Seminar

Acute myocardial infarction

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Acute myocardial infarction is a common disease with serious consequences in mortality, morbidity, and cost to the society. Coronary atherosclerosis plays a pivotal part as the underlying substrate in many patients. In addition, a new definition of myocardial infarction has recently been introduced that has major implications from the epidemiological, societal, and patient points of view. The advent of coronary-care units and the results of randomised clinical trials on reperfusion therapy, lytic or percutaneous coronary intervention, and chronic medical treatment with various pharmacological agents have substantially changed the therapeutic approach, decreased in-hospital mortality, and improved the long-term outlook in survivors of the acute phase. New treatments will continue to emerge, but the greatest challenge will be to effectively implement preventive actions in all high-risk individuals and to expand delivery of acute treatment in a timely fashion for all eligible patients.

Introduction

During the past decades, major improvements have been achieved in management of patients with acute myocardial infarction. The introduction of coronary care units in the 1960s, pharmacological reperfusion therapy in the 1980s, and the widespread application of catheter-based interventions in the 1990s have contributed to a striking fall in in-hospital mortality rates.[1–6] Additionally, chronic treatment with aspirin, β blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins have contributed to improved long-term prognosis in survivors of the acute phase of this disorder.[7–10] Despite these developments, myocardial infarction remains a major event, from a clinical, psychological, and social point of view. First, a large number of asymptomatic individuals are at serious risk of developing a first heart attack because of their genetic predisposition, smoking behaviour, unhealthy dietary habits, or physical inactivity. Second, evidence is emerging that medical practice does not adequately implement preventive actions in asymptomatic high-risk individuals and patients with established coronary disease,[11] and thus they remain at substantial risk of (recurrent) disease and death. Third, about a third of patients with evolving myocardial infarction die before they reach hospital to receive any effective treatment.[12] Finally, the improved survival of acute coronary syndromes has resulted in a growing population of patients with chronic conditions,[13] which is amplified by the ageing of the general population. Thus, myocardial infarction remains an important health problem, and merits continued attention from basic and clinical researchers, epidemiologists, and practising physicians. We review the current knowledge about acute myocardial infarction and discuss issues about the pathophysiology, diagnosis, epidemiology, treatment, and prevention of this disorder. We concentrate on the most prominent recent developments.

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Pathophysiology

The term myocardial infarction is thought to reflect death of cardiac myocytes due to prolonged ischaemia.[14] As such, myocardial infarction is an acute coronary syndrome that can occur during the natural course of coronary atherosclerosis (figure 1).[15,16] Progression of atherosclerosis is triggered and enhanced by several factors, which can cause mediating diseases or directly affect the arterial wall. In advanced stages of the disease process, atherosclerotic plaques develop. Initially, normal lumen cross-sectional area will be preserved, since coronary arteries undergo compensatory outward remodelling in relation to plaque area.[17] Development of the disease might therefore be clinically silent for years. In the long run, however, stenoses become functionally important, and coronary artery disease becomes symptomatic.

Fissuring and disruption of atherosclerotic plaques can take place at any time during this chronic process, initiating intraluminal thrombosis.[18] These events generally arise in angiographically non-significant stenoses. Intraluminal thrombi, superimposed on the ruptured plaque, can cause total occlusion of the epicardial coronary artery, so that the coronary blood flow is interrupted and delivery of nutrients to the myocardium is blocked. This situation might be further complicated by coronary vasoconstriction and thrombi micro-embolisation. If a coronary occlusion persists for longer than 30 min, irreversible damage to the myocardium—ie, myocardial infarction, might occur.[19] Long-term coronary

Search strategy and selection criteria

We identified 20 047 reports by a computerised search of Medline that were published in the English language between Jan 1, 1990, and Jan 18, 2003, with myocardial infarction as major topic, and aetiology, pathophysiology, epidemiology, diagnosis, therapy, or prevention as secondary topics. Of these, we reviewed the abstracts of 5231 reports labelled as clinical trials, meta-analysis, review, or practice guidelines. Relevant papers (n=592) were selected, and the content examined. The corresponding bibliographies were manually searched, specifically focusing on in-hospital treatment and recent developments. Additionally, we searched the scientific sessions abstracts in *Circulation*, the *Journal of the American College of Cardiology*, and the *European Heart Journal* published between 1996 and 2002.

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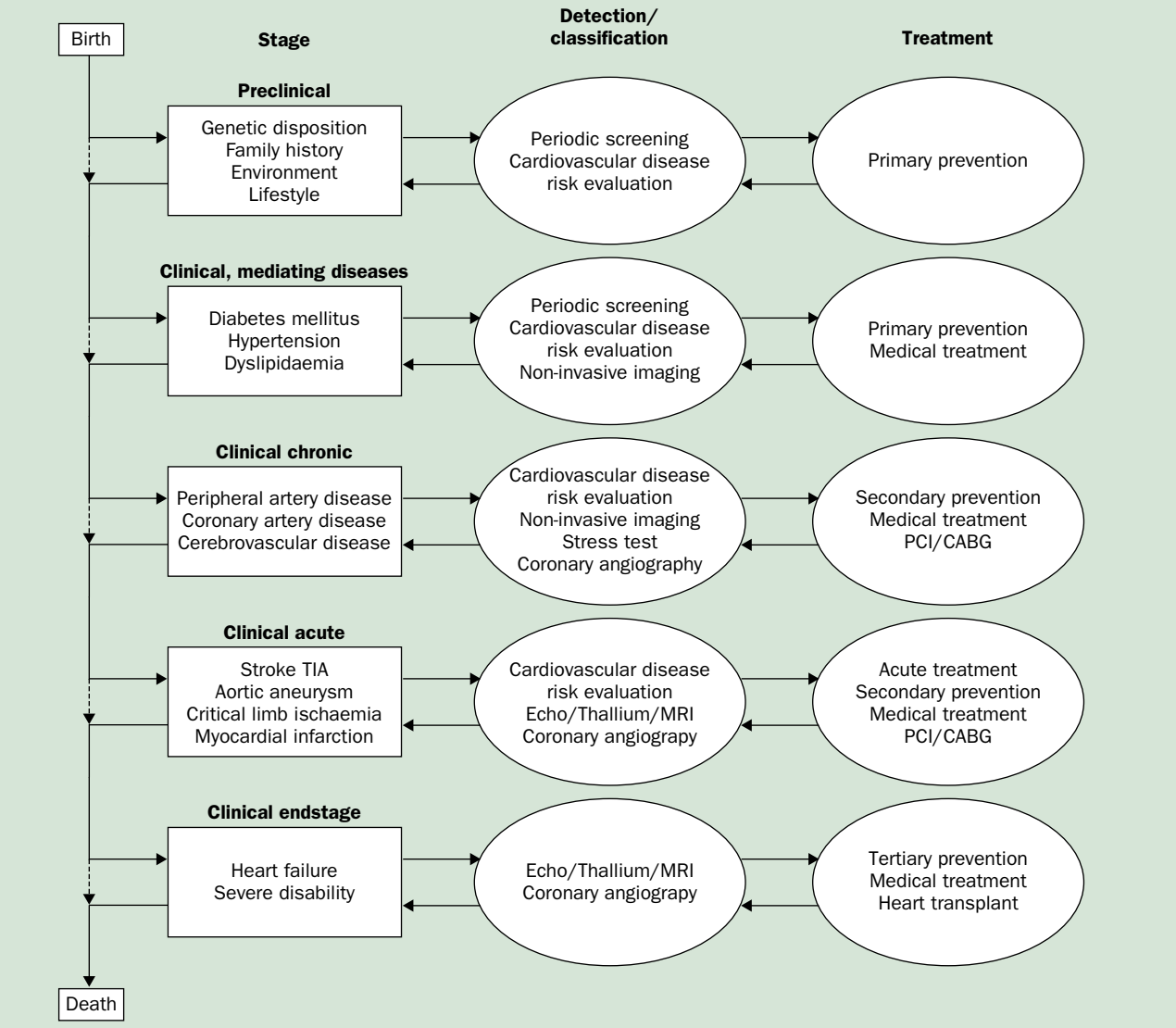

Figure 1: **Natural course of atherosclerosis**
CVD= cardiovascular disease. PCI=percutaneous coronary interventions. CABG=coronary artery bypass graft. TIA=transient ischaemic attack.

occlusion results in a progressive increase of the infarct size. After about 6 h of continuous occlusion the entire jeopardised area becomes necrotic. Loss of functional myocardium results in reduced left-ventricular function, which can affect the patient's quality of life, and generally causes premature death.

Atherosclerosis and inflammation

The development, disruption, and subsequent progression of atherosclerotic lesions is a chronic inflammatory process.[20,21] Established risk factors (panel 1), such as raised plasma low density lipoprotein cholesterol, decreased high density lipoprotein cholesterol, smoking, high blood pressure, and increased glucose concentrations,[22] all stimulate—via several pathways—the entry and activation of inflammatory cells into the arterial wall. Monocytes, which turn into activated macrophages, and lymphocytes are the main inflammatory cells entering the arterial subendothelium. These cells are rich sources of cytokines and growth factors, which induce and amplify further damage. Continuing inflammatory processes result in atherosclerotic lesions composed of a core of lipid and necrotic tissue, covered by a fibrous capsule, which are prone to rupture.

Emerging risk factors for coronary heart disease

The recognition that myocardial infarction often affects patients without established risk factors, and the knowledge that atherosclerosis is mainly an inflammatory process, has stimulated research on serum markers of inflammation as potential indicators of atherothrombosis. Several investigations have shown a positive relation between increased concentrations of C-reactive protein, serum amyloid A, interleukin-6, fibrinogen, homocysteine, lipoprotein A, and pregnancy-associated plasma protein A and the risk of acute coronary events.[23–28] Chronic infection is also an emerging risk marker in this context, although data sometimes conflict.[29–32]

The origin of coronary heart disease has an important genetic component. Insights into differences of genetic regulation of inflammatory processes between otherwise similar individuals might help to understand why some people develop the disease and others do not. Preliminary data suggest a relation between gene polymorphisms of tumour necrosis factors, transforming growth factors, interleukin 1, CD14, and adhesion proteins, and the risk of coronary disease.[33]

Research has also focused on thrombotic markers, showing an association between tissue-type plasminogen

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Panel 1: **Established and emerging cardiovascular risk factors**

Established risk factors	**Evidence**
Raised plasma low density lipoprotein cholesterol	++
Decreased plasma high density lipoprotein cholesterol	++
Smoking	++
High blood pressure	++
Increased plasma glucose concentrations	+
Physical inactivity	+
Obesity	+
Advanced age	+
Emerging risk factors	
Inflammatory markers	
C-reactive protein	+
Interleukins	+
Serum amyloid A	+
Pregnancy-associated plasma protein A	?
Chronic infection (*Chlamydophila pneumoniae*, *Helicobacter pylori*, etc)	?
Procoagulant markers	
Homocysteine	+
Tissue plasminogen activator	+
Plasminogen activator inhibitor	+
Lipoprotein A	+
Process markers	
Fibrinogen	+
D-dimer	?
Coronary artery calcification	?
Genetic factors	
Tumour necrosis factors	?
Transforming growth factors	?
Interleukin 1	?
CD14	?
Adhesion molecules	?

++=clear evidence, and modification of the risk factor decreases the risk of cardiovascular disease; +=clear evidence, but less clear whether modification of the risk factor decreases the risk of cardiovascular disease; ? risk factor under scrutiny.

activator, plasminogen activator inhibitor, and the risk of coronary events.[34] Altogether, promising results have been achieved to identify possible risk markers of acute coronary disease. However, the cause of atherosclerosis is multifactorial, and whether these new markers add to the predictive value of established risk factors remains to be seen.

The search for the vulnerable lesion

Macrophage-rich lesions, covered by a thin fibrous cap are unlikely to withstand the stress caused by the pulsatile pressure of the blood flow. Intravascular ultrasound elastography is a promising technique to identify these vulnerable lesions, based on the notion that soft material will deform more than hard material when force is applied to the tissue. The strain is determined by the ultrasound signal (figure 2). This technique is being assessed for intravascular purposes, and applied to study human arteries in vivo.[35] Investigation of temperature changes at the coronary lesion with an intravascular thermography catheter and high-resolution MRI techniques are other developing options to unmask the vulnerable lesion.[36,37]

Definitions, diagnosis, and epidemiology

According to WHO's definition, a myocardial infarction occurs if at least two of three criteria are fulfilled: typical ischaemic chest pain; raised concentrations of creatine kinase-MB in serum; and typical electrocardiographic findings, including development of pathological Q-waves.[38]

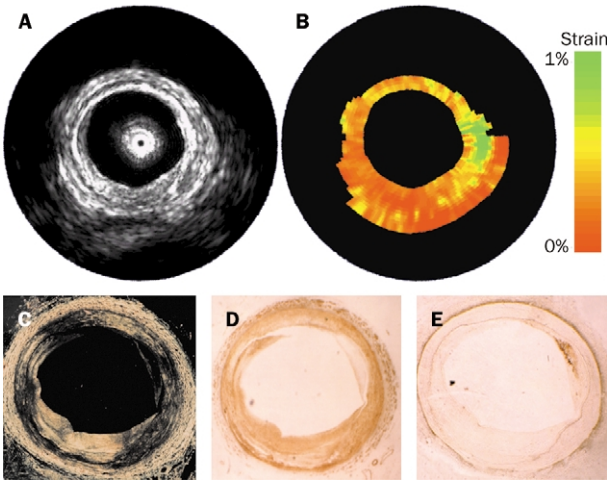

Figure 2: **Intravascular echogram (A) and elastogram (B) of a diseased human femoral artery with the corresponding histology: picro-Sirius red with polarised light microscopy (C), anti α-actin (D), and antibody to CD68 (E)**

The echogram shows an eccentric plaque from 60° to 330°. The elastogram reveals high strain in the plaque between 60° and 120°, whereas low strain values were in the remaining plaque area (both compared with the non-diseased part of the vessel). The histology reveals a fatty plaque region between 60° and 120° (absence of collagen [C] and smooth muscle cells [D]) with inflammation (rich on macrophages [E]) and a fibrous composition in the remaining part (rich on collagen [C] and smooth muscle cells [D]).

Creatine kinase-MB, however, is not a sensitive marker of myocardial necrosis. Therefore, application of the WHO definition in clinical practice results in several patients erroneously diagnosed with non-myocardial infarction, since actually irreversible myocardial damage had occurred. Indeed, for purposes of epidemiological research, the WHO definition aimed for high specificity. However, for purposes of risk stratification and subsequent treatment, a sensitive detection of cardiac injury is needed. Assays are available for much more sensitive detection of (minimum) myocardial damage, including assays for the cardiac troponins T and I, which are also highly specific (figure 3).[39] These developments formed the basis of a revised definition of myocardial infarction as recently proposed by the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) (panel 2).[14]

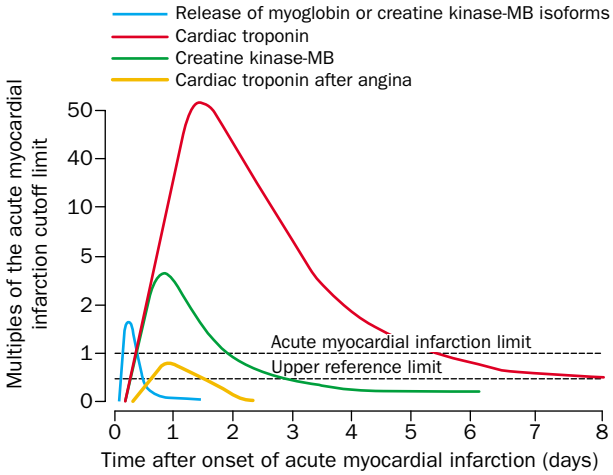

Figure 3: **Timing of release of cardiac serum markers after acute ischaemic myocardial infarction**

Data are plotted on a relative scale, where 1 is the acute myocardial cut-off concentration. Reproduced with permission from Wu and colleagues.[28]

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Panel 2: **European Society of Cardiology/American College of Cardiology definition of myocardial infarction**

Any of the following criteria satisfy diagnosis of an acute, evolving or recent myocardial infarction

1) Typical rise and gradual fall (troponin) or more rapid rise and fall (creatine kinase-MB) of biochemical markers of myocardial necrosis with at least one of the following:
   a) Ischaemic symptoms
   b) Development of pathological Q-waves on electrocardiogram
   c) Electrocardiogram changes indicative of myocardial ischaemia (ST-segment elevation or depression)
   d) Coronary artery intervention (eg, coronary angioplasty)
2) Pathological findings of an acute myocardial infarction

ESC/ACC definition of myocardial infarction

The ESC/ACC definition fits with the patient's clinical course. Patients do not present with overt myocardial infarction, but with acute chest pain suggestive of acute coronary pathology, characterised by presence or absence of ST-segment elevation, and by presence or absence of biochemical markers of myocardial injury (figure 4).[40] An acute thrombotic obstruction of a major epicardial coronary artery is most likely in patients presenting with ST-segment elevation. Most of these patients finally develop myocardial infarction, although imminent myocardial injury can be avoided by early reperfusion.[41] Myocardial infarction had also occurred in patients presenting without ST-elevation in whom raised concentrations of biochemical markers indicate irreversible cell damage. Until recently, many of these patients were diagnosed as having unstable angina. In patients undergoing percutaneous coronary interventions, procedural related enzyme leaks are indicative of cell death due to myocardial ischaemia. Therefore, the ESC/ACC definition indicates that such patients should be regarded as having myocardial infarction.

Application of the ESC/ACC definition has major implications for clinical and epidemiological research, individual patient care, and society. The ESC/ACC committee that advised on the new definition therefore recommended that information be provided about the circumstances in which the infarction had occurred, the residual left ventricular function, the extent and severity of coronary artery lesions, and the development of the disease over the recent past.[14]

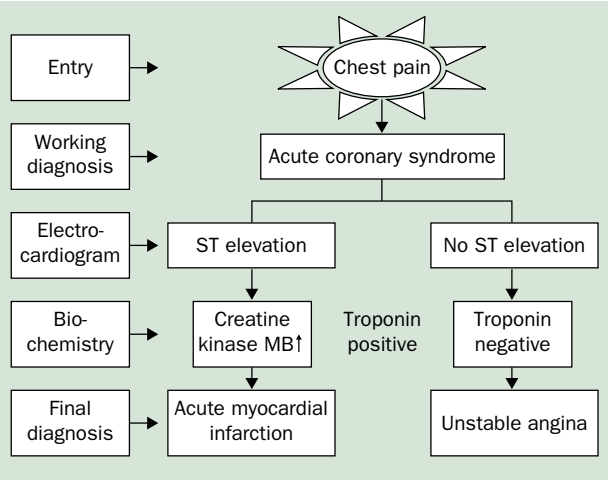

Figure 4: **Acute coronary syndrome terminology**
Reproduced with permission from Hamm and colleagues.[40]

Critics of the proposed new definition have questioned the clinical importance of minor myocardial damage, especially in coronary interventions.[42] A practical objection against application of this new definition is that available assays for troponin detection do not have the sensitivity to adequately detect small increases.[43] Finally, the ESC/ACC definition is thought to be inappropriate for general diagnostic use, since it does not cover early and fatal cases.[42]

Decreasing death rates

Death rates from coronary heart diseases—and among these, ischaemic heart diseases—have decreased in most developed countries (eg, figure 5).[44,45] Results from the WHO MONICA project[46] suggest that the decreasing number of coronary events is the major determinant of this decline, whereas improved coronary care and secondary prevention were associated with decreased event rates.[47] The decline in deaths due to coronary heart disease runs parallel with increasing numbers of patients with chronic conditions.[13] Consequently, prevalence of coronary heart disease in developed countries is still increasing. Furthermore, deaths from coronary and ischaemic heart disease have increased, and are still increasing, in most eastern European countries (Hungary and Romania are presented as examples in figure 5), and in many developing countries. Elements with a role in this regional variation include epidemiological transitions, such as fewer deaths from infectious diseases, changes in life-style and environmental risk markers, and intrinsic differences in genetic profile between populations.[48] The prevalence of risk factors varies greatly between geographical regions and ethnic groups. However, risk factors for myocardial infarction seem to have similar risk irrespective of geographical region or ethnic origin.[49]

In-hospital treatment

Since myocardial infarction was shown to be caused by an acute intracoronary thrombotic occlusion, treatment strategies have been introduced that aim at rapid, complete, and lasting restoration of coronary blood circulation. Physicians can now choose from different pharmacological reperfusion regimens based on thrombolytic, antiplatelet, and anticoagulant agents. In some hospitals, catheter-based interventions are also available.

Pharmacological lysis

GISSI-1[50] and ISIS-2[51] are the major landmark studies of thrombolytic therapy, by showing a 26% reduction in 30-day mortality in patients given streptokinase compared with placebo.[52] Streptokinase still is the most frequently used thrombolytic agent. However, since the results of the GUSTO-1 trial[53] showed a further mortality reduction by accelerated or front-loaded alteplase (100 mg infusion over 90 min, with over half of the dose within 30 min) over streptokinase, front-loaded alteplase became the gold standard for pharmacological reperfusion therapy. GUSTO-1[54] is also important because an angiographic substudy showed an association between the patency of the initially occluded coronary artery and outcome.

During the 1990s several wild-type alteplase mutants were developed with less high-affinity fibrin capacity, a longer half-life, and therefore a greater thrombolytic potency. In phase 2 trials,[55,56] the bolus injection of reteplase and lanoteplase was associated with more rapid and complete vessel patency than front-loaded alteplase. However, similar patency rates were achieved with tenecteplase when compared with front-loaded alteplase.[57]

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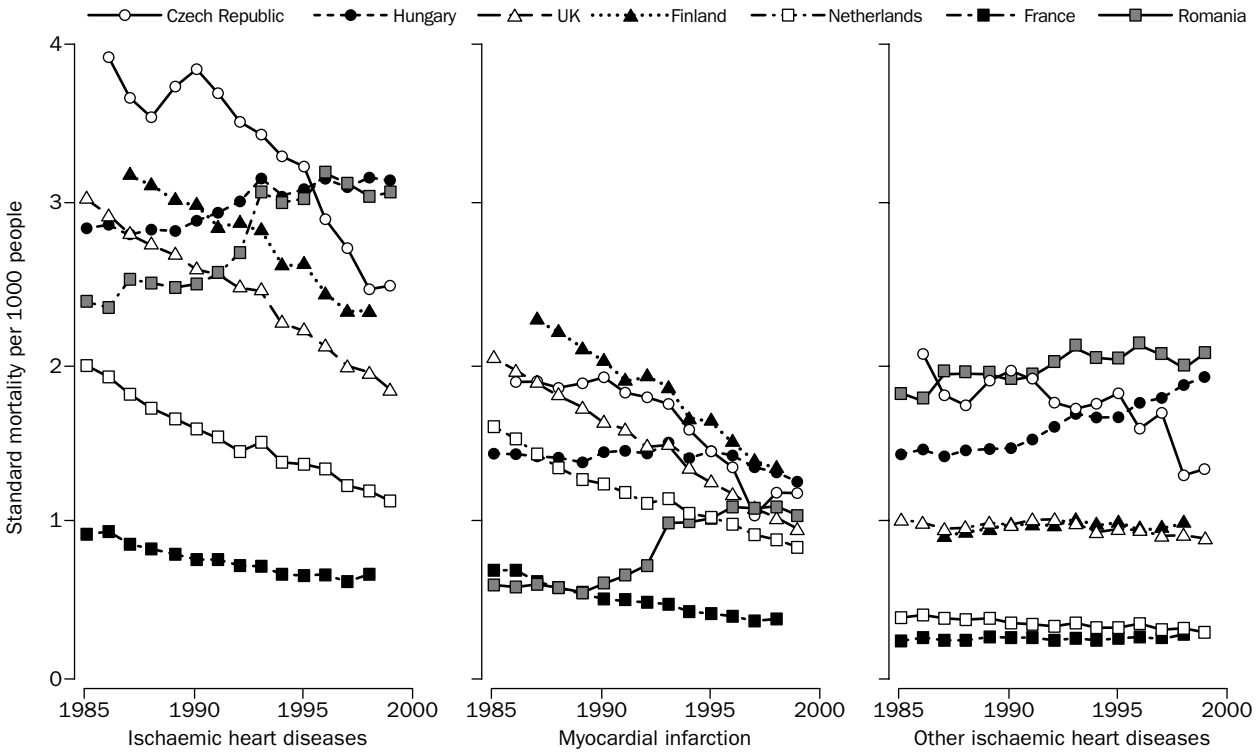

Figure 5: **Standardised ischaemic heart diseases mortality in selected European countries**
(Left) Mortality associated with ICD-9 codes 410–414 or ICD-10 codes I20–I25. (Middle) Mortality associated with ICD-9 codes 410–411 or ICD-10 codes I21–I23. (Right) Mortality associated with ICD-9 codes 412–414 or ICD-10 codes I24–I25.

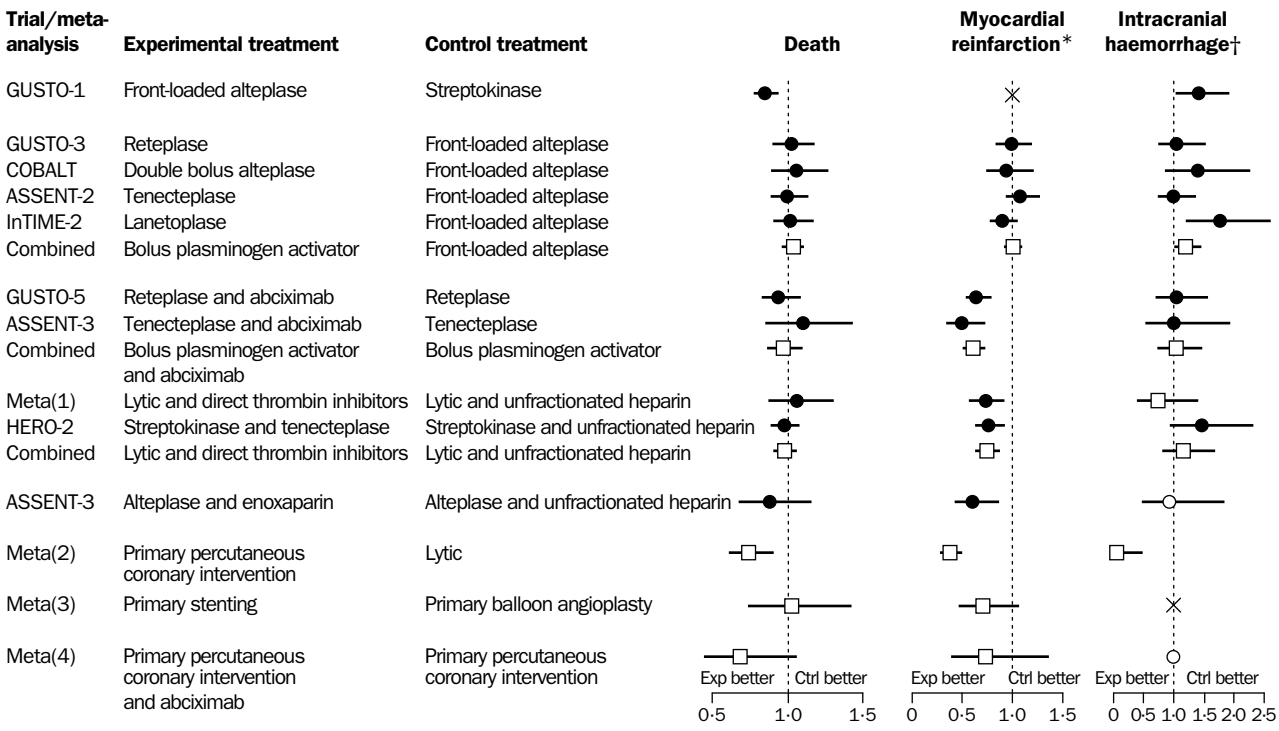

Figure 6: **Relative treatment effect associated with several acute treatment modalities in patients presenting with ST-elevation acute coronary syndromes**
Meta(1) includes data from reference 60. Meta(2) includes data from reference 4. Meta(3) includes data from reference 61. Meta(4) includes data from references 62–66. Data are odds ratios and 95% CIs. *Data for myocardial reinfarction as a single endpoint were not available for meta(3); in this case the figure presents odds ratios for the composite of death or myocardial reinfarction. †Intracranial haemorrhage was not reported in meta(1)—data were derived from the HERO-1, HIT-4, TIMI9b, and GUSTO2b trials that were included in this meta-analysis.

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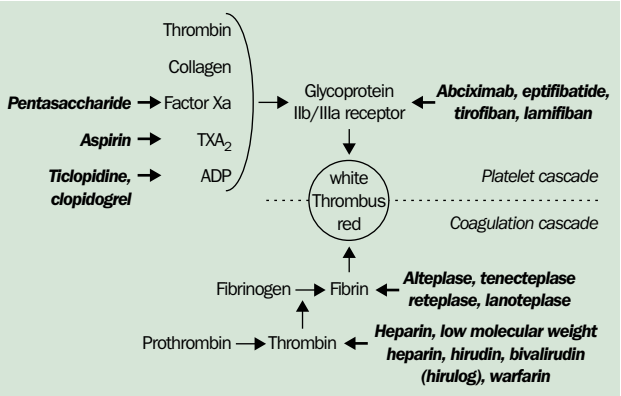

Figure 7: **The platelet and coagulation cascade that results in (intracoronary) thrombus formation**

Subsequently, large phase 3 mortality trials[58] showed no superiority with reteplase and equivalent results with tenecteplase and lanoteplase when compared with alteplase. In a meta-analysis,[59] use of bolus thrombolytic agents was associated with increased incidence of intracranial haemorrhage. However, this increased risk was not evident in patients given tenecteplase or reteplase as compared with front-loaded alteplase (figure 6).[67] Furthermore, the intensity of antithrombin treatment seems to be a confounding factor.[67] Altogether, the introduction of bolus thrombolytic agents did not result in a net clinical benefit. Yet, the major advantage is that thrombolytic agents are now available with a similar efficacy and safety profile as front-loaded alteplase, but easier to administer.

Antiplatelet treatment

Adequate vessel patency does not guarantee perfusion on myocardial tissue.[68,69] Thrombolytic treatment has three important caveats in this respect. First, the occluding thrombus might fall apart in smaller parts as a result of treatment, causing distal microembolisation. Second, treatment with a thrombolytic agent only resolves the fibrin-rich red part of the thrombus (and therefore can better be named fibrinolytic therapy), whereas the platelet-rich white part remains largely untouched (figure 7). Finally, fibrinolysis generates raised concentrations of free thrombin, and activates platelet aggregation, which might cause a further worsening of the microcirculation. To overcome these caveats, pharmacological reperfusion strategies were developed to combine fibrinolytic treatment with aggressive anti-platelet therapy.

Antiplatelet treatment has been used in patients with myocardial infarction for many years by means of aspirin administration. The ISIS-2 study[51] provided evidence for the benefits of starting aspirin early after the onset of suspected infarction. Aspirin, however, is a weak antiplatelet agent, since it inhibits only one of the pathways leading to platelet aggregation (figure 7). The final common pathway in this process is formed by activation of the platelet glycoprotein IIb/IIIa receptor. Therefore, inhibitors of the platelet glycoprotein IIb/IIIa are more potent agents than aspirin. Results of phase 2 trials[70–73] of myocardial infarction with ST-elevation showed that combined fibrinolytic therapy and glycoprotein IIb/IIIa inhibitors achieved more complete reperfusion than did fibrinolytic therapy alone. Additionally, shorter time periods to ST-segment resolution were recorded, indicating improved early reperfusion in the myocardial tissue.[74,75] In GUSTO-5,[76] combined treatment with reduced dose reteplase and abciximab was not associated with a lower 30-day mortality compared with full-dose reteplase alone (figure 6, table). Myocardial reinfarction was significantly reduced, but this endpoint did not translate into a mortality reduction beyond the 30 days.[77] Combination therapy was associated with increased frequency of major bleeding complications, especially in elderly patients. The results of the ASSENT-3 trial,[78] which compared tenecteplase plus abciximab with tenecteplase alone, fit well with GUSTO-5: no effect on mortality, significantly reduced composite endpoint that included myocardial infarction, and increased risk of major bleeding complications.

Antithrombin therapy

Release of thrombin from the thrombus, as a result of fibrinolysis, contributes to a procoagulant state (figure 7). Thus, fibrinolytic and antiplatelet therapy could be combined with anticoagulant or antithrombin therapy. GISSI-2[79] and ISIS-3[80] investigated the efficacy of subcutaneous heparin in addition to streptokinase and aspirin. The investigators recorded a non-significant reduction in 30-day death and myocardial reinfarction in patients given heparin compared with placebo. By contrast, major or severe bleeding complications increased. In GUSTO-1 no major differences were recorded between subcutaneous and intravenous heparin among patients on streptokinase. In view of these data, neither subcutaneous nor intravenous heparin probably adds much to the outcome in patients given streptokinase and aspirin. This opinion, however, is not commonly shared,[81] and unfractionated heparin is frequently used in patients with myocardial infarction who are given streptokinase. Apart from that, intravenous heparin as a component of the GUSTO-1 front-loaded alteplase regimen is widely accepted, although front-loaded alteplase without intravenous heparin has not been extensively studied.

Unfractionated heparin is an indirect thrombin inhibitor, since it requires the presence of antithrombin III. Direct thrombin inhibitors such as hirudin and bivalirudin (formerly known as hirulog), do not need this enzyme to be present, and therefore have a higher antagonistic potency. In a meta-analysis on patients presenting with ST-segment elevation, use of direct thrombin inhibitors was associated with a significant reduction in 30-day death or myocardial reinfarction compared with unfractionated heparin.[60] Death rates were not affected by direct thrombin inhibitors. Similar data were recorded in the HERO-2 trial,[82] which compared bivalirudin and unfractionated heparin in patients presenting with ST-elevation who were given streptokinase. Use of direct thrombin inhibitors was not associated with an increase in the frequency of major bleeding complications.

Similar to direct thrombin inhibitors, low molecular weight heparin has better pharmacological properties than unfractionated heparin, which offer advantages for its use in clinical practice. Results of phase 2 trials[83,84] indicate a trend toward better angiographic patency, improved ST-segment resolution, and fewer rates of reocclusion associated with enoxaparin compared with unfractionated heparin, as an adjunctive to streptokinase or front-loaded alteplase. In the ASSENT-3 trial, in which tenecteplase was used, patients randomly allocated to receive enoxaparin were significantly less likely to die or to have a myocardial reinfarction within 30 days than were those on unfractionated heparin (figure 6). Because of its ease of administration, tenecteplase plus enoxaparin seems to be

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	Experiment	Control	Effect*
GUSTO-1			
Procedure	Front-loaded alteplase, aspirin, infusion unfractionated heparin or infusion unfractionated heparin	Streptokinase, aspirin, subcutaneous unfractionated heparin	
Patients	10 396	20 251	Death
6·3%	7·3%	10±3 fewer	
Myocardial infarction	..	..	..
Stroke	1·6%	1·3%	2±1 more
Intracranial haemorrhage	0·7%	0·5%	2±1 more
GUSTO-3, COBALT, ASSENT-2, and InTIME-2			
Procedure	Reteplase, double bolus alteplase, lanoteplase or tenecteplase, aspirin, infusion unfractionated heparin	Front-loaded alteplase, aspirin, infusion unfractionated heparin	
Patients	32 222	22 015	
Death	7·0%	6·7%	2±2 more
Myocardial infarction	4·4%	4·3%	1±3 fewer
Stroke	1·8%	1·6%	1±1 more
Intracranial haemorrhage	1·0%	0·8%	2±1 more
GUSTO-5, and ASSENT-3			
Procedure	Reteplase or tenecteplase (both reduced dose), aspirin, abciximab, infusion unfractionated heparin	Reteplase or tenecteplase, aspirin, heparin infusion unfractionated	
Patients	10 345	10 298	
Death	5·8%	5·9%	1±3 fewer
Myocardial infarction	2·3%	3·6%	14±2 fewer
Stroke	1·1%	1·0%	1±1 more
Intracranial haemorrhage	0·7%	0·7%	0±1 equal
Meta-analysis†, and HERO-2			
Procedure	Streptokinase or front-loaded alteplase, aspirin, hirudin or bivalirudin (hirulog)	Streptokinase or front-loaded alteplase, aspirin, infusion unfractionated heparin	
Patients	13 664	13 356	
Death	8·3%	8·4%	1±3 fewer
Myocardial infarction	2·7%	3·5%	8±2 fewer
Stroke	1·2%	1·0%	3±1 more
Intracranial haemorrhage	0·5%	0·4%	1±1 more
ASSENT-3			
Procedure	Tenecteplase, aspirin, enoxaparin	Tenecteplase, aspirin, infusion unfractionated heparin	
Patients	2040	2038	
Death	5·3%	6·0%	6±7 fewer
Myocardial infarction	2·7%	4·2%	16±6 fewer
Stroke	1·6%	1·5%	1±4 more
Intracranial haemorrhage	0·9%	0·9%	0±3 equal
Meta-analysis‡			
Procedure	Primary PCI (balloon angioplasty or stenting)	Lytic	
Patients	3872	3867	
Death	6·9%	9·3%	23±6 fewer
Myocardial infarction	2·4%	6·8%	44±5 fewer
Stroke	0·9%	2·0%	11±3 fewer
Intracranial haemorrhage	0·05%	1·1%	11±3 fewer
Meta-analysis§			
Procedure	Primary stenting	Primary balloon angioplasty	
Patients	2050	2070	
Death	3·7%	3·6%	1±6 more
Myocardial infarction	2·1%	2·9%	8±5 fewer
Stroke	..	..	..
Intracranial haemorrhage	..	..	..
Meta-analysis¶			
Procedure	Primary PCI (balloon angioplasty or stenting) and abciximab	Primary PCI (balloon angioplasty or stenting)	
Patients	1747	1719	
Death	2·1%	3·0%	9±5 fewer
Myocardial infarction	1·0%	1·4%	4±4 fewer
Stroke	0·2%	0·2%	0±2 equal
Intracranial haemorrhage	0	0	Equal

PCI=percutaneous coronary intervention. Most commonly used doses of the drugs described above: Aspirin, 150–325 mg orally. Abciximab, 0·25 mg/kg bolus+0·125 mg/kg/min infusion (max 10 mg/kg/min). Subcutaneous unfractionated heparin, 12500 U twice daily. Infusion unfractionated heparin (infusion), 4000–5000 U weight adjusted bolus+800–1200 U/h weight adjusted infusion. Hirudin, 0·1 mg/kg bolus+0·1 mg/kg/h infusion; Bivalirudin, 0·25 mg/kg bolus+0·5 mg/kg/h infusion during the first 12 h+0·25 mg/kg/h infusion during the next 36 h. Streptokinase, 1·5 MU over 60 min. front-loaded alteplase, 15 mg bolus+0·75 mg/kg infusion (max 50 mg) over 30 min+0·50 mg/kg infusion (max 35 mg) over 60 min. Tenecteplase, 30–50 mg weight adjusted bolus. Reteplase, two 10 U boluses, 30 min apart. Lanoteplase, 120 KU/kg bolus. *Effect per 1000 patients assigned experimental treatment. †Includes data presented in reference 60. ‡Includes data presented in reference 4. §Includes data presented in reference 61. ¶Includes data presented in references 62–66.

Main efficacy and safety results of major clincal trials and meta-analyses of different reperfusion strategies in patients presenting with ST-elevation acute coronary syndromes

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an attractive alternative reperfusion regimen that warrants further investigation.

Percutaneous coronary interventions

Results of randomised trials[3,4] have shown better clinical outcomes in those receiving mechanical reperfusion than in those receiving pharmacological reperfusion. A meta-analysis[4] of 23 randomised trials showed a 27% reduction in short-term mortality in favour of primary angioplasty compared with lytic therapy (figure 6). The reduction in risk was less pronounced in fibrin-specific trials (20% risk reduction) than in streptokinase trials (47% risk reduction), with statistical evidence of heterogeneity between these two groups of trials. Primary balloon angioplasty was also associated with a significantly lower incidence of myocardial reinfarction, stroke, and intracranial haemorrhage compared with pharmacological reperfusion (figure 6). This initial benefit was maintained during long-term follow-up.[85] Overall, the results of primary angioplasty obtained in early trials were mainly achieved because of experienced operators (>75 cases per year), high-volume centres (>200 cases per year), with door-to-balloon times of less than 90 min.[86] However, after careful training, primary percutaneous coronary interventions can be done successfully at community hospitals without on-site cardiac surgery backup, as reported in the C-PORT study.[87] Five other studies[88–92] have assessed the potential benefit of a transfer for primary percutaneous coronary intervention over fibrinolytic treatment in acute myocardial infarction. Whether these results could be applied and translated into daily practice remains unclear, but practice guidelines have already changed after the release of these new data. In 1999, the ACC/AHA guidelines recommended primary percutaneous coronary intervention as an alternative treatment to fibrinolytic therapy.[86] 4 years later, the European Society of Cardiology (ESC) guidelines regarded primary percutaneous coronary intervention as the preferred therapeutic option when it can be done within 90 min after first medical contact.[93]

No significant difference in mortality was recorded between primary coronary stenting and balloon angioplasty, but primary stenting was associated with a non-significant trend for reduction in the frequency of myocardial reinfarction and a significant reduction in target vessel revascularisation.[61] Thus, coronary stenting is a safe alternative that augments the angiographic and clinical results of primary balloon angioplasty.

Use of glycoprotein IIb/IIIa inhibitors in patients with ST-elevation myocardial infarction undergoing percutaneous interventions inhibits platelet aggregation at the site of plaque rupture and balloon-induced or stenting-induced injury, potentially improving the clinical outcome. In five randomised trials[62–66] comparing primary balloon angioplasty or stenting with or without abciximab, a non-significant trend for reduction in mortality and myocardial reinfarction was noted with use of glycoprotein IIb/IIIa inhibitors, which is compatible with the benefit of glycoprotein IIb/IIIa use as seen in other studies of percutaneous coronary intervention.[94,95]

Time to treatment

Time from symptom onset to treatment is one of the most important determinants of the success of pharmacological reperfusion therapy.[96] Results of several investigations have shown that initiation of fibrinolytic treatment at the patient's home, before admission, reduces treatment delay by about an hour.[97] Two meta-analyses[98,99] of all randomised trials comparing prehospital and inhospital fibrinolysis have shown a significant mortality reduction by the prehospital treatment strategy. Prehospital fibrinolysis also seems to be associated with a three-fold increase in abortion of myocardial infarction compared with in-hospital treatment.[41] The safety of prehospital fibrinolysis is strongly dependent on a correct diagnosis in the prehospital setting. To confirm ongoing myocardial infarction, a standard 12-lead electrocardiogram is needed, which can either be transmitted via a telephone connection for interpretation by skilled cardiologists, or interpreted on-site by specifically designed computer programs. Both approaches are associated with similarly low false-positive rates.[100,101]

Primary angioplasty is associated with an increased treatment delay compared with fibrinolytic therapy, but how much extra angioplasty-related treatment delay would nullify its benefits is unclear. In a large observational study[102] of patients treated by primary angioplasty, increased mortality rates were recorded once the door-to-balloon time exceeded 2 h. Data from randomised trials[103] indicated that primary angioplasty and fibrinolytic therapy yielded equivalent mortality reductions if the angioplasty is delayed by 50 min. In other investigations,[88] however, primary angioplasty was associated with a significant reduction in major cardiac endpoints over fibrinolysis even after long delays in treatment. Analyses are hampered by the fact that only a few patients undergoing primary angioplasty are treated within 2 h from onset of symptoms.[104,105]

Prevention and long-term treatment

It is important to stratify patients according to the risk of further coronary events after acute myocardial infarction, and to take measures to prevent them. In high-risk patients, coronary interventions should be considered.[106] In general, however, effort should be devoted to actions that aim to change unhealthy life-styles, and provide individualised advice on smoking, diet, weight control, and exercise.[22] For long-term medical management, the value of aspirin, β blockers, and ACE inhibitors has been shown beyond all reasonable doubt. Weaker conclusions can be drawn about long-term treatment with statins and anticoagulants.

Aspirin

The available evidence for long-term antiplatelet treatment in patients who have had a myocardial infarction is mostly derived from a meta-analysis of 25 trials of antiplatelet therapy in secondary prevention of cardiovascular disease. This meta-analysis included ten postinfarction trials of antiplatelet therapy that showed a significant reduction in total vascular mortality, non-fatal reinfarction, non-fatal stroke and important vascular events, a composite endpoint that included total vascular mortality, non-fatal reinfarction, and non-fatal stroke.[107] There is no general consensus about the optimum duration of treatment in secondary prevention, but indirect data suggest that aspirin should be continued indefinitely after infarction.

β blockers

Use of intravenous β blockers in patients in the acute phase immediately after myocardial infarction without obvious clinical contraindications could be considered when there is tachycardia (in the absence of heart failure), hypertension, or chest pain unresponsive to opioids. Short-term treatment in the acute phase seems to be of no benefit in reducing mortality and morbidity unless

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β blockade is continued long term.[8] Moreover, data from long-term trials[108] suggest that β blockers should be continued indefinitely in all patients who have recovered from an acute myocardial infarction.

ACE-inhibitors

Based on several clinical studies, and provided that there are no major contraindications for their use, ACE-inhibitors should be initiated in the early phase after haemodynamic stabilisation.[109] These studies have shown that ACE-inhibitors reduce rates of reinfarction, and exert a favourable effect on ventricular remodelling that is usually accompanied by a decrease in development of congestive heart failure, which in turn is translated into a reduction in mortality. The efficacy is probably of greatest value in patients who are at high risk, such as elderly people, those with Killip class II or greater, and asymptomatic patients with depressed left ventricular function. If treatment is well tolerated, it should be continued indefinitely.[9]

Statins

Data from two observational studies[110,111] have shown that survivors of acute coronary syndromes who were discharged on statin treatment had a reduced mortality at 6 months and 1 year. In the MIRACL study,[10] patients with an acute coronary syndrome were randomly allocated to atorvastatin or placebo. Mortality reduction was not significant. However, statin treatment was associated with a significant reduction in the composite endpoint of death, non-fatal myocardial reinfarction, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischaemia. If statins are withdrawn after admission for an acute coronary syndrome, death and non-fatal reinfarction increase compared with patients who continue to receive them, and tended to be higher compared with patients who never received it.[112]

Anticoagulant treatment

Oral anticoagulant agents could also be used in the long term, although most of the clinical trials with these agents were undertaken before widespread use of aspirin.[113] Several clinical trials could not show a reduction in events by combined aspirin and low-intensity oral anticoagulant treatment.[113,114] However, in two clinical trials,[115,116] combined aspirin and more intensive oral anticoagulation therapy (INR>2) was associated with significantly lower frequency of death, myocardial reinfarction, and stroke than was aspirin alone, although at the cost of an increase in non-fatal bleeding complications.

Future directions

With the understanding on development of coronary atherosclerosis as an inflammatory disease, future research should concentrate on development and wide implementation of new approaches that will allow screening for serum markers of chronic low-grade vascular wall inflammation, and clinical imaging of the vulnerable plaque that will discriminate among patients who are at an increased risk for plaque rupture and infarction. However, front-line research towards new risk markers of coronary atherosclerosis should not divert our attention from what is already known. Data is emerging that we are failing to modify traditional risk factors. In the recent EUROASPIRE surveys[11] of coronary risk factors across several European countries in 1995–96 and 1999–2000, risk factor modification was not successful. Smoking prevalence increased from 19% to 21%, obesity from 25% to 33%, and diabetes from 18% to 22%. Prevalence of hypertension and hypercholesterolaemia was still as high as 54% and 59%, respectively. This was considered as a collective failure of medical practice to achieve the substantial potential among patients with coronary heart disease to reduce the risk of recurrent disease and death.[11]

A similar situation appears with regard to acute treatment. On the one hand, reperfusion therapy continues to evolve, and adjunctive therapies with adenosine and super-saturated aqueous oxygen to reduce reperfusion injury are promising, as is induction of moderate systemic hypothermia.[117–119] New developments in this respect also include investigations towards the effectiveness and safety of low-molecular weight heparins (enoxaparin), antiXa agents (pentasaccharides), glucose insulin potassium infusion, and ADP inhibitors (clopidogrel). On the other hand, treatment strategies proven to be effective, such as reperfusion therapy, are still largely underused. This was evident in two recent surveys. In GRACE[120] up to a third of eligible patients presenting with ST-segment elevation myocardial infarction within 12 h of symptom onset did not receive reperfusion therapy. Similarly, in the Euro Heart Survey[6] of acute coronary syndromes, only half the patients enrolled with ST-segment elevation received reperfusion therapy. And finally, despite compelling evidence about the importance of very early reperfusion therapy, the time from symptom onset to treatment of 2·7 h, as recorded in clinical trials in the beginning of the 1990s (GUSTO-1), has remained unchanged.[121–123]

Contributors

E Boersma was responsible for the concept and applied methods. E Boersma and N Mercado drafted the report. D Poldermans, M Gardien, J Vos, and M L Simoons were responsible for critical revision of the report.

Conflict of interest statement

None declared.

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