CHAPTER 1

General introduction and outline of the thesis

M.A. Velders

General introduction

Four million people die from cardiovascular causes in Europe every year. Almost half of these deaths are attributable to coronary heart disease (CHD), which makes CHD the single most common cause of death in European citizens.[1] CHD was estimated to cost the European Union €45 billion in 2003, with approximately 90 million working years lost due to CHD morbidity and 1 million working years lost due to CHD mortality.[2] Nevertheless, prognosis of CHD patients has been improving over the last decades.[3] As a consequence, the prevalence of CHD is increasing rapidly, which is amplified by the aging of Western populations and increases in the number of people with known risk factors such as obesity.[4,5]

The clinical syndrome responsible for most CHD morbidity and mortality is the acute coronary syndrome (ACS). Patients with suspected ACS are commonly divided into non ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) based on electrocardiographic (ECG) findings. The presence of persistent ST-segment elevation in two contiguous leads with reciprocal ST-depression on the ECG reflects transmural ischemia, which will lead to myocardial necrosis unless immediate reperfusion therapy is initiated. The main focus of this thesis is the STEMI population.

Pathophysiology of coronary heart disease

Atherosclerosis is the underlying pathophysiological process of the majority of CHD cases. It involves the formation of atheromatous plaques in the coronary and other medium to large-sized arteries throughout the body. Plaque formation is most likely initiated by irritant stimuli such as dyslipidemia, leading to expression of adhesion molecules on the endothelial surface and retention of low-density lipoproteins in the vessel wall.[6,7] Circulating leukocytes (mainly monocytes and lymphocytes) adhere to the "activated" endothelium and migrate into the vessel wall. The monocytes mature into macrophages in the intimal layer of the artery. These macrophages internalize the modified lipoproteins (thereby becoming foam cells), which results in an accumulation of lipids in the intima. Furthermore, macrophages and other leukocytes initiate an inflammatory response and cause tissue damage through the release of inflammatory cytokines, chemokines, proteases and oxygen radicals. Secreted growth factors stimulate both the migration of smooth muscle cells into the intima and the heightened synthesis of extracellular matrix such as collagen and elastin, promoting the formation of a collagenous fibrous cap that covers the plaque.[6,7] As the lesion progresses, a necrotic core filled with cell debris, lipids, proteases and procoagulant material is formed inside the plaque. In this advanced stage, the plaque becomes prone to rupture due to thinning of the fibrous cap under influence of proteases. When plaque rupture occurs, the procoagulant material from the necrotic core and the extracellular matrix come into contact with blood, thereby triggering the formation of a luminal thrombus.[6,7] Alternatively, thrombus

formation may be triggered by denudation or erosion of the endothelial layer without plaque rupture.[6] When a localized or embolized thrombus impedes the coronary blood flow towards a segment of the myocardium, ischemia and eventually myocardial necrosis occur. This gives rise to the clinical spectrum of ACS (unstable angina pectoris with or without myocardial infarction (MI)). The healing of plaque ruptures plays a role in the progressive narrowing of the coronary lumen in CHD, a process that can occur asymptomatically if coronary blood flow is not impeded.[8] The arterial wall may initially compensate for plaque progression by way of enlargement toward the adventitia (coined positive remodeling), thereby delaying the formation of a functionally significant stenosis.[9] However, the capacity for the coronary artery to increase the blood supply to the myocardium becomes increasingly limited as the narrowing of the coronary lumen progresses. This may result in myocardial ischemia during moments of increased demand (e.g. exercise, stress), creating the clinical entity of stable angina pectoris.

Risk factors

Well-established modifiable risk factors for cardiovascular disease include dyslipidemia, hypertension, diabetes mellitus and smoking, in addition to the strong unmodifiable risk factors age and gender.[10] These traditional risk factors, along with abdominal obesity, lack of physical exercise, low consumption of fruit and vegetables, high consumption of alcohol and psychosocial factors account for an estimated 90% of the worldwide populations' attributable risk of MI.[11] Risk factor reductions explained half of the reduction in CHD mortality in the United States in the last 20 years, stressing the importance of identifying patients at risk for CHD.[3] European guidelines further acknowledge the value of primary prevention, and recommend screening of the general population for risk of cardiovascular disease using risk estimation systems such as 'SCORE'.[12,13] Recently, much research has been devoted to the role of biochemical markers in improving the early identification of patients at risk for cardiovascular disease in the general population. Inflammatory markers, cardiac troponins and natriuretic peptides have been studied extensively and contribute to risk stratification, although the added value over traditional risk factors remains uncertain.[14-16]

Diagnosis of myocardial infarction

The cornerstone of the diagnosis of MI is the detection of a rise and fall in biomarkers of cardiac necrosis above the 99th percentile of the upper reference limit, in combination with other clinical signs and symptoms of myocardial ischemia or infarction (Table 1). However, the patient history and ECG findings remain the most important factors for determining the management strategy of patients with suspected MI, as biomarkers may still be undetectable in the early stages of MI.

Table 1. Criteria for acute myocardial infarction

Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and with at least one of the following: • Symptoms of ischemia • New or presumed new significant ST-segment changes or new left bundle branch block • Development of pathological Q waves in the ECG • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality • Identification of an intracoronary thrombus by angiography or autopsy

Adapted from the third universal definition of myocardial infarction.[17]

STEMI is typically accompanied by prolonged chest pain in rest (>20 minutes in duration), located in the center of the chest and commonly described as a heavy, tight or burning sensation. Additional symptoms may include but are not limited to: radiation of the pain (to arm, neck, jaw, shoulder or abdomen), nausea/vomiting, diaphoresis, dyspnea, fatigue, fear of dying and collapse.[18] Atypical symptomatology is common, especially in women, diabetics and elderly patients, and may significantly delay help-seeking behavior and timely diagnosis.[19,20]

The ECG is a vital tool for the rapid decision making in patients with suspected MI. In setting of STEMI, the ECG can be used to estimate the quantity of myocardium at risk and can in most cases identify the coronary culprit lesion.[21,22] Furthermore, ECG monitoring is essential for the detection of potentially life-threatening ventricular arrhythmias that may occur during the early stages of STEMI. In certain cases, interpretation of ST-segment changes may be limited due to the presence of bundle branch block or ventricular pacing, potentially delaying diagnosis of MI.[23,24]

Biomarkers

Currently, the most commonly used biomarkers for detection of myocardial necrosis are creatine kinase-MB (CK-MB) and cardiac troponins. Creatine kinase is an enzyme that catalyzes the transfer of high-energy phosphate from creatine phosphate to adenosine triphosphate, and is released rapidly during muscle damage. The creatine kinase system consists of different isoenzymes; CK-MM is present in large quantities in skeletal muscle and myocardium, while CK-MB is found predominantly in the myocardium, making it useful for the detection of myocardial necrosis.[25] However, small amounts of CK-MB are also found in skeletal muscle, and the ratio of CK-MB to CK-MM in skeletal muscle is influenced by factors such as heavy exercise, reducing the specificity of CK-MB for myocardial damage.[26]

Cardiac troponins are the current standard for the measurement of myocardial injury. The contractile apparatus of the myofibril consists of myosin, actin, tropomyosin and the troponin complex. The troponin complex has three sub-units; troponin-C, troponin-I and troponin-T. Although troponins are found in both skeletal and cardiac muscle, distinct cardiac isotypes exist for troponin-I and troponin-T, making these isotypes highly specific markers of myocardial injury.[25] Continuous

improvements in troponin assays have led to greatly increased sensitivity for the detection of cardiac troponins, resulting in the adoption of the term high-sensitive cardiac troponin measurements. For optimal precision, assays should have a coefficient of variation ≤10% at the 99th percentile upper reference limit of a healthy population. A rise and fall of troponin values is needed to distinguish acute from cardiac troponin elevations that are associated with structural heart disease.[27]

Treatment

The progress made in the treatment of MI in the last century has been impressive, and several important developments deserve mention. One of the first major improvements in management was the introduction of coronary care units in the 1970s. Coronary care units opened the possibility towards monitoring patients for hemodynamics and the occurrence of life-threatening arrhythmias, allowing prompt treatment when necessary.[28] The beneficial concept of the coronary care unit was extended outside the hospital walls through the introduction of ambulances with defibrillation equipment, as it was recognized that many MI patients died before hospital admission due to fatal arrhythmias.[29] The decrease in arrhythmia-related mortality increased the recognition of infarct size as the major determinant of morbidity and mortality in patients with MI.[30] Apart from initial success of beta-blockers in limiting infarct size, the real breakthrough came with the introduction of reperfusion therapy.[31] The growing realization that coronary thrombus was present in the majority of patients with STEMI and the first successful lysis of coronary thrombus through infusion of streptokinase paved the way for the use of thrombolysis in STEMI patients.[32,33]

Thrombolysis

The GISSI trial was the first large multicenter trial to randomize patients with acute MI to treatment with intravenous streptokinase compared to conventional treatment.[34] This landmark trial showed that streptokinase reduced early mortality and was safe in acute MI patients. The ISIS-2 study confirmed the strength of intravenous streptokinase in acute MI, and showed the effectiveness of the combination of streptokinase with aspirin in reducing mortality and re-infarction.[35] These and other large trials led to the widespread adoption of thrombolysis in setting of MI. Genetic engineering subsequently produced several additional thrombolytic agents, such as tissue-plasminogen activator, which was found to be superior to previous thrombolytic regimens in combination with intravenous heparin.[36] A large meta-analysis confirmed the value of the class of thrombolytic agents in acute MI, and revealed a strong association between the delay to treatment and benefit of thrombolysis.[37] This gave rise to the notion of the golden hour, the first hour after onset of symptoms, during which the patient should ideally receive reperfusion therapy.[38]

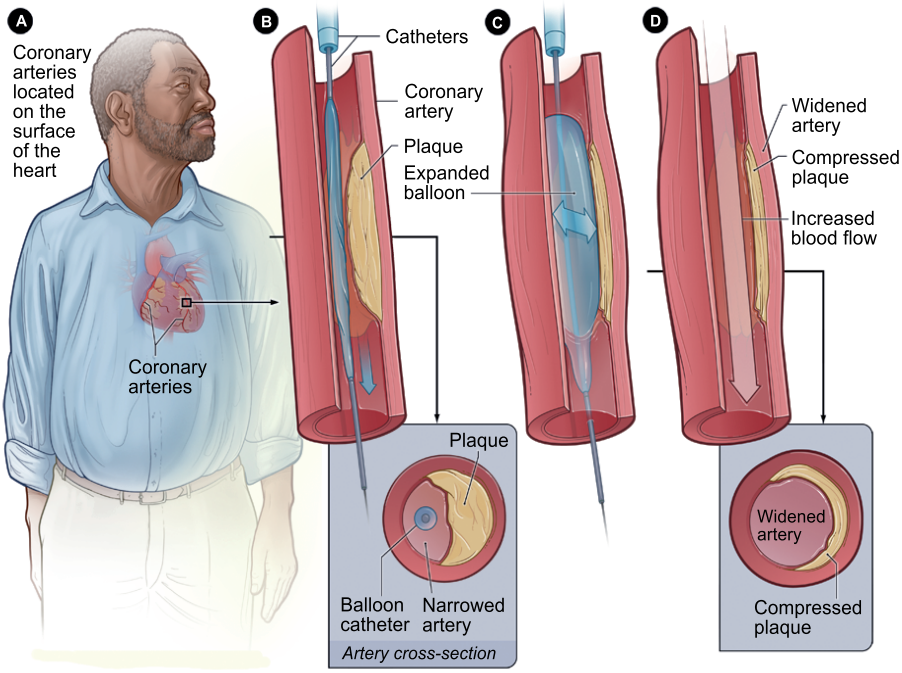

Figure 1. Coronary angioplasty. A catheter with mounted balloon is introduced into the coronary artery and passed through the coronary stenotic segment. Pressure inflation of the balloon subsequently expands the stenotic lesion, restoring the patency of the coronary vessel. Source: National Heart, Lung, and Blood Institute, National Institutes of Health; U.S. Department of Health and Human Services.

Despite the advantages and widespread availability of thrombolysis, several limitations to this therapy were noted: thrombolysis failed to restore coronary artery patency in 20-45% of patients, and re-occlusion of the coronary artery occurred in up to 30% of patients after thrombolysis.[39,40] Moreover, patients treated with thrombolysis showed a small but significant increase in intracranial hemorrhage.[37]

Primary angioplasty

Using a technique pioneered in peripheral arteries by Dotter and Judkins, Grüntzig et al. introduced the treatment of arteriosclerotic lesions in the coronary artery using catheter-mounted balloon dilatation (coronary angioplasty)[41,42] (Figure 1). The potential of angioplasty in setting of MI was soon discovered, and multiple large trials were initiated to compare "primary" angioplasty with thrombolysis in MI patients.[43] Several advantages of primary angioplasty were identified in these trials, among which higher rates of coronary patency, ability to reduce the residual coronary stenosis, lower rates of re-infarction and improvements in remaining left ventricular function compared to thrombolysis.[44,45]

A large meta-analysis finally showed that also mortality was reduced with the use of primary angioplasty, in addition to reductions in stroke and re-infarction.[46] However, management of MI using primary angioplasty is considerably more complex than thrombolysis, meaning that it can only be performed in specialized centers. As a consequence, approximately 30 minutes of additional delay until initiation of reperfusion therapy was added due to patient transfer times.[47] Sophisticated networks of care were introduced to reduce the delay between onset of STEMI and reperfusion therapy. Over the years, the optimization of MI care has led to gradual improvements in delay to treatment.[48,49] Several important strategies contribute to minimizing this delay, including the following:

- Standardization of pre- and in-hospital care and clear agreements between regional health care providers regarding the referral of STEMI patients (Figure 2).[50]
- The use of pre-hospital ECG faxed from the ambulance to the operator on call, to allow pre-hospital triage of STEMI patients.[51]
- Transport of STEMI patients straight to PCI centers.[52]
- Delivery of patients to the catheterization laboratory, bypassing the emergency room.[50,52]
- Around the clock service of intervention centers.[51]
- Monitoring of pre- and in-hospital delays to quantify the delay and identify bottlenecks.[53,54]

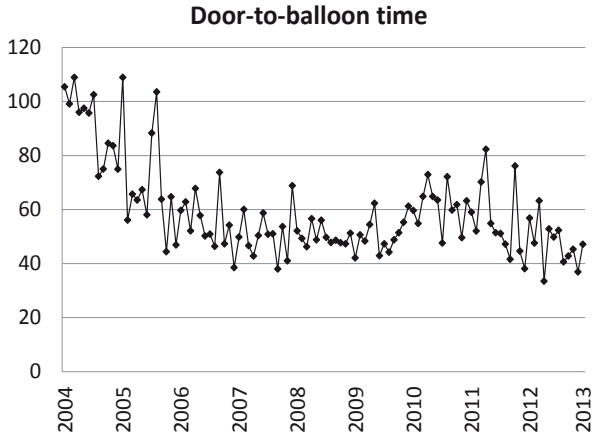

Figure 2. Influence of MISSION! implementation on door-to-balloon times. The MISSION! protocol, implemented in the Leiden University Medical Center between 2004 and 2005, is an all-phases integrated STEMI care program aimed at maximizing the use of evidence based medicine to improve the care of STEMI patients. MISSION! focuses on rapid diagnosis, minimization of treatment delay and aggressive reperfusion strategies, followed by active lifestyle improvement and structured medical therapy. Source: unpublished numbers.

In quantifying delay, the time between symptom onset and reperfusion therapy (symptom-to-balloon time) is commonly referred to as the total ischemic time, as this is theoretically the time that the myocardium is deprived from coronary blood flow. Patient delay is the time between symptom onset and seeking of health care assistance, an interval that is potentially influenced by increased awareness of symptoms of MI through public campaigns.[55] System delay starts at the moment of first medical contact, and can be divided into the overlapping time intervals of first ECG to reperfusion therapy (diagnosis-to-balloon time), and time from hospital arrival to reperfusion therapy (door-to-balloon time). Current guidelines recommend a maximum delay of 90 minutes between first medical contact and PCI. If estimated delay to PCI is longer than 120 minutes, thrombolysis is recommended with subsequent transfer to a PCI center with angiographic follow-up within 24 hours.[56]

While primary angioplasty increasingly replaced thrombolysis as the standard therapy for MI, there were some remaining disadvantages associated with balloon angioplasty: acute vessel closure occurred in 5-8% of patients, causing ischemic complications frequently requiring management with emergency coronary artery bypass grafting.[57] Also, restenosis of the treated coronary lesion occurred in up to 40% of patients.[58] Therefore, further optimization of primary angioplasty required an additional technological development. Mechanical scaffolding of the coronary artery using metallic stents proved effective in treating acute vessel closure, which led to widespread adoption of the coronary stent in clinical practice.[59]

Coronary stents

In landmark trials covering treatment of stable coronary artery disease, coronary stenting was shown to be superior to balloon angioplasty, resulting in higher rates of procedural success and less restenosis.[60,61] However, the introduction of foreign material into the body was associated with a new complication; thrombotic occlusion of the stent, or stent thrombosis (ST). This potentially catastrophic complication was found to occur in up to 1 in 5 patients.[62] Nonetheless, it was soon discovered that improved stenting technique (avoiding stent underexpansion) and use of dual antiplatelet therapy (in the form of aspirin and a thienopyridin-derivate) could drastically reduce the occurrence of ST, making coronary stenting safe for clinical practice.[63,64] Concerns about the safety of stenting in the pro-thrombotic environment of MI remained, which prompted the initiation of dedicated trials in MI patients. Suryapranata et al. were the first to randomize patients with MI to routine coronary stenting or balloon angioplasty, and were quickly followed by larger trials, most notably the CADILLAC and PAMI trials.[65-67] These trials showed that coronary stenting in setting of MI was both safe and associated with improved angiographic outcomes compared to angioplasty alone, reducing the need for revascularization procedures due to reduced restenosis rates. Subsequently, a meta-analysis of 9 trials confirmed the benefit of primary coronary stenting over primary angioplasty in reducing target vessel revascularization as well as re-infarction in setting of MI.[68]

Despite these improvements in outcome, a considerable proportion of patients still required re-intervention due to restenosis of the treated lesion. The mechanism of restenosis after stenting differed from the restenosis occurring after angioplasty, which was predominantly due to vessel recoil and negative remodeling.[69] The process involved in the re-narrowing of the in-stent lumen was coined neointimal hyperplasia. Commonly described as an excessive growth of scar tissue within the stent, this process is caused by the damaging effect of stent implantation to the vessel wall, leading to endothelial denudation, medial dissection, penetration of the lipid core and an inflammatory response to the stent struts, which results in the proliferation of smooth muscle cells on the luminal side of the stent.[70-72] To battle this iatrogenic complication of stent implantation, drug-eluting stents (DES) were developed.

Drug-eluting stents

DES are metallic stents which include a surface coating of polymer that gradually releases an antirestenotic drug which inhibits neo-intimal hyperplasia. The first DES that gained approval were the sirolimus-eluting stent (SES) (Cypher, Cordis, Bridgewater, New Jersey, United States) and the paclitaxel-eluting stent (PES) (Taxus Express/Liberté, Boston Scientific, Natick, Massachusetts). SES are based on a 140µm stainless steel stent which releases sirolimus from a layer of polyethelyne co-vinyl acetate and poly-n-butyl methacrylate polymer. The antirestenotic drug sirolimus (rapamycin) is a macrolide antibiotic with immunosuppressant properties which was found to reduce neointimal proliferation through inhibition of lymphocyte and smooth muscle cell proliferation.[73] Approximately 80 percent of the sirolimus is released within 28 days.[74]

PES are based on a 132 µm (Taxus Express) or 97 µm (Taxus Liberté) stainless steel stent which releases paclitaxel from a layer of poly(styrene-b-isobutylene-b-styrene) polymer. Paclitaxel is an antineoplastic agent that was initially isolated from bark of the Taxus tree and was found to inhibit smooth muscle cell migration and proliferation.[75] Approximately 10% of the paclitaxel is released in the first 28 days.[74]

The pivotal trials that compared SES and PES with conventional bare-metal stents (BMS) found a considerable reduction in restenosis with the use of DES in patients with stable coronary artery disease.[76-78] Importantly, no effect on mortality and reinfarction was observed.[79] However, early trials excluded patients with acute MI, and therefore several dedicated trials were initiated to investigate the use of DES in this patient category.

In setting of STEMI, use of SES was found to reduce medium term (1 to 2 year) rates of restenosis compared to BMS, while no differences in mortality, re-infarction and ST were observed.[80-86] Similarly, PES were also found to reduce restenosis rates compared to BMS at medium term follow-up.[85,87,88] In the larger trials, these results were sustained at long-term follow-up for both stent types.[89-91]

Although the beneficial effect of DES on restenosis became well established and no safety concerns were identified in individual trials, one meta-analysis did indicate a heightened rate of very late ST and re-infarction after DES implantation in setting of STEMI.[92] Furthermore, reports from real world data raised concerns on the long term safety of DES.[93] This gave rise to extensive research on the safety of DES. The standardization of the definition of ST by the Academic Research Consortium greatly facilitated the comparison of ST rates (table 2).

Table 2. Definition of stent thrombosis

Classification
• Definite ST:
Angiographic or pathological confirmation of thrombus in-stented area ± 5 mm margin and presence of one of the following criteria within a 48-hour window: acute onset of ischemic symptoms at rest, new ischemic ECG changes, typical rise and fall in cardiac biomarkers.
• Probable ST:
Any unexplained death within 30 days after PCI or any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.
• Possible ST:
Any unexplained death from 30 days after stent implantation until end of trial follow-up.
Timing of stent thrombosis
• Acute ST: 0 to 24 hours after stent implantation
• Sub-acute ST: >24 hours to 30 days after stent implantation
• Early ST: 0 to 30 days after stent implantation
• Late ST: >30 days to 1 year after stent implantation
• Very late ST: >1 year after stent implantation

Adapted from the Academic Research Consortium on clinical endpoints in coronary stent trials.[94]

Several predictors of ST have been identified, among which patient factors (diabetes mellitus, renal insufficiency, peripheral artery disease, malignancy, reduced ejection fraction), lesion factors (bifurcation lesions, complex lesions, presence of dissection, sub-optimal reperfusion, late stent malapposition), stenting technique (undersizing of stent, long stented segments, small stent diameter), medication (premature discontinuation of dual antiplatelet therapy, periprocedural bivalirudin compared to glycoprotein IIb IIIa inhibitors), setting (acute MI) and other less common factors.[95-98]

The predictors of ST show large overlap between BMS and DES. However, intravascular ultrasound and pathological studies identified specific histological correlates associated with late ST after DES implantation. Late stent malapposition was observed more frequently after SES implantation in setting of STEMI compared

to BMS.[82] Additionally, late ST was found to be strongly associated with delayed stent healing, which is more common after DES implantation due to inhibition of normal endothelial growth by the antirestenotic drug. Delayed healing is characterized by reduced endothelial strut coverage and increased fibrin deposits.[99,100] Underlying plaque morphology influences this process: vessel healing after PCI for STEMI is more delayed compared to PCI in stable coronary lesions.[101] Other local factors associated with late ST are strut penetration into the necrotic core and local hypersensitivity.[100] Besides a reaction to the stent struts, the local hypersensitivity was shown to be due to the stent polymer, causing marked local inflammation. The tissue reaction to stent struts and polymer prompted the investigations of novel DES in attempt to improve the safety and efficacy of these first generation DES.[102]

Second generation DES

The second generation DES included changes in platform, polymer and antirestenotic drug. The stainless steel stent platforms were changed to cobalt-chromium, an alloy exhibiting superior radial strength.[103] This allows thinner stent struts that may reduce thrombogenicity and improve vascular healing.[104] The Endeavor zotarolimus-eluting stent (E-ZES) (Endeavor, Medtronic Vascular, Santa Rosa, California, United States) was the first second generation DES accepted for clinical appliance. The E-ZES is based on a 91 μm cobalt-chromium stent platform eluting zotarolimus, a sirolimus-analogue. The E-ZES applies a thin layer of biocompatible phosphorylcholine polymer which has a fast elution pattern, releasing 95% of its antirestenotic drug within 14 days.[74]

The everolimus-eluting stent (EES) (Xience V, Abbott Vascular, Santa Clara, California, United States; Promus, Boston Scientific, Natick, Massachusetts, United States) is based on a thin 81 μm cobalt-chromium platform, eluting the sirolimus-analogue everolimus. The EES applies a layer of polyvinylidene fluoride co-hexafluoropropylene and poly-n-butyl methacrylate polymer which releases 80% of the everolimus within 14 days.[74]

In animal studies, EES and BMS were associated with more complete endothelialization at 14 days compared to PES, SES and E-ZES. At 28 days, this was also the case for E-ZES compared to the first generation DES.[105] In clinical studies, E-ZES was associated with reduced restenosis rates compared to BMS, reduced re-infarction and very late ST rates compared to PES and long term reductions in mortality and MI with similar clinical efficacy compared to SES.[106-109] EES were found to result in improved angiographic outcomes compared to BMS, reductions in repeat revascularization procedures, MI and ST compared to PES and reduced rates of repeat revascularization procedures and ST compared to SES.[110-115] A large meta-analysis by Palmerini et al confirmed the excellent safety of EES, reducing rates of ST compared to BMS, PES, SES and E-ZES.[116]

So far, no dedicated trials for the use of E-ZES in STEMI have been performed. EES

have been compared with BMS in 1 dedicated STEMI trial. In this trial, EES reduced the need for repeat revascularization and the rates of ST compared to BMS at 1-year.[117] Randomized comparisons of first and second generation DES in setting of STEMI have not been performed. Also, data are lacking on the optimal second generation DES in STEMI patients.

Adjunctive antithrombotic therapy

Current STEMI guidelines recommend that all STEMI patients should receive dual antiplatelet therapy in the form of acetylsalicylic acid (aspirin) and a P2Y12-receptor antagonist.[118] Aspirin inhibits platelet aggregation through cyclo-oxygenase inhibition, and was shown to reduce the risk of mortality after MI with 10 to 15% and the risk of re-infarction with 30%.[119] P2Y12-receptor antagonists inhibit platelet aggregation through direct or indirect inhibition of the ADP-activated P2Y12-receptor expressed by thrombocytes. Clopidogrel has been the most commonly used drug for this purpose, and was found to reduce mortality and re-infarction without raising bleeding risk in MI patients.[120] Recently, the more potent P2Y12-receptor antagonists prasugrel and ticagrelor were also approved for this purpose, following the large TRITON TIMI 38 and PLATO trials.[121,122] In the STEMI arms of these trials, prasugrel was shown to reduce rates of cardiovascular death, re-infarction and ST compared to clopidogrel, while TIMI major bleeding after coronary artery bypass grafting was increased.[123] Ticagrelor reduced rates of all-cause mortality, re-infarction and ST, while a slight increase in stroke was observed compared to clopidogrel.[124] European guidelines currently recommend 9-12 months of dual antiplatelet therapy after STEMI, with a strict minimum duration of 6 months after DES implantation and 1 month after BMS implantation.[118]

The third group of platelet aggregation inhibitors that may be considered as an addition to the previously described dual antiplatelet therapy consists of the glycoprotein IIb/IIIa inhibitors. These drugs are antagonists of the glycoprotein IIb/IIIa receptor which is activated by fibrinogen and von Willebrand factor. Most evidence exists for the use of acbiximab, which was shown to reduce mortality and reinfarction after primary PCI without increasing the risk of bleeding.[125] Additional mortality benefit may be achieved through the up-front administration of abciximab, a strategy performed routinely in the MISSION! protocol.[126]

In addition to antiplatelet therapy, STEMI patients should receive anticoagulation therapy around primary PCI. Traditionally, this purpose has been served by heparin, which indirectly inactivates thrombin and factor Xa through release of antithrombin. The newer direct trombin inhibitor bivalirudin may be preferable to heparine, as bivalirudin monotherapy was found to be superior to the combination of heparin and a glycoprotein IIb/IIIa inhibitor. Bivalirudin therapy resulted in a reduction in mortality and major bleeding although an increase in early ST was observed.[127] Alternatively, the 'low molecular weight heparin' enoxaparin may be preferable to

heparin due to a beneficial effect on ischemic outcomes.[128]

Risk stratification

While guidelines recommend the routine use of risk scores such as GRACE in NSTEMI patients, there remains uncertainty regarding the role of risk scores in setting of STEMI.[118] The GRACE score uses age, heart rate, systolic blood pressure, serum creatinin, Killip class and presence or absence of cardiac arrest, ST-segment deviation and cardiac enzymes to estimate the in-hospital mortality of ACS patients.[129] The TIMI risk score for STEMI differs slightly from GRACE by incorporating location of MI, history of diabetes/hypertension/angina, patient weight and time to treatment, although the strongest weighing physiological factors are similar.[130] The CADILLAC and Zwolle risk scores focus specifically on the STEMI patient treated with primary PCI, and have the advantage that angiographic characteristics are taken into account.[131,132]

An alternative approach toward improving care and stratification of STEMI patients is through the identification of high-risk sub-populations. Ideally, this allows tailoring of care to suit the specific needs of these sub-populations. For instance, more potent antiplatelet therapy with prasugrel can reduce the heightened risk of ischemic events after ACS in diabetic patients.[133] Also, newly identified or less common high-risk patient characteristics are often not included in conventional risk scores, thereby potentially underestimating the risk of adverse events in these patients.

Objective and outline of the thesis

This thesis can be divided into two distinct parts: the first part of this thesis aims to improve the risk stratification and care of STEMI patients, through the identification of high-risk sub-populations. The second part focuses on the optimization of treatment of CHD through the use of second generation drug-eluting stents.

Part 1: High-risk sub-populations

Previous studies have shown that women suffer higher mortality after ACS, due to higher age and comorbidity. However, conflicting results have been reported on the association between gender and prognosis in the STEMI population. **Chapter 2** investigates the influence of gender on ischemic times and outcomes after primary PCI for STEMI.

Out-of-hospital cardiac arrest is a common complication of STEMI which is associated with a poor prognosis. **Chapter 3** covers the angiographic determinants of out-of-hospital cardiac arrest and their association with prognosis after STEMI.

Simultaneous occurrence of cancer and CHD is increasingly frequent, and cancer patients are at a higher risk for cardiac complications due to side effects of cancer treatment and commonly present hypercoagulability. **Chapter 4** investigates the influence of cancer on the prognosis after STEMI.

As a result of aging populations in western countries, elderly patients form an increasingly large proportion of the STEMI population. However, the effects of primary PCI on the prognosis of the elderly remain poorly investigated. **Chapter 5** studies the changes in care and prognosis of elderly patients suffering STEMI during a 10-year inclusion period.

Part 2: Treatment optimization

The potentially improved safety and efficacy of second generation DES may be especially useful in the high-risk setting of STEMI. However, limited studies have focused on the comparison of second generation DES in STEMI patients. **Chapter 6** compares the long term outcome of EES and E-ZES in a real world observational cohort of STEMI patients.

No previous trials have compared first and second generation DES in setting of STEMI. Therefore, a dedicated trial was initiated to compare the second generation EES with the first generation SES in patients with acute MI. **Chapter 7** describes the results of the XAMI trial.

The routine implantation of EES has potential advantages over first generation DES in clinical practice. **Chapter 8** describes the APPENDIX-AMI trial, a randomized open label trial comparing EES and SES in all-comer patients.

The clinical response to DES implantation may differ according to clinical presentation. **Chapter 9** describes a pooled analysis of data from the XAMI and APPENDIX -AMI trials to investigate the performance of DES in patients presenting with and without STEMI during two-year follow-up.

The final chapters describe a general summary, conclusions and future perspectives in English and in Dutch.

References

1. Allender S, Scarborough P, Peto V, et al. European cardiovascular disease statistics: 2008 edition. British Heart Foundation, London (2008):112.
2. Leal J, Luengo-Fernández R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. Eur Heart J 2006;27:1610-9.
3. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med 2007;356:2388-98.
4. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet. 2009;374:1196-208. doi: 10.1016/S0140-6736(09)61460-4.
5. Heidenreich PA, Trogdon JG, Khavjou OA, et al; American Heart Association Advocacy Coordinating Committee; Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Cardiopulmonary; Critical Care; Perioperative and Resuscitation; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease; Council on Cardiovascular Surgery and Anesthesia, and Interdisciplinary Council on Quality of Care and Outcomes Research. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation 2011;123:933-44. doi: 10.1161/CIR.0b013e31820a55f5. Epub 2011 Jan 24.
6. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352:1685-95.
7. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature 2011;473:317-25. doi: 10.1038/nature10146.
8. Burke AP, Kolodgie FD, Farb A, et al. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. Circulation 2001;103:934-40.
9. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371-5.
10. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837-47.
11. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al.; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937-52.
12. Perk J, De Backer G, Gohlke H, et al.; European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012;33:1635-701. doi: 10.1093/eurheartj/ehs092. Epub 2012 May 3. No abstract available. Erratum in: Eur Heart J 2012;33:2126.
13. Conroy RM, Pyörälä K, Fitzgerald AP, et al.; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987-1003.
14. Emerging Risk Factors Collaboration. C-reactive protein, fibrinogen, and cardiovascular disease prediction. N Engl J Med 2012;367:1310-20. doi: 10.1056/NEJMoa1107477.

15. Saunders JT, Nambi V, de Lemos JA, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation 2011;123:1367-76.

16. Di Angelantonio E, Chowdhury R, Sarwar N, et al. B-type natriuretic peptides and cardiovascular risk: systematic review and meta-analysis of 40 prospective studies. Circulation 2009;120:2177-87. doi: 10.1161/CIRCULATIONAHA.109.884866. Epub 2009 Nov 16.

17. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551-67. doi: 10.1093/eurheartj/ehs184. Epub 2012 Aug 24.

18. Hamm CW, Heeschen C, Falk E, Fox KA. Acute coronary syndromes: pathophysiology, diagnosis and risk stratification. In: Camm AJ, Lüscher TF, Serruys PW. The ESC textbook of cardiovascular medicine, 2009. p346-348.

19. Ting HH, Bradley EH, Wang Y, et al. Factors associated with longer time from symptom onset to hospital presentation for patients with ST-elevation myocardial infarction. Arch Intern Med 2008;168:959-968.

20. 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;144:1012-101.

21. Foerster JM, Vera Z, Janzen DA, et al. Evaluation of precordial orthogonal vector cardiographic lead ST-segment magnitude in the assessment of myocardial ischemia injury. Circulation 1977;55:728–735

22. Zimetbaum PJ, Josephson ME. Use of the electrocardiogram in acute myocardial infarction. N Engl J Med 2003;348:933-40.

23. Shlipak MG, Lyons WL, Go AS, Chou TM, Evans GT, Browner WS. Should the electrocardiogram be used to guide therapy for patients with left bundle-branch block and suspected myocardial infarction? JAMA 1999;281:714-9.

24. Sgarbossa EB, Pinski SL, Gates KB, Wagner GS. Early electrocardiographic diagnosis of acute myocardial infarction in the presence of ventricular paced rhythm. GUSTO-I investigators. Am J Cardiol 1996;77:423-424.

25. Apple FS. Tissue specificity of cardiac troponin I, cardiac troponin T and creatine kinase-MB. Clinica chimica Acta 1999;284:151-159.

26. Apple FS, Rogers MA, Casal DC, Sherman WM, Ivy JL. Creatine kinase-MB isoenzyme adaptations in stressed human skeletal muscle of marathon runners. J Appl Physiol 1985;59:149-53.

27. Thygesen K, Mair J, Katus H, et al; Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. Recommendations for the use of cardiac troponin measurement in acute cardiac care. Eur Heart J 2010;31:2197–2204.

28. Day H. An intensive coronary care area. Dis Chest 1963;44:423-27.

29. Pantridge JF, Geddes JS. A mobile intensive-care unit in the management of myocardial infarction. Lancet 1967;2:271-3.

30. Braunwald E. Evolution of the management of acute myocardial infarction: a 20th century saga. Lancet 1998;352:1771-4.

31. Maroko PR, Braunwald E. Modification of myocardial infarct size after coronary occlusion. Ann Intern Med 1973;79:720-33.

32. De Wood MA, Spires J, Notske R, et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Eng J Med 1980;303:897-902.

33. Chazov EI, Matveeva LS, Mazaev AV, Sargin KE, Sadovskaia GV, Ruda MI. Intracoronary administration of fibrinolysin in acute myocardial infarct. Ter Arkh 1976;48:8-19.

34. Gruppo Italiano per lo Studio della Streptochinasi nell'infarto miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;1:397-402.

35. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;2:349-60.

36. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-682

37. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. Lancet 1994;343:311-22.

38. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet 1996;348:771-5.

39. Meijer A, Verheugt FW, Werter CJ, Lie KI, van der Pol JM, van Eenige MJ. Aspirin versus coumadin in the prevention of reocclusion and recurrent ischemia after successful thrombolysis: a prospective placebo-controlled angiographic study. Results of the APRICOT Study. Circulation 1993;87:1524-30.

40. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329:1615-1622.

41. Dotter CT, Judkins MP. Transluminal treatment of arteriosclerotic obstruction: description of a new technic and a preliminary report of its application. Circulation 1964;30:654-670.

42. Grüntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med 1979;301:61-8.

43. Meyer J, Merx W, Schmitz H, et al. Percutaneous transluminal coronary angioplasty immediately after intracoronary streptolysis of transmural myocardial infarction. Circulation 1982;66:905-13.

44. O'Neill W, Timmis G, Bourdillon P, et al. A prospective randomized clinical trial of intracoronary streptokinase versus coronary angioplasty for acute myocardial infarction. N Engl J Med 1986;314:812–8.

45. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328:680-4.

46. Keeley EC, Boura JA, Grines CL. Primary angioplasty vs. intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13–20.

47. Weaver WD, Simes RJ, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction> a quantitative review. JAMA 1997;278:2093-2098.

48. Kaul P, Armstrong PW, Sookram S, Leung BK, Brass N, Welsh RC. Temporal trends in patient and treatment delay among men and women presenting with ST-elevation myocardial infarction. Am Heart J 2011;161:91-7. doi: 10.1016/j.ahj.2010.09.016.

49. Jernberg T. SWEDEHEART annual report. Sweden 2011. http://www.ucr.uu.se/swedeheart/index.php/arsrapporter (accessed on August 6th, 2013).

50. Liem SS, van der Hoeven BL, Oemrawsingh PV, et al. MISSION!: optimization of acute and chronic care for patients with acute myocardial infarction. Am Heart J 2007;153:14.e1-11.

51. Terkelsen CJ, Lassen JF, Nørgaard BL, et al. Reduction of treatment delay in patients with ST-elevation myocardial infarction: impact of pre-hospital diagnosis and direct referral to primary percutanous coronary intervention. Eur Heart J 2005;26:770-7. Epub 2005 Jan 31.

52. Fosbol EL, Granger CB, Jollis JG, et al. The impact of a statewide pre-hospital STEMI strategy to bypass hospitals without percutaneous coronary intervention capability on treatment times. Circulation 2013;127:604-12. doi: 10.1161/CIRCULATIONAHA.112.118463. Epub 2012 Dec 30.

53. Bradley EH, Herrin J, Wang Y, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. N Engl J Med 2006;355:2308–2320.

54. Huber K, Goldstein P, Danchin N, et al. Enhancing the efficacy of delivering reperfusion therapy: a European and North American experience with ST-segment elevation myocardial infarction networks. Am Heart J 2013;165:123-32. doi: 10.1016/j.ahj.2012.10.032. Epub 2012 Dec 4.

55. Luepker RV, Raczynski JM, Osganian S, et al. Effect of a community intervention on patient delay and emergency medical service use in acute coronary heart disease: The Rapid Early Action for Coronary Treatment (REACT) Trial. JAMA 2000;284:60–67.

56. Steg PG, James SK, Atar D, et al; Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569-619. doi: 10.1093/eurheartj/ehs215. Epub 2012 Aug 24

57. De Feyter PJ, De Jaegere PP, Serruys PW. Incidence, predictors, and management of acute coronary occlusion after coronary angioplasty. Am Heart J 1994;127:643–51.

58. Serruys PW, Luijten HE, Beatt KJ, et al. Incidence of restenosis after successful coronary angioplasty: a time- related phenomenon: a quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months. Circulation 1988;77:361–371

59. Roubin GS, Cannon AD, Agrawal SK, et al. Intracoronary stenting for acute and threatened closure complicating percutaneous transluminal coronary angioplasty. Circulation 1992;85:916-27.

60. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med 1994;331:489-95.

61. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med 1994;331:496-501.

62. Serruys PW, Strauss BH, Beatt KJ, et al. Angiographic follow-up after placement of a self-expanding coronary-artery stent. N Engl J Med 1991;324:13-7.

63. Nakamura S, Colombo A, Gaglione A, et al. Intracoronary ultrasound observations during stent implantation. Circulation 1994;89:2026 –2034.

64. Schömig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;334:1084-9.

65. Suryapranata H, van't Hof AWJ, Hoorntje JCA, de Boer M-J, Zijlstra F. Randomized comparison of coronary stenting with balloon angioplasty in selected patients with acute myocardial infarction. Circulation 1998;97:2502–2505.

66. Stone GW, Grines CL, Cox DA, et al, for the CADILLAC investigators. Comparison of angio-plasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med 2002;346:957–966.

67. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. N Engl J Med 1999;341:1949–1956.

68. Nordmann AJ, Bucher H, Hengstler P, Harr T, Young J. Primary stenting versus primary balloon angioplasty for treating acute myocardial infarction. Cochrane Database Syst Rev 2005;2:CD005313.

69. Kimura T, Kaburagi S, Tamura T, et al. Remodeling responses of human coronary arteries undergoing coronary angioplasty and atherectomy. Circulation 1997;96:475–483.

70. Farb A, Sangiorgi G, Carter AJ, et al. Pathology of acute and chronic coronary stenting in humans. Circulation 1999;99:44-52.

71. Kornowski R, Hong MK, Tio FO, Bramwell O, Wu H, Leon MB. In-stent restenosis: contributions of inflammatory responses and arterial injury to neointimal hyperplasia. J Am Coll Cardiol 1998;31:224-30.

72. Hoffmann R, Mintz GS, Dussaillant GR, et al. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. Circulation 1996;94:1247-54.

73. Marx SO, Marks AR. Bench to bedside: the development of rapamycin and its application to stent restenosis. Circulation 2001;104:852-5.

74. Garg S, Serruys PW. Coronary stents: current status. J Am Coll Cardiol 2010;56:S1-42. doi: 10.1016/j.jacc.2010.06.007.

75. Axel DI, Kunert W, Göggelmann C, et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. Circulation 1997;96:636-45.

76. Moses JW, Leon MB, Popma JJ, et al; SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315-23.

77. Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. Circulation 2003;107:38-42.

78. Morice MC, Serruys PW, Sousa JE, et al; RAVEL Study Group. Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773-80.

79. Babapulle MN, Joseph L, Bélisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. Lancet 2004;364:583-91.

80. Díaz de la Llera LS, Ballesteros S, Nevado J, et al. Sirolimus-eluting stents compared with standard stents in the treatment of patients with primary angioplasty. Am Heart J 2007;154:164.e1-6.

81. Valgimigli M, Percoco G, Malagutti P, et al; STRATEGY Investigators. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. JAMA 2005;293:2109-17.

82. Van der Hoeven BL, Liem SS, Jukema JW, et al. Sirolimus-eluting stents versus bare-metal stents in patients with ST-segment elevation myocardial infarction: 9-month angiographic and intravascular ultrasound results and 12-month clinical outcome results from the MISSION! Intervention Study. J Am Coll Cardiol 2008;51:618-26. doi:10.1016/j.jacc.2007.09.056.

83. Spaulding C, Henry P, Teiger E, et al; TYPHOON Investigators. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. N Engl J Med 2006;355:1093-104.

84. Menichelli M, Parma A, Pucci E, et al. Randomized trial of Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction (SESAMI). J Am Coll Cardiol 2007;49:1924-30. Epub 2007 Apr 30.

85. Di Lorenzo E, De Luca G, Sauro R, et al. The PASEO (PaclitAxel or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty) Randomized Trial. JACC Cardiovasc Interv 2009;2:515-23. doi: 10.1016/j.jcin.2009.03.012.

86. Valgimigli M, Campo G, Percoco G, et al; Multicentre Evaluation of Single High-Dose Bolus Tirofiban vs Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study (MULTISTRATEGY) Investigators. Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTISTRATEGY randomized trial. JAMA 2008;299:1788-99. doi: 10.1001/jama.299.15.joc80026. Epub 2008 Mar 30.

87. Laarman GJ, Suttorp MJ, Dirksen MT, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. N Engl J Med 2006;355:1105-13.

88. Stone GW, Lansky AJ, Pocock SJ, et al; HORIZONS-AMI Trial Investigators. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. N Engl J Med 2009;360:1946-59. doi: 10.1056/NEJMoa0810116.

89. Di Lorenzo E, Sauro R, Varricchio A, et al.Benefits of drug-eluting stents as compared to bare metal stent in ST-segment elevation myocardial infarction: four year results of the PaclitAxel or Sirolimus-Eluting stent vs bare metal stent in primary angiOplasty (PASEO) randomized trial. Am Heart J 2009;158:e43-50. doi: 10.1016/j.ahj.2009.03.016.

90. Spaulding C, Teiger E, Commeau P, et al. Four-year follow-up of TYPHOON (trial to assess the use of the CYPHer sirolimus-eluting coronary stent in acute myocardial infarction treated with BallOON angioplasty). JACC Cardiovasc Interv 2011;4:14-23. doi: 10.1016/j.jcin.2010.10.007.

91. Stone GW, Witzenbichler B, Guagliumi G, et al; HORIZONS-AMI Trial Investigators. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. Lancet 2011;377:2193-204. doi: 10.1016/S0140-6736(11)60764-2. Epub 2011 Jun 12.

92. De Luca G, Dirksen MT, Spaulding C, et al; Drug-Eluting Stent in Primary Angioplasty (DESERT) Cooperation. Drug-eluting vs bare-metal stents in primary angioplasty: a pooled patient-level meta-analysis of randomized trials. Arch Intern Med 2012;172:611-21.

93. Lagerqvist B, James SK, Stenestrand U, Lindbäck J, Nilsson T, Wallentin L; SCAAR Study Group. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. N Engl J Med 2007;356:1009-19. Epub 2007 Feb 12.

94. Cutlip DE, Windecker S, Mehran R, et al; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.

95. Van Werkum JW, Heestermans AA, Zomer AC, et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. J Am Coll Cardiol 2009;53:1399-409. doi: 10.1016/j.jacc.2008.12.055.

96. Cayla G, Hulot JS, O'Connor SA, et al. Clinical, angiographic, and genetic factors associated with early coronary stent thrombosis. JAMA 2011;306:1765-74. doi: 10.1001/jama.2011.1529.

97. Brodie B, Pokharel Y, Garg A, et al. Predictors of early, late, and very late stent thrombosis after primary percutaneous coronary intervention with bare-metal and drug-eluting stents for ST-segment elevation myocardial infarction. JACC Cardiovasc Interv 2012;5:1043-51. doi: 10.1016/j.jcin.2012.06.013.

98. Hassan AK, Bergheanu SC, Stijnen T, et al. Late stent malapposition risk is higher after drug-eluting stent compared with bare-metal stent implantation and associates with late stent thrombosis. Eur Heart J 2010;31:1172-80.

99. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 2007;115:2435-41. Epub 2007 Apr 16.

100. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193-202. Epub 2006 May 5.

101. Nakazawa G, Finn AV, Joner M, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation 2008;118:1138-45.

102. Van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. Circulation 1996;94:1690-7.

103. Sketch MH Jr, Ball M, Rutherford B, Popma JJ, Russell C, Kereiakes DJ; Driver investigators. Evaluation of the Medtronic (Driver) cobalt-chromium alloy coronary stent system. Am J Cardiol 2005;95:8-12.

104. Kolandaivelu K, Swaminathan R, Gibson WJ, et al. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. Circulation 2011;123:1400-9.

105. Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol 2008;52:333-42. doi: 10.1016/j.jacc.2008.04.030.

106. Meredith IT, Ormiston J, Whitbourn R, Kay IP, Muller D, Cutlip DE. Five-year clinical follow-up after implantation of the Endeavor zotarolimus-eluting stent: ENDEAVOR I, first-in-human study. Catheter Cardiovasc Interv 2009;74:989-95.

107. Fajadet J, Wijns W, Laarman GJ, et al. Long-term follow-up of the randomised controlled trial to evaluate the safety and efficacy of the zotarolimus-eluting driver coronary stent in de novo native coronary artery lesions: five year outcomes in the ENDEAVOR II study. EuroIntervention 2010;6:562-7.

108. Kandzari DE, Mauri L, Popma JJ, et al. Late-term clinical outcomes with zotarolimus- and sirolimus-eluting stents. 5-year follow-up of the ENDEAVOR III (A Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions). JACC Cardiovasc Interv 2011;4:543-50.

109. Leon MB, Nikolsky E, Cutlip DE, et al. Improved late clinical safety with zotarolimus-eluting stents compared with paclitaxel-eluting stents in patients with de novo coronary lesions: 3-year follow-up from the ENDEAVOR IV (Randomized Comparison of Zotarolimus- and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease) trial. JACC Cardiovasc Interv 2010;3:1043-50.

110. Wiemer M, Serruys PW, Miquel-Hebert K, et al. Five-Year Long-Term Clinical Follow-Up of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Coronary Artery Lesions: The SPIRIT FIRST Trial. Catheter Cardiovasc Interv 2010;75:997-1003.

111. Garg S, Serruys PW, Miquel-Hebert K. Four-year clinical follow-up of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with de novo coronary artery lesions: the SPIRIT II trial. Catheter Cardiovasc Interv 2011;77:1012-7.

112. Applegate RJ, Yaqub M, Hermiller JB, et al. Long-term (three-year) safety and efficacy of everolimus-eluting stents compared to paclitaxel-eluting stents (from the SPIRIT III Trial). Am J Cardiol 2011;107:833-40.

113. Stone GW, Rizvi A, Sudhir K, et al. Randomized comparison of everolimus- and paclitaxel-eluting stents. 2-year follow-up from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) IV trial. J Am Coll Cardiol 2011;58:19-25.

114. Smits PC, Kedhi E, Royaards KJ, et al. 2-year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice. COMPARE (Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTÉ stent in all-comers: a randomized open label trial). J Am Coll Cardiol 2011;58:11-8.

115. Park KW, Kang SH, Velders MA, et al. Safety and efficacy of everolimus- versus sirolimus-eluting stents: a systematic review and meta-analysis of 11 randomized trials. Am Heart J 2013;165:241-50.e4. doi: 10.1016/j.ahj.2012.08.007. Epub 2012 Dec 27.

116. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;379:1393-402. doi: 10.1016/S0140-6736(12)60324-9. Epub 2012 Mar 23.

117. Sabate M, Cequier A, Iñiguez A, et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. Lancet 2012;380:1482-90. doi: 10.1016/S0140-6736(12)61223-9. Epub 2012 Sep 3.

118. Hamm CW, Bassand JP, Agewall S, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011;32:2999-3054. doi: 10.1093/eurheartj/ehr236.

119. 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 Jan 12;324(7329):71-86.

120. Chen ZM, Jiang LX, Chen YP, et al.; COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1607-21.

121. Wiviott SD, Braunwald E, McCabe CH, et al.; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15. Epub 2007 Nov 4.

122. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57. doi: 10.1056/NEJMoa0904327.

123. Montalescot G, Wiviott SD, Braunwald E, et al.; TRITON-TIMI 38 investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009;373:723-31. doi: 10.1016/S0140-6736(09)60441-4.

124. Steg PG, James S, Harrington RA, et al.; PLATO Study Group. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation 2010;122:2131-41. doi: 10.1161/CIRCULATIONAHA.109.927582. Epub 2010 Nov 8.

125. De Luca G, Suryapranata H, Stone GW, et al. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. JAMA 2005;293:1759-65.

126. De Luca G, Bellandi F, Huber K, et al. Early glycoprotein IIb-IIIa inhibitors in primary angioplasty-abciximab long-term results (EGYPT-ALT) cooperation: individual patient's data meta-analysis. J Thromb Haemost 2011;9:2361-70. doi: 10.1111/j.1538-7836.2011.04513.x.

127. Stone GW, Witzenbichler B, Guagliumi et al.; HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218-30. doi: 10.1056/NEJMoa0708191.

128. Montalescot G, Zeymer U, Silvain J, et al.; ATOLL Investigators. Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial. Lancet 2011;378:693-703. doi: 10.1016/S0140-6736(11)60876-3.

129. Granger CB, Goldberg RJ, Dabbous O, et al.; Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 2003;163:2345-53.

130. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation 2000;102:2031-7.

131. Halkin A, Singh M, Nikolsky E, et al. Prediction of mortality after primary percutaneous coronary intervention for acute myocardial infarction: the CADILLAC risk score. J Am Coll Cardiol 2005;45:1397-405.

132. De Luca G, Suryapranata H, van 't Hof AW, et al. Prognostic assessment of patients with acute myocardial infarction treated with primary angioplasty: implications for early discharge. Circulation 2004;109:2737-43. Epub 2004 May 24.

133. Wiviott SD, Braunwald E, Angiolillo DJ, et al.; TRITON-TIMI 38 Investigators. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. Circulation 2008;118:1626-36. doi: 10.1161/CIRCULATIONAHA.108.791061. Epub 2008 Aug 31.