing coronary stenting. *Circulation* 2004;**109**:2203–2206.
409. Bennett SK, Redberg RF. Acute coronary syndromes in women: is treatment different? Should it be? *Curr Cardiol Rep* 2004;**6**:243–252.
410. Klein L, Gheorghiade M. Management of the patient with diabetes mellitus and myocardial infarction: clinical trials update. *Am J Med* 2004; **116**(Suppl. 5A):47S–63S.
411. Patel MR, Roe MT. Pharmacological treatment of elderly patients with acute coronary syndromes without persistent ST segment elevation. *Drugs Aging* 2002;**19**:633–646.
412. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003;**108**:2154–2169.
413. Kochanek KD, Smith BL. Deaths: preliminary data for 2002. *Natl Vital Stat Rep* 2004;**52**:1–47.
414. Behar S, Battler A, Porath A, Leor J, Grossman E, Hasin Y, Mittelman M, Feigenberg Z, Rahima-Maoz C, Green M, Caspi A, Rabinowitz B, Garty M. A prospective national survey of management and clinical outcome of acute myocardial infarction in Israel, 2000. *Isr Med Assoc J* 2003;**5**: 249–254.
415. Wienbergen H, Gitt AK, Schiele R, Juenger C, Heer T, Vogel C, Gottwik M, Senges J. Different treatments and outcomes of consecutive patients with non-ST-elevation myocardial infarction depending on initial electrocardiographic changes (results of the Acute Coronary Syndromes [ACOS] Registry). *Am J Cardiol* 2004;**93**:1543–1546.
416. Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. *JAMA* 2001;**286**:708–713.
417. Kandzari DE, Roe MT, Chen AY, Lytle BL, Pollack CV Jr, Harrington RA, Ohman EM, Gibler WB, Peterson ED. Influence of clinical trial enrollment on the quality of care and outcomes for patients with non-ST-segment elevation acute coronary syndromes. *Am Heart J* 2005;**149**:474–481.
418. Alexander KP, Roe MT, Chen AY, Lytle BL, Pollack CV Jr, Foody JM, Boden WE, Smith SC Jr, Gibler WB, Ohman EM, Peterson ED. Evolution in cardiovascular care for elderly patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE National Quality Improvement Initiative. *J Am Coll Cardiol* 2005;**46**:1479–1487.
419. Cohen M, Antman EM, Gurfinkel EP, Radley D. Enoxaparin in unstable angina/non-ST-segment elevation myocardial infarction: treatment benefits in prespecified subgroups. *J Thromb Thrombolysis* 2001;**12**: 199–206.
420. Bach RG, Cannon CP, Weintraub WS, DiBattiste PM, Demopoulos LA, Anderson HV, DeLucca PT, Mahoney EM, Murphy SA, Braunwald E. The effect of routine, early invasive management on outcome for elderly patients with non-ST-segment elevation acute coronary syndromes. *Ann Intern Med* 2004;**141**:186–195.
421. Hasdai D, Porter A, Rosengren A, Behar S, Boyko V, Battler A. Effect of gender on outcomes of acute coronary syndromes. *Am J Cardiol* 2003; **91**:1466–1469.
422. MacIntyre K, Stewart S, Capewell S, Chalmers JW, Pell JP, Boyd J, Finlayson A, Redpath A, Gilmour H, McMurray JJ. Gender and survival: a population-based study of 201,114 men and women following a first acute myocardial infarction. *J Am Coll Cardiol* 2001;**38**:729–735.
423. Hochman JS, Tamis JE, Thompson TD, Weaver WD, White HD, Van de Werf F, Aylward P, Topol EJ, Califf RM. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. *N Engl J Med* 1999;**341**:226–232.
424. Blomkalns AL, Chen AY, Hochman JS, Peterson ED, Trynosky K, Diercks DB, Brogan GX Jr, Boden WE, Roe MT, Ohman EM, Gibler WB, Newby LK. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. *J Am Coll Cardiol* 2005;**45**:832–837.
425. Blomkalns AL, Chen AY, Hochman JS, Peterson ED, Trynosky K, Diercks DB, Brogan GX Jr, Boden WE, Roe MT, Ohman EM, Gibler WB, Newby LK; CRUSADE Investigators. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. *J Am Coll Cardiol* 2005;**45**:832–837.
426. Rosengren A, Wallentin L, Gitt AK, Behar S, Battler A, Hasdai D. Sex, age, and clinical presentation of acute coronary syndromes. *Eur Heart J* 2004;**25**:663–670.
427. Cho L, Topol EJ, Balog C, Foody JM, Booth JE, Cabot C, Kleiman NS, Tcheng JE, Califf R, Lincoff AM. Clinical benefit of glycoprotein IIb/IIIa blockade with Abciximab is independent of gender: pooled analysis from EPIC, EPILOG and EPISTENT trials. Evaluation of 7E3 for the Prevention of Ischemic Complications. Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with Abciximab GP IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stent. *J Am Coll Cardiol* 2000;**36**:381–386.
428. Newby LK, Ohman EM, Christenson RH, Moliterno DJ, Harrington RA, White HD, Armstrong PW, Van De Werf F, Pfisterer M, Hasselblad V, Califf RM, Topol EJ. Benefit of glycoprotein IIb/IIIa inhibition in patients with acute coronary syndromes and troponin t-positive status: the paragon-B troponin T substudy. *Circulation* 2001;**103**:2891–2896.
429. Roe MT, Harrington RA, Prosper DM, Pieper KS, Bhatt DL, Lincoff AM, Simoons ML, Akkerhuis M, Ohman EM, Kitt MM, Vahanian A, Ruzyllo W, Karsch K, Califf RM, Topol EJ. Clinical and therapeutic profile of patients presenting with acute coronary syndromes who do not have significant coronary artery disease. The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial Investigators. *Circulation* 2000;**102**:1101–1106.
430. Bavry AA, Kumbhani DJ, Quiroz R, Ramchandani SR, Kenchaiah S, Antman EM. Invasive therapy along with glycoprotein IIb/IIIa inhibitors and intracoronary stents improves survival in non-ST-segment elevation acute coronary syndromes: a meta-analysis and review of the literature. *Am J Cardiol* 2004;**93**:830–835.
431. Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TR, Wheatley DJ, Pocock SJ. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. *Lancet* 2002; **360**:743–751.
432. Wallentin L, Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. FRISC II Investigators. Fast Revascularisation during Instability in Coronary artery disease. *Lancet* 2000;**356**:9–16.
433. Glaser R, Herrmann HC, Murphy SA, Demopoulos LA, DiBattiste PM, Cannon CP, Braunwald E. Benefit of an early invasive management strategy in women with acute coronary syndromes. *JAMA* 2002;**288**: 3124–3129.
434. Mueller C, Neumann FJ, Roskamm H, Buser P, Hodgson JM, Perruchoud AP, Buettner HJ. Women do have an improved long-term outcome after non-ST-elevation acute coronary syndromes treated very early and predominantly with percutaneous coronary intervention: a prospective study in 1,450 consecutive patients. *J Am Coll Cardiol* 2002;**40**:245–250.
435. McGuire DK, Emanuelsson H, Granger CB, Magnus Ohman E, Moliterno DJ, White HD, Ardissino D, Box JW, Califf RM, Topol EJ. Influence of diabetes mellitus on clinical outcomes across the spectrum of acute coronary syndromes. Findings from the GUSTO-IIb study. GUSTO IIb Investigators. *Eur Heart J* 2000;**21**:1750–1758.
436. Franklin K, Goldberg RJ, Spencer F, Klein W, Budaj A, Brieger D, Marre M, Steg PG, Gowda N, Gore JM. Implications of diabetes in patients with acute coronary syndromes. The Global Registry of Acute Coronary Events. *Arch Intern Med* 2004;**164**:1457–1463.
437. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 2002;**287**: 2570–2581.
438. Dotevall A, Hasdai D, Wallentin L, Battler A, Rosengren A. Diabetes mellitus: clinical presentation and outcome in men and women with acute

coronary syndromes. Data from the Euro Heart Survey ACS. *Diabet Med* 2005;**22**:1542–1550.
439. Bartnik M, Ryden L, Ferrari R, Malmberg K, Pyorala K, Simoons M, Standl E, Soler-Soler J, Ohrvik J. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart. *Eur Heart J* 2004;**25**: 1880–1890.
440. Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, Wedel H, Welin L. Randomized trial of insulin–glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995;**26**:57–65.
441. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *BMJ* 1997;**314**: 1512–1515.
442. Malmberg K, Ryden L, Wedel H, Birkeland K, Bootsma A, Dickstein K, Efendic S, Fisher M, Hamsten A, Herlitz J, Hildebrandt P, MacLeod K, Laakso M, Torp-Pedersen C, Waldenstrom A. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005;**26**:650–661.
443. Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation* 1997;**96**:1761–1769.
444. Berger PB, Velianou JL, Aslanidou Vlachos H, Feit F, Jacobs AK, Faxon DP, Attubato M, Keller N, Stadius ML, Weiner BH, Williams DO, Detre KM. Survival following coronary angioplasty versus coronary artery bypass surgery in anatomic subsets in which coronary artery bypass surgery improves survival compared with medical therapy. Results from the Bypass Angioplasty Revascularization Investigation (BARI). *J Am Coll Cardiol* 2001;**38**:1440–1449.
445. Sedlis SP, Morrison DA, Lorin JD, Esposito R, Sethi G, Sacks J, Henderson W, Grover F, Ramanathan KB, Weiman D, Saucedo J, Antakli T, Paramesh V, Pett S, Vernon S, Birjiniuk V, Welt F, Krucoff M, Wolfe W, Lucke JC, Mediratta S, Booth D, Murphy E, Ward H, Miller L, Kiesz S, Barbiere C, Lewis D. Percutaneous coronary intervention versus coronary bypass graft surgery for diabetic patients with unstable angina and risk factors for adverse outcomes with bypass: outcome of diabetic patients in the AWESOME randomized trial and registry. *J Am Coll Cardiol* 2002;**40**:1555–1566.
446. Mehilli J, Kastrati A, Schuhlen H, Dibra A, Dotzer F, von Beckerath N, Bollwein H, Pache J, Dirschinger J, Berger PP, Schomig A. Randomized clinical trial of abciximab in diabetic patients undergoing elective percutaneous coronary interventions after treatment with a high loading dose of clopidogrel. *Circulation* 2004;**110**:3627–3635.
447. Breeman A, Bertrand ME, Ottervanger JP, Hoeks S, Lenzen M, Sechtem U, Legrand V, de Boer MJ, Wijns W, Boersma E. Diabetes does not influence treatment decisions regarding revascularization in patients with stable coronary artery disease. *Diabetes Care* 2006;**29**: 2003–2011.
448. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;**39**:S1–S266.
449. Brosius FC III, Hostetter TH, Kelepouris E, Mitsnefes MM, Moe SM, Moore MA, Pennathur S, Smith GL, Wilson PW. Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease: a science advisory from the American Heart Association Kidney and Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: Developed in Collaboration With the National Kidney Foundation. *Hypertension* 2006;**48**:751–755.
450. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**:1296–1305.
451. Arnlov J, Evans JC, Meigs JB, Wang TJ, Fox CS, Levy D, Benjamin EJ, D'Agostino RB, Vasan RS. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. *Circulation* 2005;**112**:969–975.
452. Gupta R, Birnbaum Y, Uretsky BF. The renal patient with coronary artery disease: current concepts and dilemmas. *J Am Coll Cardiol* 2004;**44**: 1343–1353.
453. Hostetter TH. Chronic kidney disease predicts cardiovascular disease. *N Engl J Med* 2004;**351**:1344–1346.
454. Shlipak MG, Fried LF, Cushman M, Manolio TA, Peterson D, Stehman-Breen C, Bleyer A, Newman A, Siscovick D, Psaty B. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. *JAMA* 2005;**293**:1737–1745.
455. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;**42**: 1206–1252.
456. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, Zelenkofske S, Leimberger JD, Califf RM, Pfeffer MA. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004;**351**:1285–1295.
457. Gruberg L, Beyar R, Bassand JP, Seabra-Gomes R, Fioretti P, Gottwik MG, Dawkins K, Cieslinski A, Hasdai D, Gitt AK, Group oBotSS. Renal insufficiency in patients undergoing percutaneous coronary intervention: results of the SHAKESPEARE Registry. *J Am Coll Cardiol* 2005; **99**(suppl):31A.
458. Hemmelgarn BR, Southern D, Culleton BF, Mitchell LB, Knudtson ML, Ghali WA. Survival after coronary revascularization among patients with kidney disease. *Circulation* 2004;**110**:1890–1895.
459. Hemmelgarn BR, Southern DA, Humphries KH, Culleton BF, Knudtson ML, Ghali WA. Refined characterization of the association between kidney function and mortality in patients undergoing cardiac catheterization. *Eur Heart J* 2006;**27**:1191–1197.
460. Santopinto JJ, Fox KA, Goldberg RJ, Budaj A, Pinero G, Avezum A, Gulba D, Esteban J, Gore JM, Johnson J, Gurfinkel EP. Creatinine clearance and adverse hospital outcomes in patients with acute coronary syndromes: findings from the global registry of acute coronary events (GRACE). *Heart* 2003;**89**:1003–1008.
461. Tokmakova MP, Skali H, Kenchaiah S, Braunwald E, Rouleau JL, Packer M, Chertow GM, Moye LA, Pfeffer MA, Solomon SD. Chronic kidney disease, cardiovascular risk, and response to angiotensin-converting enzyme inhibition after myocardial infarction: the Survival And Ventricular Enlargement (SAVE) study. *Circulation* 2004;**110**:3667–3673.
462. Kirtane AJ, Piazza G, Murphy SA, Budiu D, Morrow DA, Cohen DJ, Peterson E, Lakkis N, Herrmann HC, Palabrica TM, Gibson CM. Correlates of bleeding events among moderate- to high-risk patients undergoing percutaneous coronary intervention and treated with eptifibatide: observations from the PROTECT-TIMI-30 trial. *J Am Coll Cardiol* 2006; **47**:2374–2379.
463. Maeder M, Klein M, Fehr T, Rickli H. Contrast nephropathy: review focusing on prevention. *J Am Coll Cardiol* 2004;**44**:1763–1771.
464. Marenzi G, Assanelli E, Marana I, Lauri G, Campodonico J, Grazi M, De Metrio M, Galli S, Fabbiocchi F, Montorsi P, Veglia F, Bartorelli AL. N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. *N Engl J Med* 2006;**354**:2773–2782.
465. Pannu N, Wiebe N, Tonelli M. Prophylaxis strategies for contrast-induced nephropathy. *JAMA* 2006;**295**:2765–2779.
466. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004;**44**:1393–1399.
467. Mueller C, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, Marsch S, Roskamm H. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med* 2002;**162**:329–336.
468. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* 1994;**331**:1416–1420.
469. Coca SG, Krumholz HM, Garg AX, Parikh CR. Underrepresentation of renal disease in randomized controlled trials of cardiovascular disease. *JAMA* 2006;**296**:1377–1384.
470. James SK, Lindback J, Tilly J, Siegbahn A, Venge P, Armstrong P, Califf R, Simoons ML, Wallentin L, Lindahl B. Troponin-T and N-terminal pro-B-type natriuretic peptide predict mortality benefit from coronary revascularization in acute coronary syndromes: a GUSTO-IV substudy. *J Am Coll Cardiol* 2006;**48**:1146–1154.
471. Januzzi JL, Cannon CP, DiBattiste PM, Murphy S, Weintraub W, Braunwald E. Effects of renal insufficiency on early invasive

management in patients with acute coronary syndromes (The TACTICS-TIMI 18 Trial). *Am J Cardiol* 2002;**90**:1246–1249.
472. deFilippi C, Wasserman S, Rosanio S, Tiblier E, Sperger H, Tocchi M, Christenson R, Uretsky B, Smiley M, Gold J, Muniz H, Badalamenti J, Herzog C, Henrich W. Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. *JAMA* 2003;**290**:353–359.
473. Gruberg L, Mehran R, Waksman R, Dangas G, Fuchs S, Wu H, Kent KM, Pichard AD, Satler LF, Stone GW, Leon MB. Creatine kinase-MB fraction elevation after percutaneous coronary intervention in patients with chronic renal failure. *Am J Cardiol* 2001;**87**:1356–1360.
474. Mallamaci F, Zoccali C, Parlongo S, Tripepi G, Benedetto FA, Cutrupi S, Bonanno G, Fatuzzo P, Rapisarda F, Seminara G, Stancanelli B, Bellanuova I, Cataliotti A, Malatino LS. Troponin is related to left ventricular mass and predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 2002;**40**:68–75.
475. Androne AS, Katz SD, Lund L, LaManca J, Hudaihed A, Hryniewicz K, Mancini DM. Hemodilution is common in patients with advanced heart failure. *Circulation* 2003;**107**:226–229.
476. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure. *Circulation* 2003;**107**: 223–225.
477. Foley RN, Parfrey PS. Cardiac disease in chronic uremia: clinical outcome and risk factors. *Adv Ren Replace Ther* 1997;**4**:234–248.
478. Hannisdal E, Kildahl-Andersen O, Grottum KA, Lamvik J. Prognostic factors in multiple myeloma in a population-based trial. *Eur J Haematol* 1990;**45**:198–202.
479. Hogue CW Jr, Goodnough LT, Monk TG. Perioperative myocardial ischemic episodes are related to hematocrit level in patients undergoing radical prostatectomy. *Transfusion* 1998;**38**:924–931.
480. Jurkovitz CT, Abramson JL, Vaccarino LV, Weintraub WS, McClellan WM. Association of high serum creatinine and anemia increases the risk of coronary events: results from the prospective community-based atherosclerosis risk in communities (ARIC) study. *J Am Soc Nephrol* 2003;**14**: 2919–2925.
481. Nelson AH, Fleisher LA, Rosenbaum SH. Relationship between postoperative anemia and cardiac morbidity in high-risk vascular patients in the intensive care unit. *Crit Care Med* 1993;**21**:860–866.
482. Al Falluji N, Lawrence-Nelson J, Kostis JB, Lacy CR, Ranjan R, Wilson AC. Effect of anemia on 1-year mortality in patients with acute myocardial infarction. *Am Heart J* 2002;**144**:636–641.
483. Nikolsky E, Aymong ED, Halkin A, Grines CL, Cox DA, Garcia E, Mehran R, Tcheng JE, Griffin JJ, Guagliumi G, Stuckey T, Turco M, Cohen DA, Negoita M, Lansky AJ, Stone GW. Impact of anemia in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: analysis from the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Trial. *J Am Coll Cardiol* 2004;**44**:547–553.
484. World Health Organization. Nutritional anaemias: report of a WHO Scientific Group. Report No.: Technical Report Series No. 405. Geneva: World Health Organization; 1968.
485. Zakai NA, Katz R, Hirsch C, Shlipak MG, Chaves PH, Newman AB, Cushman M. A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort: the Cardiovascular Health Study. *Arch Intern Med* 2005;**165**:2214–2220.
486. Lee PC, Kini AS, Ahsan C, Fisher E, Sharma SK. Anemia is an independent predictor of mortality after percutaneous coronary intervention. *J Am Coll Cardiol* 2004;**44**:541–546.
487. Dauerman HL, Lessard D, Yarzebski J, Gore JM, Goldberg RJ. Bleeding complications in patients with anemia and acute myocardial infarction. *Am J Cardiol* 2005;**96**:1379–1383.
488. Carson JL, Duff A, Poses RM, Berlin JA, Spence RK, Trout R, Noveck H, Strom BL. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996;**348**:1055–1060.
489. Vaglio J, Safley DM, Rahman M, Kosiborod M, Jones P, Thompson R, Krumholz HM, Spertus JA. Relation of anemia at discharge to survival after acute coronary syndromes. *Am J Cardiol* 2005;**96**:496–499.
490. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med* 1987;**316**:1371–1375.
491. Prinzmetal M, Kennamer R, Merliss R, Wada T, Bor N. Angina pectoris. I. A variant form of angina pectoris; preliminary report. *Am J Med* 1959;**27**:375–388.
492. Antman E, Muller J, Goldberg S, MacAlpin R, Rubenfire M, Tabatznik B, Liang CS, Heupler F, Achuff S, Reichek N, Geltman E, Kerin NZ, Neff RK, Braunwald E. Nifedipine therapy for coronary-artery spasm. Experience in 127 patients. *N Engl J Med* 1980;**302**:1269–1273.
493. Prizel KR, Hutchins GM, Bulkley BH. Coronary artery embolism and myocardial infarction. *Ann Intern Med* 1978;**88**:155–161.
494. Bugiardini R. Normal coronary arteries: clinical implications and further classification. *Herz* 2005;**30**:3–7.
495. Bugiardini R, Manfrini O, De Ferrari GM. Unanswered questions for management of acute coronary syndrome: risk stratification of patients with minimal disease or normal findings on coronary angiography. *Arch Intern Med* 2006;**166**:1391–1395.
496. Bybee KA, Kara T, Prasad A, Lerman A, Barsness GW, Wright RS, Rihal CS. Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. *Ann Intern Med* 2004;**141**:858–865.
497. Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. *Eur Heart J* 2006;**27**:1523–1529.
498. Hasin Y, Danchin N, Filippatos GS, Heras M, Janssens U, Leor J, Nahir M, Parkhomenko A, Thygesen K, Tubaro M, Wallentin LC, Zakke I. Recommendations for the structure, organization, and operation of intensive cardiac care units. *Eur Heart J* 2005;**26**:1676–1682.
499. Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, Daly C, De Backer G, Hjemdahl P, Lopez-Sendon J, Marco J, Morais J, Pepper J, Sechtem U, Simoons M, Thygesen K, Priori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL. Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *Eur Heart J* 2006;**27**:1341–1381.
500. Rahimi K, Watzlawek S, Thiele H, Secknus MA, Hayerizadeh BF, Niebauer J, Schuler G. Incidence, time course, and predictors of early malignant ventricular arrhythmias after non-ST-segment elevation myocardial infarction in patients with early invasive treatment. *Eur Heart J* 2006;**27**:1706–1711.
501. Avezum A, Makdisse M, Spencer F, Gore JM, Fox KA, Montalescot G, Eagle KA, White K, Mehta RH, Knobel E, Collet JP. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J* 2005;**149**:67–73.
502. Budaj A, Brieger D, Steg PG, Goodman SG, Dabbous OH, Fox KA, Avezum A, Cannon CP, Mazurek T, Flather MD, Van De Werf F. Global patterns of use of antithrombotic and antiplatelet therapies in patients with acute coronary syndromes: insights from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J* 2003;**146**: 999–1006.
503. Fox KA, Goodman SG, Anderson FA Jr, Granger CB, Moscucci M, Flather MD, Spencer F, Budaj A, Dabbous OH, Gore JM. From guidelines to clinical practice: the impact of hospital and geographical characteristics on temporal trends in the management of acute coronary syndromes. The Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2003;**24**:1414–1424.
504. Granger CB, Steg PG, Peterson E, Lopez-Sendon J, Van de Werf F, Kline-Rogers E, Allegrone J, Dabbous OH, Klein W, Fox KA, Eagle KA. Medication performance measures and mortality following acute coronary syndromes. *Am J Med* 2005;**118**:858–865.
505. Mukherjee D, Fang J, Chetcuti S, Moscucci M, Kline-Rogers E, Eagle KA. Impact of combination evidence-based medical therapy on mortality in patients with acute coronary syndromes. *Circulation* 2004;**109**: 745–749.
506. Norhammar A, Malmberg K, Ryden L, Tornvall P, Stenestrand U, Wallentin L. Under utilisation of evidence-based treatment partially explains for the unfavourable prognosis in diabetic patients with acute myocardial infarction. *Eur Heart J* 2003;**24**:838–844.
507. Roe MT, Peterson ED, Pollack CV Jr, Newby LK, Li Y, Christenson RH, Peacock WF, Fesmire FM, Diercks D, Kirk JD, Smith SC Jr, Ohman EM, Gibler WB. Influence of timing of troponin elevation on clinical outcomes and use of evidence-based therapies for patients with non-ST-segment elevation acute coronary syndromes. *Ann Emerg Med* 2005;**45**:355–362.
508. Stenestrand U, Lindback J, Wallentin L. Hospital therapy traditions influence long-term survival in patients with acute myocardial infarction. *Am Heart J* 2005;**149**:82–90.
509. Ellerbeck EF, Kresowik TF, Hemann RA, Mason P, Wiblin RT, Marciniak TA. Impact of quality improvement activities on care for acute myocardial infarction. *Int J Qual Health Care* 2000;**12**:305–310.

510. Flynn MR, Barrett C, Cosio FG, Gitt AK, Wallentin L, Kearney P, Lonergan M, Shelley E, Simoons ML. The Cardiology Audit and Registration Data Standards (CARDS), European data standards for clinical cardiology practice. *Eur Heart J* 2005;**26**:308–313.
511. LaBresh KA, Ellrodt AG, Gliklich R, Liljestrand J, Peto R. Get with the guidelines for cardiovascular secondary prevention: pilot results. *Arch Intern Med* 2004;**164**:203–209.
512. Mehta RH, Das S, Tsai TT, Nolan E, Kearly G, Eagle KA. Quality improvement initiative and its impact on the management of patients with acute myocardial infarction. *Arch Intern Med* 2000;**160**:3057–3062.
513. Mehta RH, Montoye CK, Faul J, Nagle DJ, Kure J, Raj E, Fattal P, Sharrif S, Amlani M, Changezi HU, Skorcz S, Bailey N, Bourque T, LaTarte M, McLean D, Savoy S, Werner P, Baker PL, DeFranco A, Eagle KA. Enhancing quality of care for acute myocardial infarction: shifting the focus of improvement from key indicators to process of care and tool use: the American College of Cardiology Acute Myocardial Infarction Guidelines Applied in Practice Project in Michigan: Flint and Saginaw Expansion. *J Am Coll Cardiol* 2004;**43**:2166–2173.
514. Mehta RH, Montoye CK, Gallogly M, Baker P, Blount A, Faul J, Roychoudhury C, Borzak S, Fox S, Franklin M, Freundl M, Kline-Rogers E, LaLonde T, Orza M, Parrish R, Satwicz M, Smith MJ, Sobotka P, Winston S, Riba AA, Eagle KA. Improving quality of care for acute myocardial infarction: The Guidelines Applied in Practice (GAP) Initiative. *JAMA* 2002;**287**:1269–1276.

Clinical vignette

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A left atrial thrombus too big to embolize

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A 72-year-old woman with rheumatic mitral valve stenosis was admitted to the hospital after an episode of syncope. She had no prior history of stroke. She was in atrial fibrillation since several months and received oral anticoagulation. At the time of admission, the international normalized ratio was low (1.15), indicating inadequate anticoagulation. Neurological examination was normal. A transthoracic echocardiogram confirmed the presence of severe mitral valve stenosis, with a mitral valve area of 0.5 cm^2, and showed a big highly mobile free-floating left atrial thrombus, which caused intermittent occlusion of the mitral valve (panels A–D and video clip). Such an unattached, freely moving clot in the left atrium is called a left atrial ball thrombus. The patient was submitted to surgical mitral valve replacement. The examination of the left atrium showed a giant free thrombus (T, panels E–G) and a severe mitral valve (MV) stenosis. She made an uneventful recovery and was doing well a few months later.