Optimization of care for ST-elevation myocardial infarction

Matthijs A. Velders

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The research described in this thesis was performed at the departments of cardiology of the Leiden University Medical Center and the Medical Center Leeuwarden, the Netherlands, and the Uppsala Clinical Research Center, Sweden.

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"If you wish to make an apple pie from scratch, you must first invent the universe."

Carl Sagan

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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]

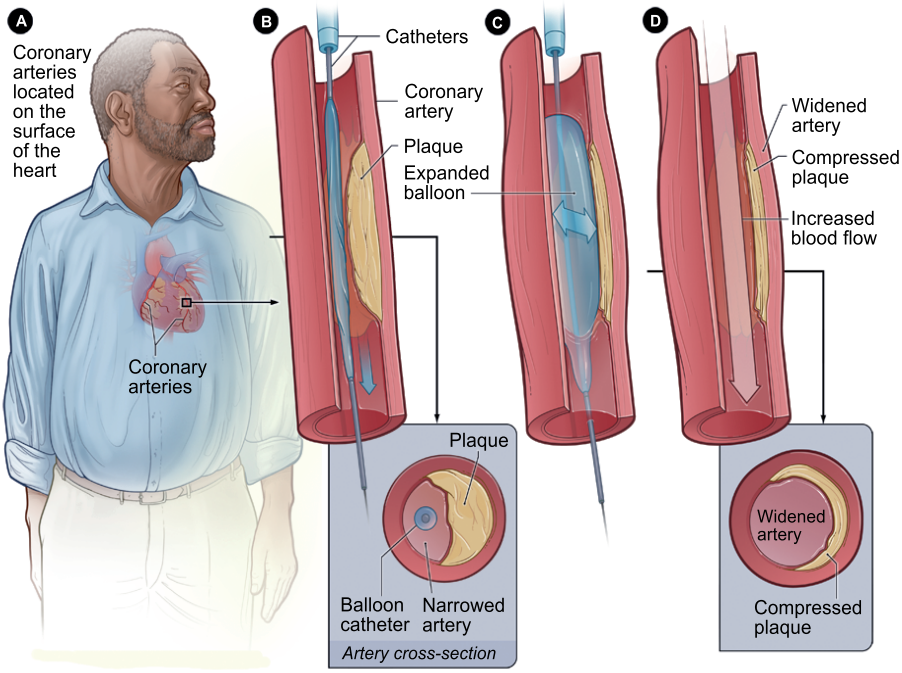

Figure 1. Coronary angioplasty. A catheter with mounted balloon is introduced into the coronary artery and passed through the coronary stenotic segment. Pressure inflation of the balloon subsequently expands the stenotic lesion, restoring the patency of the coronary vessel. Source: National Heart, Lung, 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]

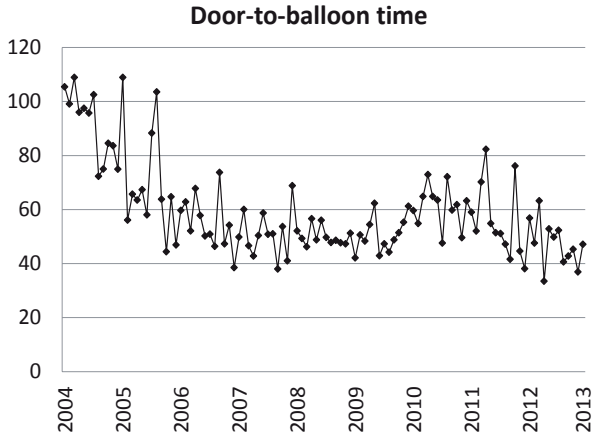

Figure 2. Influence of MISSION! implementation on door-to-balloon times. The MISSION! protocol, implemented in the Leiden University Medical Center between 2004 and 2005, is an all-phases integrated STEMI care program aimed at maximizing the use of evidence based medicine to improve the care of STEMI 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.

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PART 1

High-risk sub-populations

CHAPTER 2

Influence of gender on ischemic times and outcomes after ST-elevation myocardial infarction

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Abstract

Previous studies investigating the influence of gender on ST-elevation myocardial infarction (STEMI) have reported conflicting results. The aim of this study was to assess the influence of gender on ischemic times and outcomes after ST-elevation myocardial infarction in patients treated with primary percutaneous coronary intervention (PCI) in modern day practice. The present multicenter registry included consecutive patients with ST-elevation myocardial infarction treated with primary PCI at 3 hospitals. Adjusted mortality rates were calculated using Cox proportional-hazards analyses. In total, 3483 patients were included, of whom 868 women (25%). Women were older, had a higher risk factor burden and more frequently had histories of malignancy. Men more often had cardiac histories and peripheral vascular disease. Ischemic times were longer in women (median 192 min (IQR 141-286) vs. 175 min (128-279) in men, p=0.002). However, multivariable linear regression showed that this was due to age and co-morbidity. All-cause mortality was higher at 7 days (6.0% in women vs. 3.0% in men, p<0.001) and 1 year (9.9% in women vs. 6.6% in men, p=0.001). After adjustment, female gender predicted both 7 day all-cause mortality (HR 1.61, 95% CI 1.06-2.46) and cardiac mortality (HR 1.58, 95% CI 1.03-2.42) but not 1-year mortality. Moreover, gender was an independent effect modifier for cardiogenic shock, leading to substantially worse outcome in women. In conclusion, ischemic times remain longer in women because of age and comorbidity. Female gender independently predicted early all-cause and cardiac mortality after primary PCI and a strong interaction between gender and cardiogenic shock was observed.

Introduction

Coronary artery disease (CAD) is the leading cause of death in Western men and women.[1] In 2003, the total cost of CAD in the European Union was an estimated 45 billion euro, with approximately 1 million working years lost due to CAD mortality.[2] To reduce the huge burden of CAD, research aimed at the optimal recognition and treatment of CAD in men and women is essential. Nonetheless, women are underrepresented in clinical trials of CAD.[3] It is known that risk factors for CAD bear different weight among men and women and that women with anginal complaints more frequently show non-obstructive CAD on coronary angiography compared to men.[4-7] Moreover, women have consistently shown higher mortality rates after acute coronary syndromes (ACS), due to higher age and more co-morbidities.[8,9] However, in the specific ST-elevation myocardial infarction (STEMI) population conflicting results have been reported.[8-14] Furthermore, previous studies lacked guideline recommended treatment with primary percutaneous coronary intervention (PCI) or excluded high risk patients commonly encountered in daily practice. Our goal was to investigate the influence of gender on ischemic times and outcomes after STEMI treated with primary PCI in modern day practice.

Methods

The present Dutch multicenter registry prospectively included consecutive patients treated with primary percutaneous coronary intervention (PCI) for STEMI in 3 tertiary centers in the Netherlands. Two high-volume centers in the north of the Netherlands, the Medical Center Alkmaar and the Medical Center Leeuwarden, provide 24/7 cardiac care for an area of 450.000 and 650.000 inhabitants respectively. The Leiden University Medical Center serves an area of approximately 750.000 inhabitants.

Consecutive patients who underwent primary PCI for STEMI between January 2006 and December 2009 were included in the analysis. Interventions included passing of guidewire through a thrombus, thrombosuction and/or percutaneous coronary balloon angioplasty with or without placement of coronary stents. In case of out-of-hospital cardiac arrest, only patients with return of spontaneous circulation on moment of arrival at the catheterization laboratory were included. Furthermore, patients permanently living outside the Netherlands were excluded to make follow-up through municipality records possible. STEMI was defined as symptoms of angina lasting >30 minutes along with typical electrocardiographical changes (ST-segment elevation ≥0.2 mV in ≥2 contiguous leads in V1 through V3 or ≥0.1 mV in other leads or presumed new left bundle branch block). Pre-hospital protocols included triage by 12-lead electrocardiogram in the field faxed to the operator on call and in-ambulance treatment with aspirin, intravenous heparin bolus and a loading dose of clopidogrel. Glycoprotein IIb/IIIa inhibitors were administered frequently, using up-front administration in the Leiden University Medical Center and

periprocedural administration in the other hospitals. On arrival at the hospital, patients were transferred as soon as possible to the catheterization laboratory. Procedures were performed according to current clinical guidelines.

Patients treated in the Leiden University Medical Center were treated according to the institutional MISSION! protocol, a standardized prehospital, in-hospital and outpatient clinical framework for decision making and treatment.[15] After hospital discharge, these patients were intensively monitored and managed at the outpatient clinic for 1 year, after which they were referred back to the general practitioner or referred to regular, generally regional, cardiological outpatient clinics. At the other centers, local residents were managed in the outpatient clinics and patients referred from regional hospitals were referred back for further management after primary PCI by regional cardiologists.

Hospitals prospectively included patients treated with primary PCI, registering baseline and procedural data. Definitions of variables were synchronized among centers. Cardiogenic shock was defined as systolic blood pressure <90 mmHg with signs of tissue hypoperfusion requiring treatment in form of resuscitation, inotropic agents or assistant devices. Symptom-to-balloon time was defined as the time between the onset of symptoms and balloon inflation. Diagnosis-to-balloon time was defined as the time between the first diagnostic ECG, mostly the ambulance triage ECG, and balloon inflation. Door-to-balloon time was the time between patient arrival at the tertiary hospital and balloon inflation. Close cooperation with regional emergency medical system providers supplied prehospital times. Vital status was obtained using municipality records.

The 3 databases were pooled into a patient-level database, and stratification was done according to gender. Continuous variables are presented as mean with standard deviation or as medians with interquartile range and were compared using Student's t-test for means and nonparametric tests for medians. Categorical variables are expressed as counts and percentages and were compared by means of Pearson's χ^2 test. All statistical tests were 2-tailed and p-values <0.05 were considered statistically significant. Time to endpoint was analyzed using Kaplan-Meier plots and the log-rank test was applied to compare cumulative incidences of the endpoint between groups. Linear regression models were used to analyze variables predictive of log-transformed treatment delay. Univariable predictors of delay were added into multivariable linear regression models using a cut-off p-value of 0.10. To evaluate the effect of gender as an independent predictor of mortality, multivariable cox proportional hazards models were performed using a forward stepwise method. A cut-off p-value of <0.10 was applied to enter significant univariable predictors of outcome into the multivariable models. Gender was forced to stay in the multivariable models to allow calculation of adjusted hazard ratios for all outcomes.

Results

During the inclusion period, 3483 consecutive STEMI patients were treated with primary PCI, of whom 868 were women (24.9%) and 2615 were men (75.1%). Baseline characteristics (Table 1) showed that women were on average older and had a higher risk factor burden with a higher prevalence of insulin-dependent diabetes mellitus and hypertension. Furthermore, women more often had histories of malignancy. In contrast, men had had previous myocardial infarctions more frequently and a larger proportion of men had undergone PCI or bypass surgery. Additionally, peripheral vascular disease was more common in men, and their median peak creatine kinase level was higher compared to women.

Table 1. Baseline characteristics

Variable	**Men** (N=2615)	**Women** (N=868)	p-Value
Age (yrs)	61.8 ± 11.9	67.6 ± 13.1	<0.001
Body mass index (kg/m^2)	26.6 ± 3.7	26.3 ± 4.8	0.110
Risk factors			
Diabetes mellitus, non-insulin dependent	214 (8.3%)	80 (9.3%)	0.346
Diabetes mellitus, insulin dependent	50 (1.9%)	42 (4.9%)	<0.001
Hypertension*	841 (32.5%)	394 (45.9%)	<0.001
Hypercholesterolemia†	608 (23.6%)	187 (21.8%)	0.282
Family history of cardiovascular disease‡	994 (40.2%)	335 (41.2%)	0.646
Current smoker	1222 (47.8%)	344 (40.6%)	0.001
Number of risk factors	1.52 ± 1.05	1.60 ± 1.10	0.036
Previous myocardial infarction	314 (12.1%)	61 (7.1%)	<0.001
Previous PCI	238 (9.2%)	52 (6.0%)	0.004
Previous coronary artery bypass grafting	76 (2.9%)	9 (1.0%)	0.002
Previous peripheral vascular disease	136 (5.3%)	28 (3.3%)	0.016
Previous cerebrovascular disease	157 (6.1%)	59 (6.9%)	0.418
Previous malignancy	142 (5.5%)	68 (8.0%)	0.011
Previous renal insufficiency§	86 (3.3%)	41 (4.8%)	0.053
Anemia on admission, moderate to severe‖	41 (1.6%)	14 (1.6%)	0.911
Out-of-hospital cardiac arrest	176 (6.7%)	48 (5.5%)	0.212
Cardiogenic shock	162 (6.2%)	65 (7.5%)	0.181
Intra-aortic balloon pump placement	144 (4.4%)	35 (4.0%)	0.680
Creatine phosphokinase peak (U/l)	1420 (649-2715)	1170 (566-2335)	<0.001
Symptom-to-balloon time (minutes)	175 (128-279)	192 (141-286)	0.002
Diagnosis-to-balloon time (minutes)	78 (64-99)	81 (66-101)	0.037
Door-to-balloon time (minutes)	46 (33-67)	46 (33-68)	0.405

* Blood pressure ≥140/90 mmHg or previous pharmacological treatment; † Total cholesterol ≥190 mg/dl or previous pharmacological treatment; ‡ First degree family member suffering cardiovascular disease before the age of 60 years; § eGFR<60 ml/min/1.73m^2; ‖Admission hemoglobin <9.7 g/dl for women and <10.5 g/dl for men.

Time between onset of symptoms and balloon inflation (ischemic time) was significantly longer in women (Table 1). In addition, time between first diagnosis of STEMI and balloon inflation was marginally longer. Multivariable linear regression analysis of log transformed ischemic time revealed that age per 10 year increase (beta 0.03, 95% CI 0.01-0.05, p=0.001), history of diabetes mellitus (beta 0.10, 95% CI 0.03-0.18, p=0.006) and history of renal insufficiency (beta 0.15, 95% CI 0.02-0.27, p=0.020) were independent predictors of longer ischemic time, whereas gender was not (beta 0.03, 95% CI -0.03-0.08, p=0.295).

Table 2. Procedural characteristics

Variable	**Men** (N=2615)	**Women** (N=868)	p-Value
Coronary culprit vessel			0.049
Left anterior descending	1026 (39.3%)	381 (43.9%)	0.016
Left circumflex	435 (16.6%)	118 (13.6%)	0.033
Right	1082 (41.4%)	352 (40.6%)	0.657
Left main	36 (1.4%)	11 (1.3%)	0.807
Bypass graft	34 (1.3%)	6 (0.7%)	0.144
Number of vessels narrowed >50%			0.152
1	1204 (46.1%)	433 (49.9%)	
2	837 (32.0%)	257 (29.6%)	
3	571 (21.9%)	178 (20.5%)	
Stenting	2503 (95.8%)	828 (95.4%)	0.616
Drug-eluting stents	1806 (72.6%)	603 (73.6%)	0.584
Bare-metal stents	688 (27.7%)	221 (27.0%)	0.701
Abciximab treatment	1964 (75.9%)	596 (69.2%)	<0.001
Preprocedural TIMI flow grade*			0.078
0	1809 (69.3%)	566/ (65.2%)	
1	274 (10.5%)	112 (12.9%)	
2	298 (11.4%)	100 (11.5%)	
3	229 (8.8%)	90 (10.4%)	
Postprocedural TIMI flow grade ≥2	2558 (98.0%)	846 (97.6%)	0.488
Admission duration (days)	3.7 ± 6.2	4.0 ± 6.9	0.415
Discharge medication			
Aspirine / warfarin derivative	2438 (96.7%)	782 (96.0%)	0.305
Clopidogrel	2472 (98.1%)	798 (97.9%)	0.745
Beta-blocker	2277 (90.7%)	714 (88.0%)	0.029
Ace-inhibitor / Angiotensin II antagonist	1791 (71.4%)	578 (71.3%)	0.938
Statin	2345 (93.4%)	743 (91.6%)	0.093

* TIMI = Thrombolysis in myocardial infarction.

Procedurally, a higher percentage of women presented with left anterior descending artery as the culprit vessel, balanced by a lower percentage with the circumflex artery as the culprit vessel (Table 2). Abciximab treatment was more common in men and TIMI flow before and after procedure was similar between men and women. Beta-blocking agents were more frequently prescribed in men; other medications were balanced between the genders.

One-year survival status was known in 3479 patients. Both all-cause and cardiac mortality were more common in women compared to men during the entire follow-up period (Table 3). Landmark analysis, with a cut-off point at 7 days (Figure 1), showed that this was due to higher early mortality, with similar prognoses for men and women after this period.

Table 3. All-cause and cardiac mortality

Variable	**Men** (N=2615)	**Women** (N=868)	p-Value
All-cause mortality			
Seven days	78 (3.0%)	52 (6.0%)	<0.001
Unadjusted HR (95% CI)	0.49 (0.35-0.70)	2.04 (1.43-2.89)	<0.001
Adjusted HR (95% CI)	0.62 (0.41-0.95)	1.61 (1.06-2.46)	0.027
One year	173 (6.6%)	86 (9.9%)	0.001
Unadjusted HR (95% CI)	0.65 (0.50-0.84)	1.54 (1.19-1.99)	0.001
Adjusted HR (95% CI)	0.98 (0.73-1.32)	1.02 (0.76-1.37)	0.900
Cardiac mortality			
Seven days	77 (2.9%)	50 (5.8%)	<0.001
Unadjusted HR (95% CI)	0.50 (0.35-0.72)	1.98 (1.39-2.83)	<0.001
Adjusted HR (95% CI)	0.63 (0.41-0.97)	1.58 (1.03-2.42)	0.037
One year	132 (5.1%)	75 (8.7%)	<0.001
Unadjusted HR (95% CI)	0.57 (0.43-0.76)	1.75 (1.32-2.32)	<0.001
Adjusted HR (95% CI)	0.79 (0.57-1.10)	1.26 (0.91-1.75)	0.168

HR were calculated using Cox proportional-hazards models. CI = confidence interval.

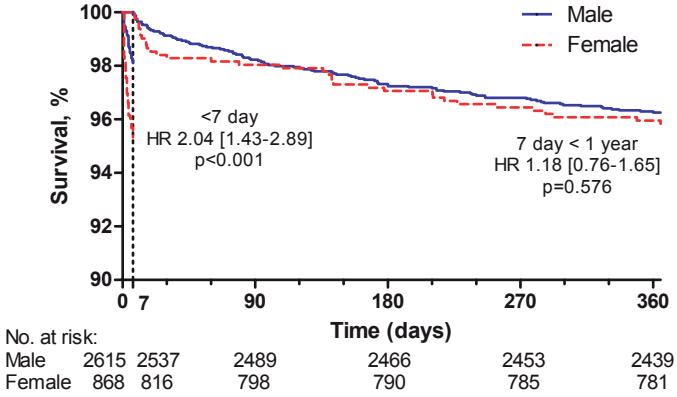

Figure 1. Landmark analysis of 1-year survival with 7-day cut-off.

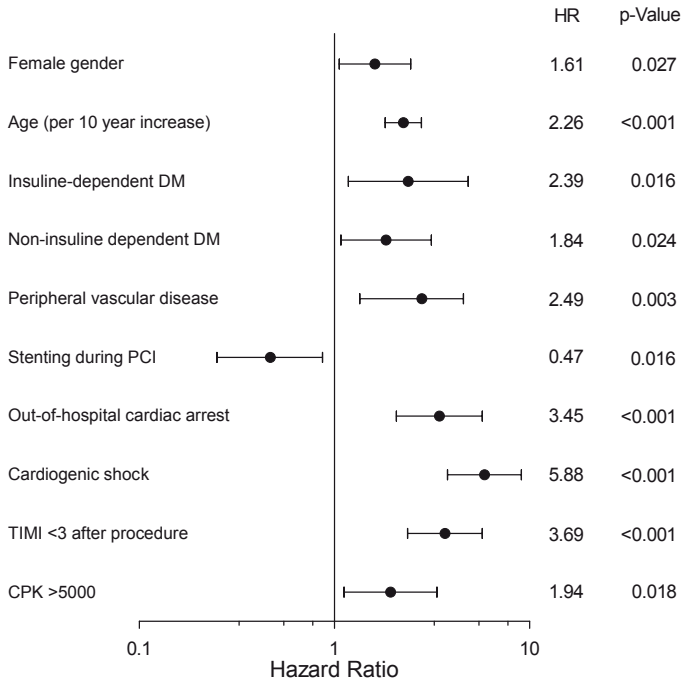

Figure 2. Independent multivariable predictors of 7-day all-cause mortality. (CPK = creatine phosphokinase; DM = diabetes mellitus; TIMI = thrombolysis in myocardial infarction.).

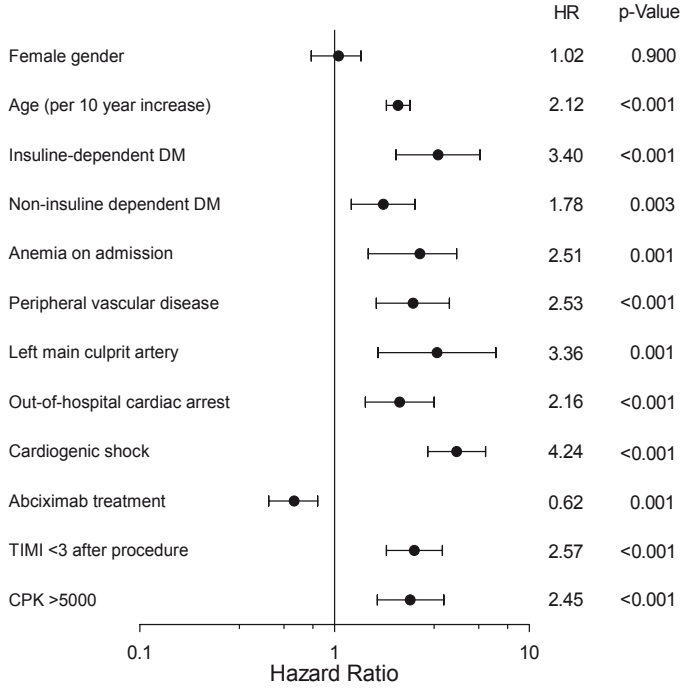

Figure 3. Independent multivariable predictors of 1-year all-cause mortality. (LAD = left anterior descending artery; LM = left main artery; MI = myocardial infarction; RCA = right coronary artery; RCX = ramus circumflex.).

Multivariable Cox modeling showed that female gender predicted 7-day all-cause mortality (Figure 2) and 7-day cardiac mortality (Table 3). The association between ischemic time and 7 day mortality was investigated separately, resulting in a HR of 1.01 (95% CI 1.00-1.01) for every 10 minute increase in ischemic time. After 1 year, gender no longer influenced all-cause (Figure 3) and cardiac mortality (Table 3). The interaction of gender with predictors of all-cause mortality was investigated through multivariable modeling. After correction for confounders, female gender modified the effect of cardiogenic shock on 1-year mortality with an HR of 1.94 (95% CI 1.04-3.62, p=0.038). For men with cardiogenic shock, an HR of 0.52 (95% CI 0.28-0.96) or an approximately 50% lower hazard of dying from the developed cardiogenic shock was observed during 1 year compared to women. Gender did not influence other predictors of all-cause mortality.

Discussion

The key findings of the present multicenter registry comparing men and women treated with primary PCI for STEMI are as follows: 1. Female gender independently predicted early all-cause and cardiac mortality. After this early period, prognoses were identical between men and women up to 1 year; 2. Ischemic times continue to be longer in women, explained by a higher prevalence of comorbidity and older age; 3. Women with cardiogenic shock had substantially worse outcomes compared to men.

The influence of gender on CAD has long been a topic of debate.[16] Traditional risk factors for CAD bear different weight between men and women and female-specific risk factors influence the development of CAD.[4-6] Although women are more likely to present with atypical symptoms of ischemia, lower rates of obstructive CAD are observed.[7,17,18] In contrast, women show longer delay to treatment in setting of STEMI, underlining the difficulties that exist regarding appropriate referral for coronary angiography.[19] Moreover, women consistently show higher short term mortality after ACS.[8,9] Although confounding factors were found responsible for this, focus on the STEMI population has produced conflicting results. In the present analysis, women were older than men and had a higher prevalence of risk factors, mirroring previous observations.[20] After adjustment, female gender predicted short term mortality. The difference in outcome was due to particularly high mortality in the first days of admission. Similarly, Jneid et al.[10] found that higher early mortality in women was due to the first day after infarction. Two other studies observed that female gender predicted short-term but not long-term mortality.[11,12] Contradicting this, Berger et al. reported that female gender predicted 30-day mortality but observed that this effect disappeared when only patients who underwent angiography were selected.[8] Also, a recent study found no effect of gender on survival, although a strong trend for higher mortality in women was observed.[13] Moreover, a registry resembling our population found no effect of gender on early mortality.[14] Closer examination of these studies reveals that a substantial portion of patients

did not undergo reperfusion therapy,[10,11] or that patients received thrombolysis only.[8] Furthermore, high risk patients who would normally be encountered in daily practice were excluded because of longer ischemic times or transfer from referring hospitals.[13,14] In contrast, the current analysis included patients from 3 centers incorporating modern systems of care with short time to treatment delays, full use of primary PCI and no exclusion based on delay or angiographic factors; following guideline recommended treatment and reflecting a population faced in daily practice.

Explanations for the higher early mortality in women remain speculative. It has been suggested that less aggressive treatment is applied in women.[18] In the present study, women were treated less often with abciximab but this did not explain the mortality difference. Women have also been shown to suffer more bleeding complications during admission, events that are associated with mortality.[13,21,22] However, female gender also predicted cardiac mortality in the current analysis, excluding bleeding as a cause. Besides this, longer ischemic times negatively influence prognosis of STEMI.[23,24] In our population, ischemic times were longer in women because of older age and greater prevalence of diabetes mellitus and renal insufficiency. These factors have been previously linked to painless myocardial infarction, most likely explaining the longer delays in the current analysis.[25] The observation that gender by itself did not predict but age and comorbidity did predict longer delay suggests that focus should be on recognition of STEMI in these subgroups in men and women. Because the association of ischemic time and mortality was small in this study, the delay failed to explain the mortality gap. Because the difference in outcome lay in the early days of hospital admission, the previous observation that more men die before reaching the hospital might explain the difference between men and women because of a sicker female population being admitted to the hospital.[26] Therefore, prehospital mortality rates should be incorporated in future investigations.

The predictors of mortality established in the present study reflect those found in previous investigations.[27-30] Strikingly, female gender was found to modify the effect of cardiogenic shock on mortality, causing higher mortality due to cardiogenic shock in women compared to men. It has been noted that women developing cardiogenic shock have higher rates of ventricular septal rupture and severe mitral regurgitation, possibly explaining the difference in outcome between men and women.[31] Supporting this, Engström et al found that severe mitral regurgitation was more common in women with STEMIs and identified it as a predictor of mortality.[32] However, the clinical implications of these findings are unclear, and additional research is required to uncover the optimal treatment for these patients. The present analysis had several limitations. The study was observational and thus shares the limitations of all observational analyses. Additionally, because left ventricular ejection fractions were not available for all patients, peak creatine phosphokinase during admission was used as a surrogate for infarction size, which may have underestimated actual infarction size. There may have been other measured or unmea-

sured confounding variables that, had they been adjusted for, might have modified the relation between gender and outcome. Finally, because our cohort only included patients treated with primary PCI, it cannot be ruled out that a disproportionate number of men and women died before arrival at the hospitals.

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CHAPTER 3

Association between angiographic culprit lesion and out-of-hospital cardiac arrest in ST-elevation myocardial infarction patients

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Abstract

Background: Factors related to the occurrence of out-of-hospital cardiac arrest (OHCA) in ST-elevation myocardial infarction (STEMI) are still poorly understood. The current study sought to compare STEMI patients presenting with and without OHCA to identify angiographic factors related to OHCA.

Methods: This multicenter registry consisted of consecutive STEMI patients, including OHCA patients with return-of-spontaneous circulation. Patients were treated with primary percutaneous coronary intervention (PCI) and therapeutic hypothermia when indicated. Outcome consisted of in-hospital neurological recovery, scored using the Cerebral Performance Categories (CPC) scale, and 1-year survival. Logistic regression was used to identify factors associated with OHCA and survival was displayed with Kaplan Meier curves and compared using log rank tests.

Results: In total, 224 patients presented with OHCA and 3259 without OHCA. Average age was 63.3 years and 75% of patients were male. OHCA occurred prior to ambulance arrival in 68% of patients and 48% required intubation. Culprit lesion was associated with OHCA: risk was highest for proximal left coronary lesions and lowest for right coronary lesions. Also, culprit lesion determined the risk of cardiogenic shock and sub-optimal reperfusion after PCI, which were strongly related to survival after OHCA. Neurological recovery was acceptable (CPC≤2) in 77.1% of OHCA patients and did not differ between culprit lesions.

Conclusions: In the present STEMI population, coronary culprit lesion was associated with the occurrence of OHCA. Moreover, culprit lesion influenced the risk of cardiogenic shock and success of reperfusion, both of which were related to prognosis of OHCA patients.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a common and life threatening condition frequently caused by coronary artery disease.[1] Historically, prognosis of OHCA has been poor.[2] Revascularization techniques in OHCA have been under investigation for some time in an attempt to improve the prognosis of these patients. While thrombolysis during resuscitation failed to proof beneficial, coronary angiography with angioplasty showed promising results.[3,4] Early or primary percutaneous coronary intervention (PPCI) has been shown to improve survival after OHCA due to ST-elevation myocardial infarction (STEMI) and at present, PPCI is readily available in the Netherlands for STEMI patients suffering an OHCA due to extensive nationwide networks of care designed to minimize ischemic times.[5-7]

Although PPCI for OHCA due to STEMI is commonly performed, factors associated with the occurrence of OHCA in setting of STEMI are still poorly understood. The current study sought to compare STEMI patients presenting with and without OHCA to identify angiographic factors related to the occurrence and prognosis of OHCA treated with PPCI and therapeutic hypothermia (TH).

Methods

Design and patients

The current Dutch registry prospectively included STEMI patients treated in 3 high-volume tertiary centers in the Netherlands. The design of this registry has been described previously.[8] In short, all consecutive STEMI patients undergoing PPCI between January 2006 and December 2009 were included. STEMI was defined as symptoms of angina lasting longer than 30 minutes along with typical electrocardiographical changes (ST-segment elevation ≥0.2 mV in ≥2 contiguous leads in V1 through V3 or ≥0.1 mV in other leads or presumed new left bundle branch block) or presumed new regional wall motion abnormalities on echocardiogram when these criteria were unavailable or inconclusive. In case of OHCA, only patients with return-of-spontaneous-circulation (ROSC) on arrival at the catheterization laboratory were included. Patients permanently living outside the Netherlands were excluded to make follow-up through municipality records possible.

Emergency medical services (EMS) were staffed with nurses trained in advanced cardiac life support. Patients were triaged in the field by 12-lead electrocardiogram faxed to the operator on call. In-ambulance medication included aspirin, intravenous heparin bolus and loading dose of clopidogrel. Glycoprotein IIb/IIIa inhibitors were administered up-front in the Leiden University Medical Center and periprocedurally in the other hospitals. Upon arrival at the hospital, unresponsive patients were admitted to the emergency department and following stabilization transferred directly to the catheterization laboratory. Stable patients were transferred directly

to the catheterization laboratory. Procedures were performed according to current clinical guidelines. Patients remaining unresponsive (Glasgow Coma Scale <8) after resuscitation were transferred to the intensive care unit, where TH (32-34°C) was induced for 24 hours using ice packs, cooling blankets and intravenous NaCl 0.9% of 4°C, if necessary. After this period, TH was ceased and as body temperature returned to normal values sedation was weaned. Patients remaining unresponsive (Glasgow Coma Scale motor response <5) 24 hours after reaching normothermia and weaning of sedation underwent sensory evoked potentials testing. Severe and permanent neurologic dysfunction was diagnosed if the N20 response was bilaterally absent. Patients with a positive N20 response remaining comatose after 72 hours underwent neurological clinical examination and electro-encephalography after which further treatment strategy was decided.

Patients treated in the Leiden University Medical Center were treated according to the institutional MISSION! protocol, a standardized pre-hospital, in-hospital and outpatient clinical framework for STEMI care.[9] These patients were intensively monitored at the outpatient clinic for 1 year, after which they were referred to the general practitioner or regional cardiology clinic. In the other centers, local residents were managed at the outpatient clinics and patients referred from regional hospitals were referred back for further management by regional cardiologists.

Data collection

All hospitals prospectively registered patients. Close collaboration with regional EMS supplied pre-hospital times and resuscitation characteristics. Vital status was obtained using municipality records. In-hospital outcome was a composite of all-cause mortality and neurological outcome. Neurological outcome was scored retrospectively using the Cerebral Performance Categories (CPC) scale consisting of 5 categories: 1. Conscious, good cerebral performance, able to work; 2. Conscious, moderate cerebral disability, able to work in a sheltered environment; 3. Conscious, severe cerebral disability, dependent on others; 4. Coma or vegetative state; 5. Brain death.[10] Long term outcome consisted of 1-year all-cause mortality. Deaths were considered cardiac unless a clear non-cardiac cause could be identified.

Statistical analyses

Continuous variables are presented as mean ± standard deviation or median (25th to 75th percentile) and were compared using Student's t-test in case of mean and Mann-Whitney U test in case of median. Categorical variables are expressed as counts and percentages and were compared by means of Pearson's χ^2 test. All statistical tests were 2-tailed and a p-value <0.05 was considered statistically significant. Univariable logistic regression was performed to investigate the association of angiographic factors with OHCA and other prognostic factors. Cumulative incidences of endpoints were displayed visually using Kaplan-Meier plots and compared with log rank tests. Analyses were performed using IBM SPSS Statistics version 20.

Results

Of the 3483 consecutive STEMI patients treated during the inclusion period, 224 (6.4%) presented with OHCA and 3259 (93.6%) without cardiac arrest. Baseline characteristics (Table 1) showed that symptom-to-balloon time was shorter in patients presenting with OHCA. In contrast, door-to-balloon time was longer in OHCA patients compared to non-arrest patients. During angiography, patients presenting with OHCA more frequently showed left coronary artery culprit lesions compared to patients without arrest. Also, OHCA patients were more often in cardiogenic shock and were treated more commonly with intra-aortic balloon pumps. Thrombolysis-in-myocardial infarction flow pre- and post-procedure was comparable between the groups.

Table 1. Baseline and procedural characteristics

	OHCA (N=224)	**No OHCA** (N=3259)	p-Value
Age, years, mean ± standard deviation	62.5 ± 12.1	63.3 ± 12.5	0.365
Male sex	78.6 (176/224)	74.8 (2439/3259)	0.212
Diabetes mellitus	9.1 (20/219)	11.3 (366/3230)	0.318
Previous myocardial infarction	10.9 (24/221)	10.8 (351/3241)	0.989
Previous percutaneous coronary intervention	6.8 (15/221)	8.5 (275/3241)	0.378
Previous coronary artery bypass grafting	3.2 (7/221)	2.4 (78/3246)	0.477
Symptoms-to-balloon time, median minutes	150 (116-192)	181 (131-285)	<0.001
Door-to-balloon time, median minutes	53 (36-79)	46 (33-66)	0.014
Culprit artery			<0.001
Left main	3.1 (7/224)	1.2 (40/3257)	0.017
Left anterior descending	55.8 (125/224)	39.4 (1282/3257)	<0.001
Left circumflex	21.9 (49/224)	15.5 (504/3257)	0.011
Right coronary artery	18.3 (41/224)	42.8 (1393/3257)	<0.001
Bypass graft	0.9 (2/224)	1.2 (38/3257)	0.710
Multivessel disease	50.9 (114/224)	53.1 (1729/3256)	0.522
Stenting	96.9 (217/224)	95.6 (3114/3257)	0.367
Cardiogenic shock during PCI	30.8 (69/224)	4.8 (158/3259)	<0.001
Intra-aortic balloon pump implantation	25.4 (57/224)	2.8 (92/3259)	<0.001
TIMI flow ≤1 pre-procedure	79.9 (179/224)	79.3 (2582/3254)	0.841
TIMI flow 3 post-procedure	91.1 (204/224)	91.5 (2976/3254)	0.842

Values are percentage (n) or median (25^{th} to 75^{th} percentile). TIMI = Thrombolysis in myocardial infarction. *defined as systolic blood pressure lower than 90 mmHg with signs of tissue hypoperfusion requiring treatment in form of inotropic agents or assistant devices.

Table 2 shows the characteristics of the OHCA patients according to moment of arrest. Approximately two thirds of patients suffered a cardiac arrest before arrival of EMS. Most OHCAs were witnessed and delay in basic life support occurred in a quarter of patients with OHCA before EMS arrival. In most cases, the first observed rhythm was ventricular fibrillation or tachycardia. Intubation was performed in 108 patients. Of these patients, 95.4% (103/108) survived PCI and 88.0% (95/108) underwent TH. The rest had no indication for TH due to return of consciousness.

Table 2. Characteristics and treatment of out-of-hospital cardiac arrest

	OHCA witnessed by EMS (N=71)	**OHCA not witnessed by EMS** (N=153)
Delay in basic life support >5 minutes*	0.0 (0/71)	24.2 (37/153)
Bystander witnessed arrest	100 (71/71)	90.8 (139/153)
First observed rhythm		
Ventricular fibrillation / tachycardia	95.8 (68/71)	93.4 (142/152)
Bradycardia	2.8 (2/71)	2.0 (3/152)
Asystole / Pulseless electrical activity	1.4 (1/71)	4.6 (7/152)
Treatment performed		
Automatic external defibrillator	0.0 (0/71)	17.6 (27/153)
Defibrillation	95.7 (3/70)	94.1 (143/152)
Average number of shocks	1 (1-2)	2 (1-4)
Chest compressions	51.4 (36/70)	88.2 (135/153)
Intubation	10.0 (7/70)	66.0 (101/153)
Therapeutic hypothermia†	100 (7/7)	87.1 (88/101)

Values are percentage (n) or median (25^{th} to 75^{th} percentile).
*Based on history from bystanders; † The denominator is intubated patients.

Factors associated with OHCA

Angiographic culprit lesion was associated with risk of OHCA (Figure 1, Table 3). Lesions located in the left coronary artery (with the exception of diagonal branch lesions) were found to result in the highest risk of OHCA. In addition, proximally located left coronary artery lesions displayed a higher risk of OHCA compared to non-proximally located left coronary artery lesions: OR 1.43 (95% CI 1.05-1.95, p=0.025). Separately, proximal vs. non-proximal left anterior descending or left circumflex culprit lesions were not significantly associated with higher risk. Left main and proximal left anterior descending artery lesions were also associated with development of cardiogenic shock (Table 3, Figure 1). Moreover, culprit lesions in the left main and bypass grafts were associated with sub-optimal TIMI flow after PCI (Table 3).

Table 3. Association of angiographic culprit location with OHCA, cardiogenic shock and TIMI flow

Culprit artery	**OHCA**	OR (95% CI)	p-Value	**CarSh**	OR (95% CI)	p-Value	**TIMI <3 after PCI**	OR (95% CI)	p-Value
Right coronary									
Proximal (N=530)	2.4 (12)	Reference	-	5.0 (25)	Reference	-	8.7 (44)	Reference	-
Non-proximal (N=834)	3.1 (29)	1.31 (0.66-2.59)	0.436	4.5 (42)	0.90 (0.54-1.50)	0.685	8.8 (82)	1.00 (0.68-1.47)	0.984
Left main (N=43)	16.3 (7)	7.96 (2.95-21.45)	<0.001	51.2 (22)	20.03 (9.74-41.18)	<0.001	18.6 (8)	5.96 (2.37-14.99)	<0.001
Left anterior descending									
Proximal (N=816)	10.0 (82)	4.57 (2.47-8.47)	<0.001	8.9 (73)	1.88 (1.18-3.00)	0.008	9.2 (75)	1.06 (0.72-1.56)	0.780
Non proximal (N=521)	7.5 (39)	3.31 (1.71-6.40)	<0.001	4.4 (23)	0.88 (0.49-1.58)	0.674	7.9 (41)	0.90 (0.57-1.40)	0.624
Side branch (N=72)	5.6 (4)	2.41 (0.76-7.68)	0.138	2.8 (2)	0.55 (0.13-2.36)	0.418	4.2 (3)	0.45 (0.14-1.50)	0.195
Circumflex									
Proximal (N=220)	10.0 (22)	4.55 (2.21-9.36)	<0.001	8.2 (18)	1.70 (0.91-3.19)	0.096	6.8 (15)	0.76 (0.42-1.40)	0.384
Non-proximal (N=216)	7.9 (17)	3.50 (1.64-7.45)	0.001	5.1 (11)	1.03 (0.50-2.12)	0.945	4.6 (10)	0.51 (0.25-1.03)	0.059
Side branch (N=134)	7.5 (10)	3.30 (1.39-7.81)	0.007	6.0 (8)	1.21 (0.54-2.76)	0.643	9.8 (13)	1.13 (0.59-2.17)	0.712
Bypass graft (N=22)	2 (9.1)	4.09 (0.86-19.52)	0.077	13.6 (3)	3.02 (0.84-10.88)	0.091	8 (36.4)	2.38 (1.04-5.46)	0.040

CarSh = cardiogenic shock; OR = odds ratio; other abbreviations as in table 1.

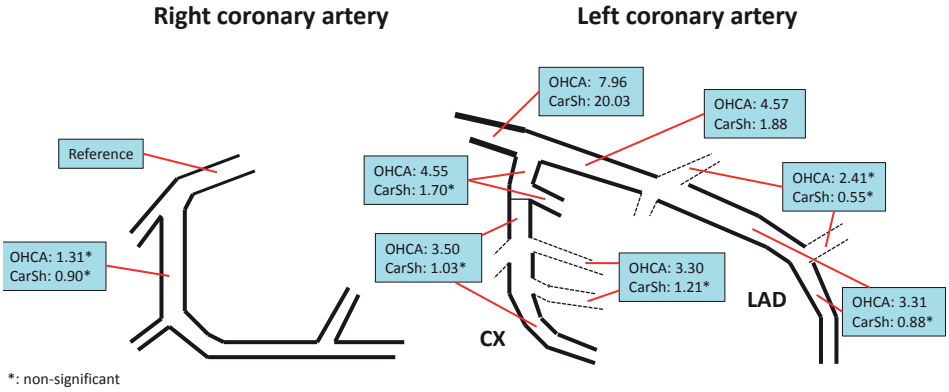

Figure 1. Culprit location and risk of out-of-hospital cardiac arrest and cardiogenic shock. Values are odds ratios. CarSh = cardiogenic shock; CX = circumflex artery; LAD = left anterior descending artery; OHCA = out-of-hospital cardiac arrest.

Neurological recovery and outcome during 1-year follow-up

Discharge CPC was known in 218 OHCA patients (97.3%) (Figure 2). The majority of patients had acceptable CPC scores (CPC≤2 in 77.1%, n=168). Thirty-five patients were in CPC 5/dead, of which 21 patients were brain dead and 14 patients suffered cardiac death. Of the 107 patients with a proximal left coronary culprit lesion, 77 recovered (72.0%). This rate was slightly higher for the patients with a non-proximal left culprit lesion (84.1%, 58/69 patients recovered) and the patients with a right culprit lesion (80%, 32/40 patients recovered). Of the 2 patients with a bypass graft culprit lesion, one died due to neurological causes. The p-value for trend between the culprit groups was 0.212.

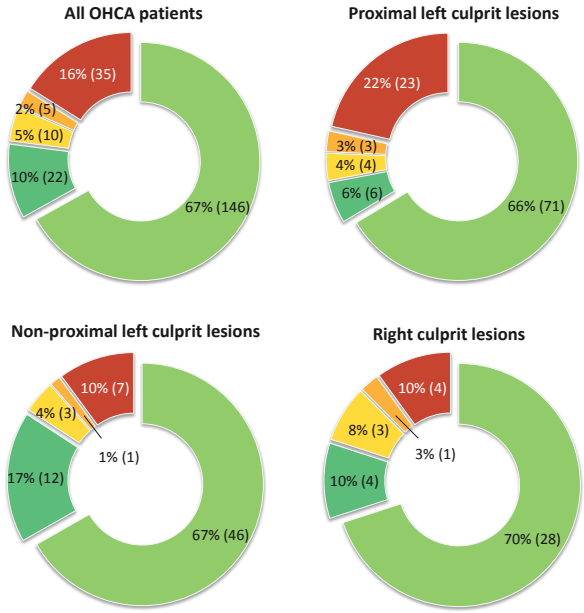

Figure 2. In-hospital Cerebral Performance Categories scale according to culprit lesion. CPC = cerebral performance categories scale. Other abbreviations as in figure 1.

One-year survival status was known in 3479 patients. In-hospital mortality was higher in OHCA patients compared to patients without OHCA (16.5% vs. 3.1%, p<0.001). Also, 1-year mortality (19.2% vs. 6.6%, p<0.001) was higher, which was due to in-hospital mortality as post-discharge survival was similar between patients with and without OHCA (3.2% vs. 3.6%, p=0.774). Figure 3A and 3B show the association between culprit location and mortality during follow-up in patients with and without OHCA. Figure 3C and 3D shows the association of cardiogenic shock and success of reperfusion with survival. OHCA patients with optimal TIMI flow after PCI had a better prognosis than OHCA patients with a sub-optimal TIMI flow after procedure, regardless of cardiogenic shock during PCI. In contrast, presence of cardiogenic shock was more important than success of reperfusion in patients without OHCA.

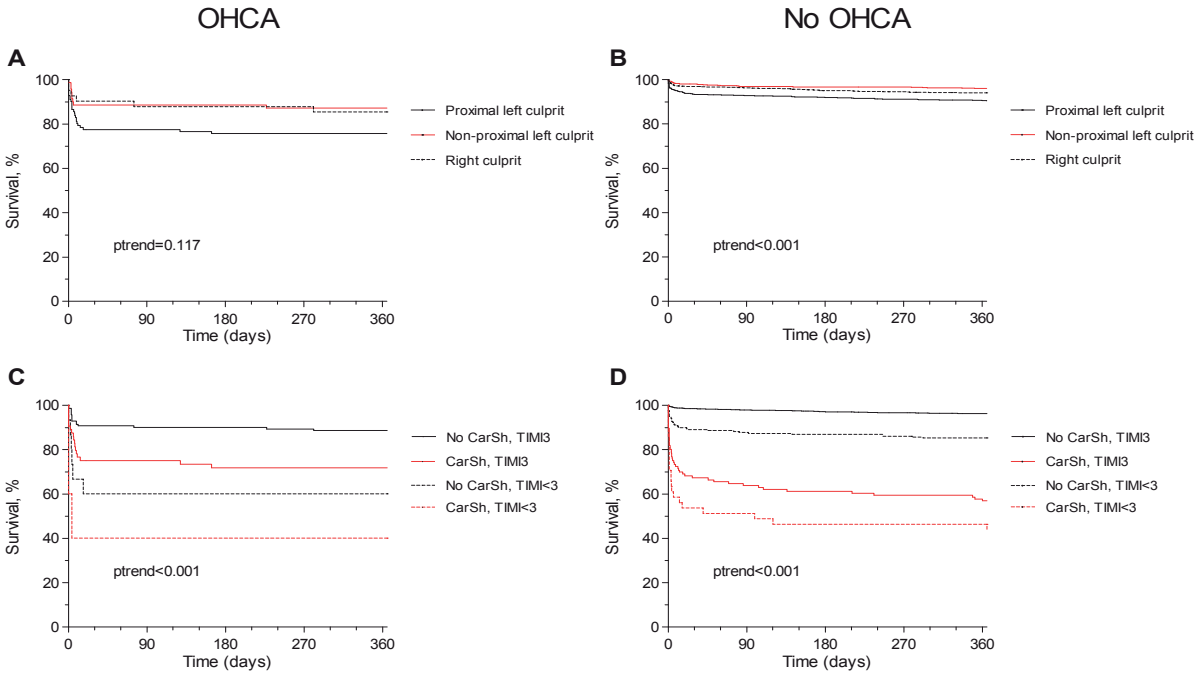

Figure 3. Survival in patients with and without OHCA according to **A)** and **C)** culprit lesion, **B)** and **D)** cardiogenic shock and TIMI flow after PCI.

Discussion

The present multicenter registry identified an association between angiographic culprit location and the occurrence of OHCA in STEMI patients: left proximal coronary lesions were associated with the highest risk for OHCA and right coronary lesions with the lowest. Moreover, culprit location was associated with cardiogenic shock and sub-optimal reperfusion after PCI, both of which were driving factors of prognosis after OHCA.

Attempts to improve the historically poor prognosis of OHCA led to investigation of revascularization techniques for OHCA patients.[2] While thrombolysis during resuscitation failed to prove beneficial, coronary angiography with angioplasty showed promise from early on.[3,4] At present, extensive networks of care make PPCI readily available for patients suffering an OHCA due to STEMI. In the current STEMI population, symptom-to-balloon times were strongly reduced in OHCA patients, a finding also observed by others, possibly reflecting the severity of symptoms leading to early initiation of professional care by either patient or bystanders.[5,6] In contrast, the prolonged door-to-balloon times in OHCA patients were likely related to time needed for in-hospital patient stabilization. Patients presenting with OHCA were more frequently in cardiogenic shock on arrival, due to impaired coronary perfusion during cardiac arrest and culprit lesion location. Culprit location varied between OHCA and non-arrest patients and was found to be associated with occurrence of OHCA. Left coronary lesions resulted in the highest and right coronary artery lesions in the lowest risk for OHCA. Moreover, proximally located culprit lesions within the left coronary artery were associated with higher risk of OHCA compared to non-proximally located lesions. This is likely explained by the larger area of myocardium-at-risk in proximal left lesions, which was supported by the finding that left main and proximal left anterior descending artery culprits were also associated with cardiogenic shock.[11] The lower percentage of right coronary artery culprit lesions is possibly explained by the commonly occurring vagal reaction in inferior MI, which may have a protective effect against VF.[12] However, it cannot be completely ruled out that inferior MI may have caused more severe ischemia, preventing ROSC and thus inclusion in this registry.

In-hospital and 1-year outcome rates stratified according to culprit lesion were similar in OHCA patients. Nevertheless, location of culprit lesions contributed indirectly to mortality due to the association with cardiogenic shock and sub-optimal reperfusion. Left main lesions were the highest risk lesions for STEMI patients, due to the strong association with OHCA, cardiogenic shock and sub-optimal reperfusion, which is supported by other reports.[13] Also, bypass graft culprit lesions were associated with reperfusion failure. The no-reflow phenomenon in setting of STEMI has multiple mechanisms, among which distal embolization and ischemic injury.[14] The occurrence of distal embolization is notorious in PCI of saphenous vein grafts and remains a challenge for operators.[15] The importance of optimal reperfusion in OHCA patients was stressed by the lower survival rates for sub-optimally reperfused OHCA patients without cardiogenic shock during PCI compared to optimally reperfused OHCA patients with cardiogenic shock during PCI. No-reflow possibly reflects the duration of ischemia prior to PCI in OHCA patients and the effect on prognosis may therefore also be explained by a prolonged resuscitation. In contrast, presence of cardiogenic shock was a stronger factor than failed reperfusion in patients without OHCA. This was likely explained by a smaller area of myocardium at risk in these patients due to the different distribution of culprit lesions.

Using a combined treatment strategy of primary PCI and TH, 77% of the OHCA population was discharged with acceptable neurological outcome and 1-year survival was 81%. The combination of PPCI and TH was previously investigated in the PROCAT registry, where the investigators reported an overall in-hospital survival rate of 40%, rising to 54% in STEMI patients after successful PCI which predicted improved prognosis.[7] Furthermore, the positive influence of both PCI and TH on long term survival was established in a cohort of OHCA patients, which included a large percentage of STEMI patients.[16] Also, a recent smaller study focusing specifically on use of TH in STEMI complicated by OHCA reported a neurological recovery rate comparable to the rate observed in the population treated with TH in the current study, supporting the accuracy of our findings.[17]

Limitations

Our investigation represents one of the largest studies covering outcomes in OHCA patients due to STEMI. However, our study was observational and thus shares the limitations of all observational analyses. Because the registry only included STEMI patients with ROSC, no data was available on OHCA patients without ROSC or patients not referred for PPCI. Data covering these patients may have provided more insight into the full community experience.

Conclusions

Location of angiographic culprit lesion was associated with the occurrence of OHCA in the current STEMI population. Moreover, angiographic culprit location predicted cardiogenic shock and success of reperfusion, both of which were associated with the prognosis of OHCA patients.

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CHAPTER 4

Outcome after ST-elevation myocardial infarction in cancer patients treated with primary percutaneous coronary intervention

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Abstract

The simultaneous occurrence of cancer and coronary heart disease is increasing in the Western world. Nevertheless, the influence of cancer on ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI) has not been investigated extensively. This multicenter registry included STEMI patients treated with primary PCI from 2006 to 2009. Patients were stratified according to history of cancer and primary focus lay on all-cause and cardiac mortality during 1-year follow-up. Adjusted effect sizes were calculated using Cox proportional hazard models. In total, 208 patients had a history of cancer (diagnosed ≤6 months ago in 20.7%, 6 months-3 years ago in 21.7% and >3 years ago in 57.6%) and 3215 patients had no history of cancer. Chemotherapy had been administered previously to 23% of patients with cancer. Patients with cancer were older, more frequently women, and more commonly known with previous MI or anemia. Reperfusion rates were similar after PCI. Patients with cancer showed greater all-cause (17.4% vs. 6.5% in other patients) and cardiac mortality at 1-year (10.7% vs. 5.4% in other patients), due to high early cardiac death (23.8%) in recently diagnosed cancer patients. After adjustment, a recent cancer diagnosis predicted cardiac mortality at 7-days (HR 3.34, 95% CI 1.57-7.08). The adverse prognosis was partly explained by anemia and occurrence of cardiogenic shock, whereas outcome was independent of cancer treatment. In conclusion, patients with cancer showed greater mortality after STEMI. A cancer diagnosis in the 6 months prior to primary PCI was strongly associated with early cardiac mortality.

Introduction

Coronary heart disease (CHD) and cancer are the most common causes of death in the Western world, together responsible for 3.5 million deaths in Europe every year.[1] Simultaneous occurrence of CHD and cancer is increasingly frequent because of high incidences and improving life expectancies for these patients. Moreover, frequently applied treatment methods for cancer have known cardiovascular side effects, which may predispose these patients to cardiac disease. Chemotherapeutic regimens like anthracyclines and antimetabolites have cardiotoxic properties potentially leading to irreversible cardiomyopathy or cardiac ischemia.[2] External radiation to the thorax is associated with cardiac sequelae including accelerated coronary artery disease, valvular disease, constrictive pericarditis and/or restrictive cardiomyopathy.[3] In addition, cancer is commonly associated with a hypercoagulable state,[4] increasing the risk for venous and possibly arterial thrombosis.[5,6] Regardless of the numerous factors influencing development and prognosis of CHD in patients with cancer, there is little to no data covering the influence of cancer on outcome after myocardial infarction.

The aim of the present multicenter study was to investigate the influence of cancer and cancer treatment on outcome after ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI).

Methods

The current Dutch registry prospectively included STEMI patients treated in 3 tertiary centers in the Netherlands. The design of this registry has been described previously.[7] In short, all consecutive patients undergoing primary PCI for STEMI between January 2006 and December 2009 were included. Patients without return of spontaneous circulation after out-of-hospital cardiac arrest were excluded, as well as patients permanently living outside the Netherlands to allow follow-up through municipality records. Approval from local ethics committees was not required.

Protocols included field triage faxed to the operator on call and in-ambulance treatment with aspirin, heparin and loading dose of clopidogrel. Glycoprotein IIb/IIIa inhibitors were administered up-front in one center and during procedure in the other centers. Patients treated in the Leiden University Medical Center were treated according to the institutional MISSION! protocol, a standardized prehospital, in-hospital and outpatient clinical framework for STEMI care.[8] These patients were intensively monitored at the outpatient clinic for 1 year, after which they were referred to the general practitioner or regional cardiology clinic. In the other centers, local residents were managed at the outpatient clinics and patients referred from regional hospitals were referred back for further management by regional cardiologists.

STEMI was defined as symptoms of angina lasting >30 minutes along with typical electrocardiographical changes (ST-segment elevation ≥0.2 mV in ≥2 contiguous leads in V1 through V3 or ≥0.1 mV in other leads or presumed new left bundle branch block) and a typical rise and fall of cardiac biomarkers. Patients with a history of non-melanoma skin cancer were included in the group without cancer. The cancer population was further subdivided according to time elapsed between diagnosis of cancer and primary PCI (diagnosed >3 years ago, 6 months to 3 years ago or ≤6 months ago). First moment of diagnosis was used, unless the patient had recently been diagnosed with progression of disease. For example, cancer diagnosed 5 years ago but identified to have metastasized in the 6 months prior to PCI was considered to be diagnosed in the last 6 months. However, metastasized disease identified 5 years ago was considered to be diagnosed more than 3 years ago.

Socioeconomic status was based on the average socioeconomic class of the patient's residential address using income, access to employment and educational level. These scores are measured yearly by the 'Netherlands Institute for Social Research', an independent government agency.[9] Vital status was obtained using municipality records. Hospital records and general practitioners provided causes of death. Deaths were considered cardiac unless a clear non-cardiac cause could be identified.

Stratification was done according to history of cancer and subsequently according to time of diagnosis. Continuous variables are presented as mean with standard deviation or median with interquartile range and were compared using Student's t-test or non-parametrical tests where appropriate. Categorical variables are expressed as counts and percentages and were compared by means of Pearson's χ^2 test. All statistical tests were 2-tailed and a p-value <0.05 was considered statistically significant. Time to endpoint was analyzed using Kaplan-Meier plots and the log-rank test was applied to compare cumulative incidences of the endpoint between groups. To evaluate cancer as a predictor of mortality, multivariable Cox proportional hazard models were used. Univariable predictors of mortality were incorporated in the multivariable models using a forward stepwise approach with a cut-off p-value of <0.10. Second, a confounder model was created in order to investigate the theoretical causal pathway between cancer and mortality. The model included age, gender, socioeconomic status and smoking status. Confounders were chosen according to their relation with both the occurrence of cancer and mortality. Subsequently, explanatory factors were added to the confounder model. Only those factors that could possibly be a consequence of the presence of cancer were added (previous MI, out-of-hospital cardiac arrest, anemia on admission, cardiogenic shock during PCI, TIMI flow after procedure, stent placement, treatment with abciximab, enzymatic infarct size, cancer treatment). Analyses were performed using SPSS version 21 (IBM, Armonk, New York).

Results

During the inclusion period, 208 patients (6.0%) treated for STEMI had a history of cancer (hereafter referred to as patients with cancer) and 3215 patients (92.3%) had no known history of cancer. Cancer history was uncertain in 60 patients (1.7%). Baseline characteristics are shown in Table 1.

Patients with cancer were on average older, more often women and more frequently suffered from hypertension compared to patients without a history of cancer. Patients with cancer were less frequently smokers but more commonly had a previous myocardial infarction. Furthermore, previous peripheral vascular disease, cerebrovascular disease, renal insufficiency and anemia were more common in patients with a history of cancer. Also, the time interval between diagnosis and balloon inflation was significantly longer in patients with a history of cancer compared to patients without a history of cancer.

Table 1. Baseline characteristics

	History of cancer		p-Value
Variable	**Yes** (N=208)	**No** (N=3215)	
Age (years ± standard deviation)	69.6 ± 11.0	62.8 ± 12.4	<0.001
Male gender	141 (67.8)	2427 (75.5)	0.013
Diabetes mellitus, non-insulin dependent	17 (8.3)	275 (8.6)	0.871
Diabetes mellitus, insulin-dependent	6 (2.9)	86 (2.7)	0.843
Hypertension*	88 (42.7)	1135 (35.4)	0.034
Hypercholesterolemia†	46 (22.4)	738 (23.1)	0.839
Current smoker	61 (31.0)	1487 (46.8)	<0.001
Previous myocardial infarction	35 (17.0)	335 (10.4)	0.003
Previous percutaneous coronary intervention	21 (10.2)	267 (8.3)	0.345
Previous coronary artery bypass grafting	5 (2.4)	79 (2.5)	0.970
Prior peripheral vascular disease	18 (8.8)	146 (4.5)	0.006
Prior cerebrovascular disease	24 (11.7)	191 (5.9)	0.001
Prior renal insufficiency‡	17 (8.3)	109 (3.4)	<0.001
Anemia on admission §	53 (11.8)	152 (5.2)	<0.001
Out of hospital cardiac arrest	18 (8.7)	203 (6.3)	0.183
Cardiogenic shock during PCI ‖	18 (8.7)	196 (6.1)	0.140
Creatine phosphokinase peak (median U/l, IQR)	1360 (686-2790)	1365 (616/2611)	0.894
Symptom-to-balloon time (median minutes, IQR)	186 (136-259)	180 (130-284)	0.708
Diagnosis-to-balloon time (median minutes, IQR)	86 (68-107)	79 (65-99)	0.024
Door-to-balloon time (median minutes, IQR)	52 (37-77)	46 (33-67)	0.077

Values are expressed as counts (percentages). * Blood pressure ≥140/90 mmHg or previous pharmacological treatment; † Total cholesterol ≥190 mg/dl or previous pharmacological treatment; ‡ eGFR<60 ml/min/1.73m^2; § Admission hemoglobin <12 g/dl (<7.4 mmol/l) for women and <13 g/dl (<8.1 mmol/l) for men. ‖ defined as systolic blood pressure lower than 90 mmHg with signs of tissue hypoperfusion requiring treatment in form of inotropic agents or assistant devices.

Table 2. Procedural characteristics

	History of cancer		p-Value
Variable	**Yes** (N=208)	**No** (N=3215)	
Coronary culprit vessel			0.826
Left anterior descending	91 (43.8)	1291 (40.2)	
Left circumflex	32 (15.4)	509 (15.8)	
Right	79 (38.0)	1337 (41.6)	
Left main	3 (1.4)	40 (1.2)	
Bypass graft	3 (1.4)	36 (1.1)	
Number of vessels narrowed >50%			0.293
1	87 (41.8)	1522 (47.4)	
2	71 (34.1)	1005 (31.3)	
3	50 (24.0)	685 (21.3)	
Stenting	192 (92.3)	3082 (95.9)	0.014
Drug-eluting stents	124 (60.8)	2263 (70.8)	0.002
Bare-metal stents	67 (32.8)	812 (25.4)	0.019
Intra-aortic balloon pump use	14 (6.7)	124 (3.9)	0.041
TIMI flow pre-procedure			0.058
Grade 0	132 (63.5)	2198 (68.5)	
Grade 1	26 (12.5)	356 (11.1)	
Grade 2	35 (16.8)	358 (11.1)	
Grade 3	15 (7.2)	299 (9.3)	
TIMI flow post-procedure ≤2	21 (10.1)	270 (8.4)	0.384
Abciximab treatment	137 (67.2)	2397 (75.1)	0.012
Discharge medication			
Aspirine / Coumadin derivative	187 (98.4)	3097 (99.3)	0.202
Clopidogrel	186 (97.9)	3058 (98.0)	0.885
Beta-blocker	160 (84.2)	2812 (90.5)	0.005
Ace-inhibitor / Angiotensin II antagonist	139 (73.2)	2220 (71.5)	0.622
Statin	171 (90.0)	2897 (93.2)	0.095

Values are expressed as counts (percentages). TIMI = Thrombolysis in myocardial infarction. Other abbreviations as in table 1.

During PCI, cancer patients were less likely to receive coronary stents (Table 2). In case of stenting, the percentage of patients receiving bare-metal stents was higher in patients with a history of cancer although the majority of patients received drug-eluting stents. Additionally, patients with cancer were more frequently treated with intra-aortic balloon pumps. Finally, patients with cancer were less likely to receive abciximab treatment compared to patients without a history of cancer and were less frequently discharged on beta-blocker therapy.

Table 3. Cancer characteristics

Variable	Diagnosis >3 years ago			Diagnosis 6 months < 3 years ago			Diagnosis ≤6 months ago			
Cancer location	n (%)	*Chemo*	**Radiation**	n (%)	*Chemo*	**Radiation**	n (%)	*Chemo*	**Radiation**	**Total**
Oral cavity	3 (1.5)	*0/3*	**0/3**	3 (1.5)	*0/3*	**1/3**	-	-		6 (3.0)
Larynx	7 (3.4)	*0/7*	**5/7**	2 (1.0)	*0/2*	**2/2**	1 (0.5)	*0/1*	**0/1**	10 (4.9)
Lung	3 (1.5)	*1/3*	**1/3***	3 (1.5)	*2/3*	**1/3***	4 (2.0)	*1/4*	**2/4***	10 (4.9)
Breast	25 (12.3)	*4/25*	**12/25***	5 (2.5)	*2/5*	**4/5***	3 (1.5)	*1/3*	**1/3***	33 (16.3)
Esophagus	1 (0.5)	*1/1*	**1/1**	2 (1.0)	*0/2*	**0/2**	2 (1.0)	*2/2*	**0/2**	5 (2.5)
Stomach	1 (0.5)	*0/1*	**0/1**	-	-		1 (0.5)	*0/1*	**0/1**	2 (1.0)
Pancreas	-	-		-	-		2 (1.0)	*0/2*	**0/2**	2 (1.0)
Colorectal	17 (8.4)	*2/17*	**0/17**	4 (2.0)	*0/4*	**1/4**	8 (3.9)	*1/8*	**1/8**	29 (14.3)
Kidney	7 (3.4)	*0/7*	**0/7**	1 (0.5)	*0/1*	**0/1**	1 (0.5)	*0/1*	**0/1**	9 (4.4)
Bladder	12 (5.9)	*3/12*	**0/12**	6 (3.0)	*0/6*	**0/6**	7 (3.4)	*3/7*	**0/7**	25 (12.3)
Prostate	6 (3.0)	*0/6*	**1/6**	14 (6.9)	*8/14*	**7/14**	10 (4.9)	*5/10*	**1/10**	30 (14.8)
Testis	5 (2.5)	*1 /5*	**2/5**	-	-		-	-		5 (2.5)
Ovary	1 (0.5)	*0/1*	**0/1**	1 (0.5)	*0/1*	**0/1**	-	-		2 (1.0)
Uterus / cervical	5 (2.5)	*0/5*	**1/5**	-	-		-	-		5 (2.5)
Skin (melanoma)	8 (3.9)	*0/8*	**0/8**	1 (0.5)	*0/1*	**0/1**	-	-		9 (4.4)
Lymphoma	11 (5.4)	*7/11*	**7/11**	2 (1.0)	*1/2*	**2/2**	1 (0.5)	*1/1*	**1/1**	14 (6.9)
Other†	5 (2.5)	*1/5*	**0/5**	-	-		-	-		5 (2.5)
Primary tumor unknown	-	-		-	-		2 (1.0)	*0/2*	**0/2**	2 (1.0)
Total	117 (57.6)	*20/117*	**30/117**	44 (21.7)	*13/44*	**18/44**	42 (20.7)	*14/42*	**6/42**	203 (100)

Note: hormone treatment was counted as chemotherapy.
*: Left sided chest radiation was performed in 9 breast cancer patients (6 with diagnosis >3 years ago , 3 with diagnosis 6 months – 3 year ago and 1 with diagnosis ≤6 months ago) and in 0 lung cancer patients.
†: leukemia (N=1), sarcoma (N=1), carcinoid (N=1) and mandibular neoplasm (N=2).

The characteristics of cancer history are shown in table 3. Exact moment of diagnosis was unknown in 5 patients. One year survival status was available in 99.8% of patients. Patients with cancer showed significantly greater all-cause mortality compared to patients without a history of cancer (in-hospital 9.1% vs. 3.4%, p<0.001; 7-day 9.7% vs. 3.1%, p<0.001; 1-year 17.4% vs. 6.5%, p<0.001, Figure 1A). Moreover, cardiac mortality was greater in patients with cancer compared to patients without a history of cancer (in-hospital 8.7% vs. 3.4%, p<0.001; 7-day 9.2% vs. 3.1%, p<0.001; 1-year 10.7% vs. 5.4%, p=0.002, Figure 1B). Stratification on moment of diagnosis showed that patients with cancer diagnosed ≤6 months ago suffered the highest rates of all-cause (in-hospital 19.0%, 7-day 23.8%, 1-year 50.0%, Figure 1C) and cardiac mortality (in-hospital 19.0%, 7-day 23.8%, 1-year 28.9%, Figure 1D).

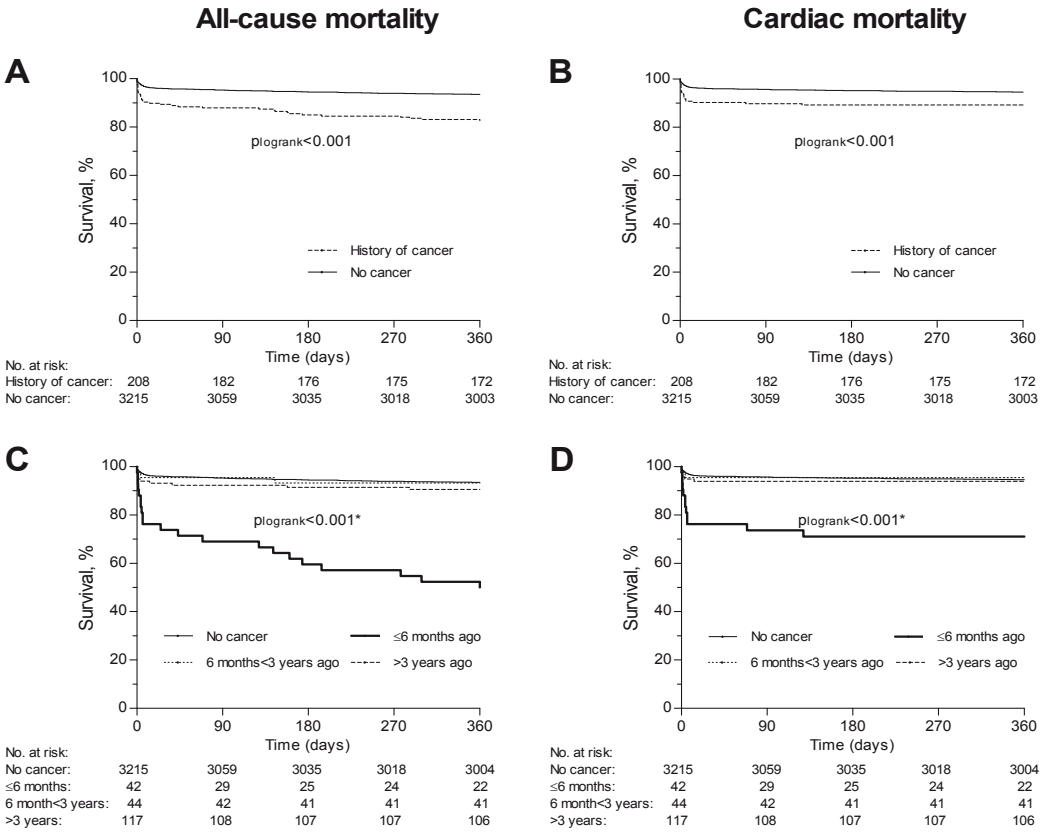

Figure 1: (A) Freedom from 1-year all-cause mortality according to history of cancer. **(B):** Freedom from 1-year cardiac mortality according to history of cancer. (**C):** Freedom from 1-year all-cause mortality according to moment of cancer diagnosis. **(D):** Freedom from 1-year cardiac mortality according to moment of cancer diagnosis.
*plogrank<0.001 for comparison between cancer diagnosis ≤6 months ago and other groups for both all-cause and cardiac mortality. Other comparisons were non-significant.

Table 4. Cancer and cardiac mortality after STEMI

Variable	Cardiac mortality, 7-day				Cardiac mortality, 1-year			
	Cum. Inc.	Crude HR 95% CI	Adjusted HR* 95% CI	p-Value	Cum. Inc.	Crude HR, 95% CI	Adjusted HR† 95% CI	p-Value
No cancer	3.1	Reference	Reference	-	5.4	Reference	Reference	-
Any cancer	9.2	3.06 (1.87-5.00)	2.15 (1.26-3.68)	0.005	10.7	2.09 (1.34-3.25)	1.14 (0.69-1.87)	0.611
Diagnosis								
>3 years ago	5.2	1.70 (0.75-3.88)	1.29 (0.52-3.21)	0.589	6.0	1.15 (0.54-2.44)	0.71 (0.29-1.75)	0.459
6 months < 3 years ago	4.5	1.48 (0.37-5.99)	1.83 (0.44-7.61)	0.406	4.5	0.85 (0.21-3.44)	0.83 (0.20-3.38)	0.795
≤ 6 months ago	23.8	8.27 (4.32-15.85)	3.34 (1.57-7.08)	0.002	28.9	6.31 (3.51-11.33)	1.80 (0.91-3.54)	0.090

Cum. incidence = cumulative incidence of events based on Kaplan-Meier curve.
*Adjusted for age, gender, history of diabetes mellitus, history of peripheral vascular disease, previous myocardial infarction, anemia, out-of-hospital cardiac arrest, cardiogenic shock during PCI, stenting, thrombolysis-in-myocardial infarction flow <3 after procedure and enzymatic infarct size.
†Adjusted for age, history of diabetes mellitus, history of peripheral vascular disease, culprit lesion, out-of-hospital cardiac arrest, cardiogenic shock during PCI, stenting, thrombolysis-in-myocardial infarction flow <3 after procedure, enzymatic infarct size.

Table 5. Factors associated with the effect of cancer on 7-day cardiac mortality

Variable	Crude HR, 95% CI	Adjusted HR, 95% CI
Confounder model (age, gender, socioeconomic status, smoking)	8.27 (4.32-15.85)	5.49 (2.54-11.88)
Confounder model + anemia	-	3.40 (1.52-7.57)
Confounder model + anemia, cardiogenic shock	-	2.71 (1.21-6.09)
Confounder model + anemia, cardiogenic shock, previous chemotherapy	-	3.44 (1.43-8.26)

Abbreviations as in table 4.

Table 4 lists the association of cancer with cardiac mortality during follow-up. After multivariable adjustment, any history of cancer was found to predict cardiac mortality at 7-days. Stratification on moment of diagnosis showed that this was driven by patients with a cancer diagnosis in the last 6 months, which strongly predicted early cardiac mortality. The explanatory analyses (table 5) showed that anemia at admission explained a major part of the effect size of recent cancer on cardiac mortality. The rate of admission anemia was already high in the total cancer population (11.8% compared to 5.2% in the population without cancer), but in patients with recent cancer diagnosis the rate of anemia was even higher at 65.9%.

The other major contributing factor was cardiogenic shock during PCI, which occurred in 16.7% of these patients.

Individual corrections for the following variables were performed (the values of the variables are mentioned in parentheses, comparing patients with a recent cancer diagnosis to patients without a history of cancer): previous MI (19% vs. 10.4%), out-of-hospital cardiac arrest (9.5% vs. 6.3%), TIMI flow (TIMI 3 achieved in 92.7% vs. 91.6%), stenting (90.5% vs. 95.9%), treatment with abciximab (48.8% vs. 75.1%) or enzymatic infarct size (median 1342 U/l (IQR 689 to 2854) vs. 1360 U/l (IQR 686 to 2790)) did not provide any additional reduction in the effect size. Finally, previous treatment with chemotherapy was added to the confounder models, which had been administered in one third of patients with a recent cancer diagnosis. However, no association between chemotherapy and cardiac mortality was observed. Previous thoracic radiation was not added to the explanatory models because none of the patients that had received thoracic radiation suffered cardiac death.

Discussion

The present multicenter study evaluated the influence of cancer on the prognosis of STEMI patients. Most notably, a cancer diagnosis in the 6 months prior to primary PCI was a strong predictor of early cardiac mortality. The adverse effect of cancer on prognosis after STEMI was partly explained by a high prevalence of anemia and the occurrence of cardiogenic shock, whereas outcome was independent of cancer treatment.

In the present population, patients with cancer were on average older and more often female. Previous myocardial infarctions were more frequent compared to patients without cancer because of higher average age, but also likely influenced by a greater risk of cardiac events.[5] In contrast, patients with cancer were less likely to smoke. As expected, cancer patients showed higher all-cause mortality compared to patients without a history of cancer. Strikingly, also cardiac mortality was more common in cancer patients, due to high mortality in patients with a recent cancer diagnosis. A large part of the effect on mortality could be explained by anemia, which was very common after a recent cancer diagnosis. Factors contributing to cancer-related anemia include impaired erythropoiesis, hemolysis, chemotherapy, nutritional deficiencies and interaction between tumor and immune system.[10] Anemia is known to predict cardiovascular death and heart failure in STEMI patients, due to the increased myocardial oxygen demand associated with the increased stroke volume and tachycardia required to maintain adequate systemic oxygen delivery.[11] Additionally, presence of cardiogenic shock explained part of the adverse outcome. The higher rate of previous infarctions in patients with cancer most likely contributed to the increased rate of cardiogenic shock. Also, patients with cancer were less likely to receive coronary stenting during primary PCI. Whether

this reflects a more conservative approach or was intended to shorten the need for dual antiplatelet therapy is unclear. The higher rate of implanted bare-metal stents supports the latter theory. Moreover, the higher rate of intra-aortic balloon pump implantation suggests that in general they were not withheld from aggressive treatment. As final TIMI flow was similar to patients without cancer, failed reperfusion did not appear to contribute to the development of cardiogenic shock. Furthermore, correction for stenting, abciximab treatment, TIMI flow and infarct size did not change the effect of recently diagnosed cancer on cardiac death, suggesting that the higher mortality rate was unrelated to the procedure and infarct size.

Contrary to expectations, no association between adverse outcome and chemotherapy or radiation was observed, and therefore a cancer-specific effect on prognosis after STEMI was suspected. The observed cancer types in these patients support this, as they have all been associated with risk of CHD.[5] Cancer is commonly associated with a hypercoagulable state due to reduced fibrinolysis and expression of procoagulant factors by tumors.[4,12] The most characterized factors are cancer procoagulant and tissue factor. Tissue factor has been related to increased myocardial ischemia-reperfusion injury in animal studies as well as mortality and reinfarction in patients with acute myocardial infarction.[13-16] Moreover, cancer is a known predictor of stent thrombosis.[17]

Recently diagnosed patients with cancer represent a challenge for the operator performing primary PCI. Antithrombotic treatment and vascular access increase the risk of bleeding which may worsen the anemia present in many of these patients, increasing the risk of heart failure. At the same time, antithrombotic treatment is essential to avoid ischemic complications associated with hypercoagulability. Another complicating factor is the frequent need for surgical procedures, potentially causing cessation of antiplatelet therapy and increased risk of stent thrombosis.[18] It might be preferable to use balloon angioplasty without stents to limit the duration of dual antiplatelet therapy. If stents need to be used, those with fast endothelialization rates, i.e. bare-metal or everolimus-eluting stents, should likely be preferred to minimize the risk of stent thrombosis.[19] Also, coronary artery bypass grafting may have advantages over stenting. However, these suggestions remain speculative without definitive randomized data.

To our knowledge, this multicenter registry was the first cohort to systematically investigate the association between cancer and prognosis after STEMI. The wide range of patients included across 3 regions in the Netherlands supports the generalizability of the findings. However, the observational design limits conclusions of causality, and findings should be considered hypothesis-generating. Additional research is needed to fully clarify the mechanism behind the adverse prognosis. Furthermore, the number of cancer patients was relatively small and the enzymatic correction for infarct size may have underestimated the actual infarct size. Also, it was not possible to measure whether all individual cancer patients received the same treatment as patients without cancer. However, there were no signs of lim-

itations in the care applied to the cancer population. Finally, follow-up data on re-infarction and stent thrombosis after PCI may have provided more insight into the mechanisms of death but were not available.

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CHAPTER 5

Prognosis of elderly patients suffering ST-elevation myocardial infarction during 2001-2011: a report from the SCAAR registry

Submitted

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Abstract

Background: Elderly patients constitute a growing part of the population presenting with ST-elevation myocardial infarction (STEMI). The use of primary percutaneous coronary intervention (PCI) in this high-risk population remains poorly investigated.

Methods: Using the SCAAR registry, we identified consecutive elderly STEMI patients (aged≥80 years) undergoing primary PCI during a 10-year period. Temporal trends in care and 1-year prognosis were investigated and long term outcome was compared to a control group of PCI treated patients aged 70-79 years. Relative survival was calculated by dividing the observed survival rate with the expected survival rate of the general population. Adjusted endpoints were calculated using Cox regression.

Results: In total, 4876 elderly STEMI patients were included. During the study period, average age and presence of comorbidity increased, as well as the use of antithrombotic therapy. Procedural success remained constant. One-year mortality was exclusively reduced between the most recent versus the earliest cohort, while the risk of re-infarction, heart failure, stroke and bleeding remained similar. The risk of death was higher for elderly patients early after PCI, after which the prognosis was slightly better compared to the general population. Long term risk of adverse events increased markedly with age.

Conclusions: The prognosis of patients over 80 years of age treated with PCI for STEMI was relatively unchanged during the study period, despite changes in patient characteristics and treatment. Advanced age increased the risk of adverse events, but survivors of the early phase after primary PCI had a slightly improved prognosis compared to the general population.

Introduction

The average age of patients presenting with an acute coronary syndrome is rising as a consequence of the aging populations in the Western world.[1-2] The increasing burden of elderly patients on health care resources stresses the need for research focused specifically on this part of the population. Nevertheless, elderly patients are underrepresented in clinical trials.[3] It is known that elderly patients presenting with ST-elevation myocardial infarction (STEMI) are less likely to receive revascularization compared to younger patients and that average delay to treatment is longer when referred for revascularization.[4-5] Over the recent years, the use of primary percutaneous coronary intervention (PCI) and other evidence-based treatments in elderly patients have been increasing and improvements in outcome have been reported.[6-8] However, most studies focused exclusively on survival and little is known about the long term results of primary PCI in these patients.

In the present population-based cohort study we sought to investigate temporal changes in presentation, treatment and prognosis of octogenarians and nonagenarians treated with PCI for STEMI over a 10 year period.

Methods

Objectives and endpoints

Our objective was to investigate temporal trends in patient and treatment characteristics, as well as changes in 1-year all-cause mortality, re-infarction, heart failure admissions, stroke and bleeding over a 10 year period in patients over 80 years of age. Long term outcome rates of the elderly population (stratified according to ages 80-89 and >90 years) were compared to a control group of patients aged 70-79 years. Additionally, survival of the elderly population was compared to the general population and driving factors of safety endpoints, i.e. stroke and bleeding, were investigated.

Patient selection

All consecutive patients over 80 years of age undergoing primary PCI for STEMI in Sweden between January 1st 2001 and December 31st 2010 were identified through the national comprehensive Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Analyses were based on first recorded invasive coronary procedure during the inclusion period to avoid duplicate entries. In addition, a control group of patients aged 70-79 years was identified using identical criteria. Primary PCI was defined as any use of a guidewire for more than diagnostic purposes in patients with STEMI or a new left bundle branch block and suspicion of ongoing ischemia. Patients without a Swedish personal identification number were excluded.

SCAAR is a Swedish nationwide registry for angiography and PCI and is a part of the SWEDEHEART registry, which also enrolls patients hospitalized in coronary care units and those undergoing cardiac surgery in the country.[9] Data in SCAAR are collected prospectively and are audited and monitored as previously described.[10] Vital status and date of death were obtained from the Swedish National Population Register until December 31st 2010. Information on previous medical history and patient follow-up were obtained from the National Inpatient Register, which holds information on discharge diagnoses of all hospitalizations in Sweden according to ICD (International Classification of Diseases) code.[11] In-hospital major bleeding was obtained from SCAAR and was defined as any bleeding associated with a hemoglobin drop of ≥5 g/dl or intracranial bleeding.

Merging of SCAAR with the national databases was performed by the Epidemiologic Center of the Swedish National Board of Health and Welfare using Swedish personal identification numbers. The merging was approved by the ethics committee of Uppsala University and the study complied with the Declaration of Helsinki. The SCAAR registry is sponsored by the Swedish Health Authorities and is independent of commercial funding.

Statistical analyses

Elderly patients were divided into cohorts according to year of PCI; 2001-2004, 2005-2006, 2007-2008 and 2009-2010. Patient grouping was based on comparability of group size and a median follow-up of 1 year. The years 2001 to 2004 were grouped together due to the relatively smaller numbers of patients treated in those years. Categorical variables are presented as frequency values and proportions. Continuous variables are presented as mean ± standard deviation or median and interquartile range where appropriate. Cox proportional hazards analyses were used to adjust for confounders. The log minus log test was evaluated to test the proportional hazard assumption. The multivariable models that corrected for patient characteristics incorporated the following variables: age, gender, diabetes mellitus, hypertension, hyperlipidemia, smoking, prior myocardial infarction, prior coronary artery bypass grafting, peripheral vascular disease, previous kidney failure, previous stroke, cancer in the last 3 years, number of vessel disease and hospital of PCI. Subsequently, multivariable correction was performed for treatment characteristics, adding the following variables to the patient characteristics model: stenting technique and type, aspirin use before/during PCI, P2Y12 receptor inhibitor use before/during PCI, glycoprotein IIb/IIIa inhibitor use before/during PCI and thrombolysis prior to PCI. Effect sizes were reported as hazard ratios (HR) with 95% confidence interval (CI).

Long term cumulative incidences of outcome were compared using Kaplan Meier curves and log rank tests. To investigate an excess of mortality in the elderly STEMI population after primary PCI, interval specific relative survival rates were calculated using intervals 0-0.05, 0.05-0.2, 0.2-0.5, 0.5-1, 1-2, 2-3 and 3-4 years. Relative

survival was measured as the absolute survival rate of the elderly STEMI population divided by the expected survival rate in the year of intervention from the general population with identical gender and age. Age, gender and intervention year mortality estimates of the general population were obtained from life tables of Statistics Sweden. Finally, forward stepwise Cox proportional hazard models were performed to identify factors associated with stroke and bleeding at 1-year, with a p-value for inclusion of <0.05. Calculations were performed using SPSS version 20 (IBM corporation, Armonk, NY, USA). STATA 12 (Statacorp LP, College Station, TX, USA) was used for the relative survival analysis.

Table 1. Baseline characteristics

	2001-2004 (N=814)	**2005-2006** (N=1222)	**2007-2008** (N=1427)	**2009-2010** (N=1413)	**p for trend**
Age, mean years ± SD	83.1 ± 2.7	83.7 ± 3.1	84.0 ± 3.2	84.0 ± 3.3	<0.001
Age ≥90 years	23 (2.8)	61 (5.0)	92 (6.4)	98 (6.9)	<0.001
Male gender	449 (55.2)	641 (52.5)	720 (50.5)	716 (50.7)	0.130
Diabetes mellitus	114 (14.3)	170 (13.9)	187 (13.1)	205 (14.5)	0.813
Hypertension	291 (36.1)	514 (42.1)	628 (44.0)	746 (52.8)	<0.001
Hyperlipidemia	91 (11.7)	138 (11.3)	192 (13.5)	243 (17.2)	<0.001
Current smoker	53 (6.6)	76 (6.2)	94 (6.6)	102 (7.2)	0.775
History of					
Myocardial infarction	189 (23.4)	222 (18.2)	190 (13.3)	189 (13.4)	<0.001
Coronary artery bypass grafting	17 (2.1)	28 (2.3)	37 (2.6)	41 (2.9)	0.010
Peripheral vascular disease	38 (4.7)	51 (4.2)	53 (3.7)	60 (4.2)	0.737
Stroke	99 (12.2)	182 (14.9)	184 (12.9)	180 (12.7)	0.241
Kidney failure	9 (1.1)	17 (1.4)	29 (2.0)	42 (3.0)	0.006
Cancer in the last 3 years	31 (3.8)	45 (3.7)	47 (3.3)	70 (5.0)	0.131
Onset symptoms to PCI, median min (IQR)	317 (169-865)	255 (163-485)	230 (148-451)	235 (145-450)	0.003
First ECG to PCI, median min (IQR)	82 (37-173)	84 (50-148)	77 (49-131)	78 (50-120)	0.074
Follow-up duration, median years (IQR)	7.1 (6.4-8.2)	4.9 (4.4-5.4)	2.9 (2.5-3.4)	1.0 (0.5-1.5)	-

Results

During the study period, 5471 patients over 80 years of age underwent primary PCI for STEMI. After exclusion of duplicate procedures, a total of 4876 patients remained. Baseline characteristics are shown in Table 1. Within this group, the average age increased gradually over time and so did the proportion of patients of very advanced age. The ratio of male to female patients was the same during the study period. Hypertension, hyperlipidemia, prior coronary artery bypass grafting and a

history of kidney failure were more common over time, while the percentage of patients with prior myocardial infarctions declined. A reduction in time from symptom onset to PCI was observed between the earliest and the later cohorts. Additionally, presence of cardiogenic shock decreased over time.

Procedural characteristics showed a pronounced increase in the use of the radial approach during PCI (Table 2). The total rate of stenting was stable over time, although stent type varied. Procedural success was similar over the years and was over 90% for all cohorts. The use of antithrombotic therapy increased while glycoprotein IIb/IIIa inhibitor treatment was common in the earlier years but gradually decreased and bivalirudin use increased.

Table 2. Angiographic and procedural characteristics

	2001-2004 (N=814)	**2005-2006** (N=1222)	**2007-2008** (N=1427)	**2009-2010** (N=1413)	**p for trend**
Vascular access					<0.001
Femoral access	610 (94.3)	1056 (86.4)	1103 (77.3)	820 (58.1)	
Radial access	37 (5.7)	163 (13.3)	320 (22.4)	588 (41.6)	
Angiographic findings					<0.001
Single vessel disease	274 (37.4)	393 (32.8)	533 (37.4)	512 (36.3)	
Dual vessel disease	192 (26.2)	346 (28.9)	403 (28.2)	405 (28.7)	
Triple vessel disease	185 (25.2)	341 (28.4)	369 (25.9)	343 (24.3)	
Left main disease	80 (10.9)	109 (9.1)	104 (7.3)	114 (8.1)	
Treatment technique					<0.001
Balloon angioplasty	80 (9.9)	116 (9.5)	175 (12.3)	169 (12.0)	
Bare-metal stenting	650 (80.0)	816 (66.7)	1175 (82.5)	1106 (78.4)	
Drug-eluting stenting	82 (10.1)	290 (23.8)	74 (5.2)	135 (9.6)	
Stent length, mean mm ± SD	17.1 ± 6.1	18.0 ± 6.2	17.6 ± 5.8	17.8 ± 5.8	0.003
Stent diameter, mean mm ± SD	3.1 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	0.041
Procedural success	725 (92.6)	1110 (91.0)	1303 (91.5)	1287 (91.4)	0.651
Medication					
Any anti-thrombotic treatment before PCI	505 (62.7)	1054 (87.5)	1227 (86.2)	1235 (87.7)	<0.001
Aspirin before PCI	482 (59.4)	1015 (83.2)	1152 (80.9)	1167 (82.9)	<0.001
P2Y12 inhibitor before PCI	192 (23.8)	636 (52.3)	956 (67.1)	1030 (73.2)	<0.001
GPIIb/IIIa inhibitor before PCI	42 (5.2)	113 (9.3)	108 (7.6)	42 (3.0)	<0.001
GPIIb/IIIa inhibitor during PCI	400 (49.3)	657 (53.8)	570 (40.0)	334 (23.7)	<0.001
Bivalirudin during PCI	-	166 (15.7)	485 (34.1)	779 (55.3)	<0.001
Thrombolysis before PCI	95 (11.8)	43 (3.6)	17 (1.2)	17 (1.2)	<0.001

In the beginning of the study period, slightly more than 10% of patients received thrombolysis prior to PCI, compared to marginal numbers of patients in later years.

Temporal trends in outcome

Stratification of outcome according to year of treatment in general showed similar rates of 1-year mortality (Table 3). The only statistically significant difference

Table 3. Trends in 1-year clinical outcome over time

	2001-2004 (N=814)	2005-2006 (N=1222)	2007-2008 (N=1427)	2009-2010 (N=1413)
Mortality				
Any event	213 (26.4)	308 (25.2)	346 (24.3)	302 (23.1)
Age-adjusted, HR (95% CI)	1.25 (1.04-1.49)	1.12 (0.96-1.32)	1.05 (0.90-1.22)	Reference
Comorbidity-adjusted, HR (95% CI)*	1.12 (0.93-1.36)	1.11 (0.95-1.31)	1.09 (0.93-1.27)	″
Treatment-adjusted, HR (95% CI)†	1.00 (0.81-1.23)	1.12 (0.94-1.33)	1.06 (0.90-1.24)	″
Myocardial infarction				
Any event	102 (15.4)	149 (14.8)	182 (15.1)	145 (13.4)
Age-adjusted, HR (95% CI)	1.13 (0.87-1.45)	1.06 (0.85-1.34)	1.09 (0.88-1.36)	Reference
Comorbidity-adjusted, HR (95% CI)*	1.12 (0.85-1.47)	1.04 (0.83-1.32)	1.12 (0.90-1.40)	″
Treatment-adjusted, HR (95% CI)†	1.08 (0.81-1.45)	1.12 (0.88-1.44)	1.14 (0.91-1.42)	″
Heart failure admission				
Any event	141 (21.6)	203 (20.3)	255 (21.2)	190 (18.2)
Age-adjusted, HR (95% CI)	1.20 (0.97-1.50)	1.11 (0.91-1.36)	1.17 (0.97-1.41)	Reference
Comorbidity-adjusted, HR (95% CI)*	1.14 (0.90-1.45)	1.12 (0.91-1.37)	1.20 (0.99-1.45)	″
Treatment-adjusted, HR (95% CI)†	1.15 (0.89-1.47)	1.15 (0.93-1.42)	1.21 (1.00-1.47)	″
Stroke				
Any event	27 (4.2)	50 (5.1)	65 (5.5)	40 (4.5)
Age-adjusted, HR (95% CI)	1.02 (0.62-1.66)	1.21 (0.79-1.83)	1.30 (0.88-1.93)	Reference
Comorbidity-adjusted, HR (95% CI)*	1.17 (0.70-1.96)	1.27 (0.83-1.94)	1.38 (0.93-2.06)	″
Treatment-adjusted, HR (95% CI)†	1.18 (0.69-2.03)	1.35 (0.86-2.11)	1.40 (0.94-2.10)	″
Bleeding, post-discharge				
Any event	30 (4.7)	58 (5.9)	59 (5.0)	51 (5.2)
Age-adjusted, HR (95% CI)	0.91 (0.58-1.43)	1.14 (0.78-1.65)	0.96 (0.66-1.40)	Reference
Comorbidity-adjusted, HR (95% CI)*	0.95 (0.59-1.53)	1.16 (0.79-1.70)	0.98 (0.67-1.44)	″
Treatment-adjusted, HR (95% CI)†	0.88 (0.53-1.46)	1.18 (0.78-1.78)	1.01 (0.69-1.48)	″

* Adjusted for: Age, gender, DM, hypertension, hyperlipidemia, smoking, prior MI, prior CABG, peripheral vascular disease, previous kidney failure, previous stroke, cancer, number of vessel disease, hospital.

† Adjusted for characteristics under * and stenting technique and type, aspirin before/under PCI, P2Y12 before/under PCI, GPI before/under PCI, thrombolysis.

in mortality was observed between the earliest and the most recent cohorts, which was eliminated after correction for comorbidity and treatment factors. Re-infarction and heart failure admissions did not change over time. Additionally, post-discharge stroke and bleeding rates remained stable. In-hospital major bleeding was rare (1.5% in 2001-2004, 0.7% in 2005-2006, 0.1% in 2007-2008 and 0.1% in 2009-2010) and adjusted in-hospital bleeding rates were not calculated due to the low number of events.

Long term results

Long term outcome was stratified according to age: 4593 patients were aged 80-89 years (mean 83.3 ± 2.6 years) and 274 patients were older than 90 years (mean 91.3 ± 1.7 years). The control group consisted of 8169 PCI treated patients aged 70-79 years (mean 74.4 ± 2.8 years). An approximate doubling of mortality risk per decade increase in age was observed (Figure 1). Mortality early after PCI explained a major part of the differences between the age groups, although curves continued to diverge during follow-up.

Relative survival analyses showed a lower survival of elderly STEMI patients compared to the general population in the first few months after PCI (Figure 2). After this early period, survival was slightly higher compared to the general population up to 3-years.

Compared to patients aged 70-79 years, the risks of a new myocardial infarction or heart failure were higher for patients over 80 years of age during follow-up (Figure 3A and 3B). Moreover, stroke rates were higher in patients over 80 years compared to those aged 70-79 years, with an early peak in stroke in the population above 90 years (Figure 4A). During the first year after PCI, stroke rates were 2.8%, 4.8% and 6.9% for patients aged 70-79 years, 80-89 years and more than 90 years, respectively. In the patients aged 80 years and above, a previous history of stroke was the sole predictor of another stroke during the first year of follow-up (HR 2.38, 95% CI 1.69-3.35).

Bleeding was more common in patients over 80 years of age (Figure 4B). During the first year after PCI, bleeding rates were 3.9%, 5.3% and 4.6% for patients aged 70-79 years, 80-89 years and more than 90 years, respectively. Multivariable analyses showed that male gender (HR 1.70, 95% CI 1.27-2.29); a history of peripheral vascular disease (HR 2.11, 95% CI 1.22-3.64) and cancer in the last 3 years (HR 1.99, 95% CI 1.17-3.38) were associated with bleeding during the first year of follow-up in patients aged 80 years or higher.

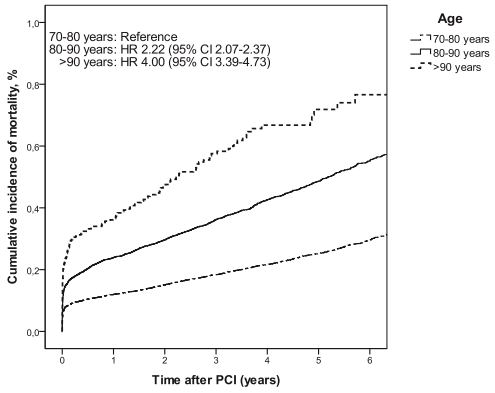

Figure 1. Long term mortality during follow-up.

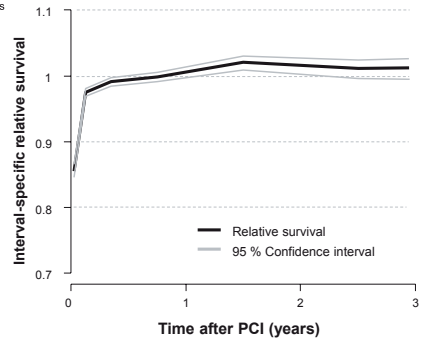

Figure 2. Relative survival of the elderly STEMI population (≥80 years) compared to the general population during 3-year follow-up.

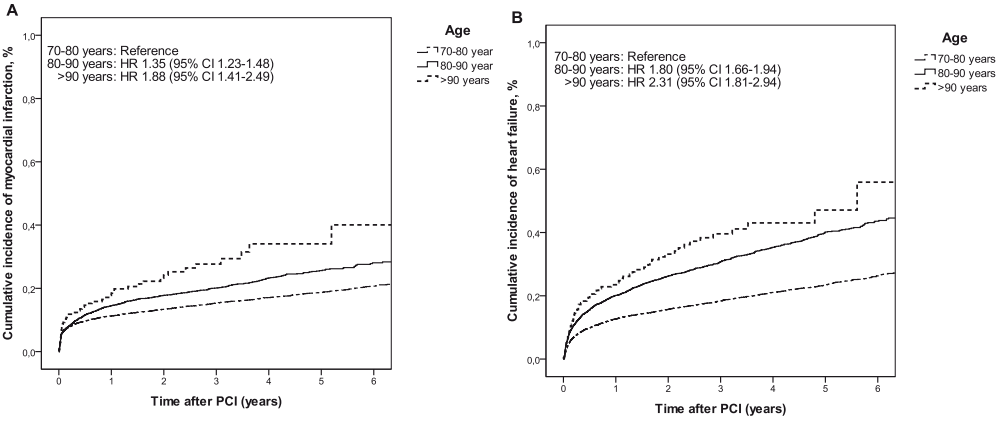

Figure 3: (A) Myocardial infarction and (**B**) heart failure during long term follow-up.

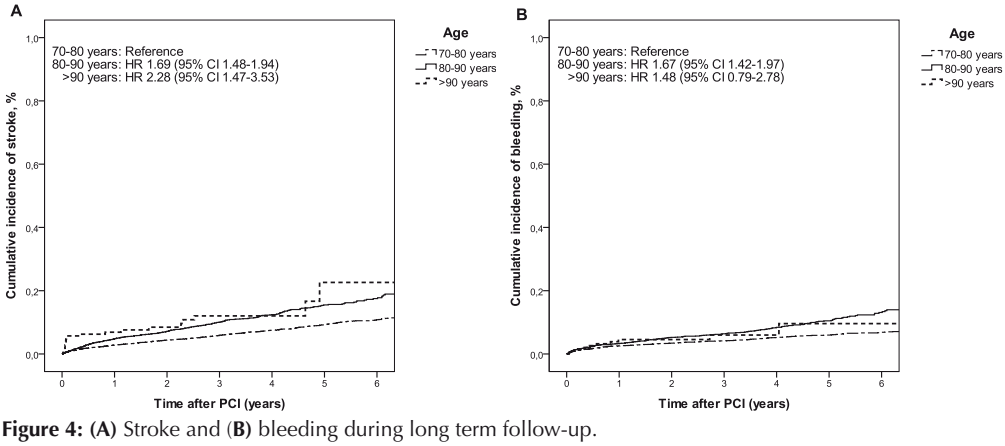

Figure 4: (A) Stroke and (**B**) bleeding during long term follow-up.

Discussion

Our main findings were that patients with STEMI over the age of 80 years treated with primary PCI during the 10-year inclusion period of the present population-based cohort study generally showed a similar prognosis over time, despite changes in patient and treatment characteristics. Importantly, elderly STEMI patients showed a similar and even slightly improved long term survival after the early phase from PCI compared to the general population. Nonetheless, the long term risk of adverse events increased with age, stressing the importance of appropriate risk stratification in older patients.

Elderly patients constitute a growing part of the population presenting with STEMI and the use of invasive and antithrombotic therapy is increasing in these patients.[2,6] However, the impact of these developments on the prognosis remains unclear. In the present study, the average age in the group of patients over 80 years of age rose gradually over time and the proportion of nonagenarians more than doubled. The increase in age was associated with higher comorbidity, although a sharp decline in prior myocardial infarctions was seen. The 1-year prognosis of elderly patients suffering an STEMI was relatively unchanged, with the exception of a significant difference in mortality between the earliest and the most recent cohorts. Thus, the temporal improvements in mortality were smaller than other reports.[4,6,8] However, the survival benefit reported in these previous studies was largely driven by the increased appliance of PCI, whereas the population in our study consisted exclusively of invasively treated patients.

During the study period, the occurrence of cardiogenic shock was observed to decrease, which may have been related to both decreases in prior myocardial infarctions and improving symptom to PCI times. The overall use of antithrombotic medication during and after PCI increased, and adjunctive treatment shifted gradually from glycoprotein IIb/IIIa inhibitor use to bivalirudin. The shift toward bivalirudin, increased radial access and decreased use of thrombolysis could probably explain the decrease in in-hospital major bleedings.[12,13] Interestingly, the rates of radial approach were markedly higher compared to other reports, suggesting a high level of comfort with radial access among Swedish operators.[14] Bleeding and stroke rates after discharge did not change over times. Whether this indicates a relatively similar dual antiplatelet strategy over the years is unclear, as data on dual antiplatelet therapy compliance were not available.

During long term follow-up, a strong association between advanced age and the occurrence of adverse events was observed. However, the relative survival analysis indicated that long term prognosis was comparable and even slightly improved in patients over 80 years of age compared to the expected survival rate of the general population (based on age, gender and year of birth), although survival was reduced in the first few months after primary PCI. Survival rates in our investigation were similar to a recent Danish study, but our study showed a slightly higher mortality of

nonagenarians.[15] The higher rates of a new myocardial infarction and heart failure in old patients are generally explained by more extensive coronary artery disease and comorbidity with age.[16,17]

Stroke rates diverged early after PCI and remained increased in patients over 80 years of age compared to patients 70-79 years of age during long term follow-up. The early peak in stroke in nonagenarians suggested a possible procedure related association. Patients with a previous stroke were found to be at risk a new stroke, an observation that may help to tailor therapy in these patients.[18] Bleeding during long term follow-up was doubled in patients aged 80-89 years compared to those aged 70-79 years. Reassuringly, bleedings were rare in patients during the first year after PCI. Risk factors of bleeding in elderly patients with STEMI during the first year after PCI included a history of peripheral vascular disease, potentially explained by the increased use of anticoagulants in these patients, and concomitant cancer.[19] The etiology of bleeding in cancer patients is multifactorial, including abnormalities in platelet number and function due to cancer treatment, need for invasive procedures and use of anticoagulants for prevention of deep venous thromboembolism.[20] Male gender also predicted bleeding events, which contrasts with the commonly reported observation that women have a higher risk of bleeding after PCI.[21] The higher bleeding risk possibly reflected a generally worse state of health of male patients in the elderly population.[22]

Limitations

The current study was observational and thus shares the limitations of all observational analyses. Nevertheless, registry studies remain important to study clinical outcomes and practices in populations underrepresented in clinical trials. The current study only included elderly patients treated with PCI, which limits the generalizability of our results to invasively treated patients. Additionally, in-hospital bleeding was not based on ICD codes. Although in-hospital registration may have varied during the observation period, registration rates generally improved over time and therefore the higher rates of bleeding in the earlier cohorts are unlikely to be influenced by this. Furthermore, 1-year follow-up was not available for patients treated in 2010, potentially influencing the comparison between the cohorts. However, a sensitivity analysis showed similar findings after exclusion of patients treated in the year 2010.

Conclusions

In this large population-based study of elderly patients with STEMI, we found a generally unchanged prognosis over a 10-year time period, despite changes in patient characteristics and medical treatment. Although higher age was associated with increased risk of adverse events, elderly patients surviving the early phase after primary PCI showed a similar and even slightly improved relative survival compared

the general population, supporting the use of primary PCI in these high-risk patients.

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PART 2

Treatment optimization

CHAPTER 6

Long-term outcome of second-generation everolimus-eluting stents and Endeavor zotarolimus-eluting stents in a prospective registry of ST-elevation myocardial infarction patients

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Abstract

Aims: The optimal drug-eluting stent (DES) in ST-elevation myocardial infarction (STEMI) patients remains unclear. We sought to compare the long term performance of everolimus-eluting stents (EES) and Endeavor zotarolimus-eluting stents (E-ZES) in STEMI.

Methods and results: The current analysis of a prospective registry included consecutive patients treated with EES or E-ZES for STEMI. Adjustment for measured confounders was done using Cox regression. In total, 931 patients met the inclusion criteria (412 EES and 519 E-ZES). Baseline characteristics were balanced, apart from a lower rate of renal insufficiency in EES. Median follow-up duration was 2.4 years (IQR 1.6-3.1). Mortality outcomes were similar. Up to three year follow-up, the composite endpoint of cardiac death, target vessel-related myocardial infarction and target lesion revascularization (TLR) was lower in EES; 9.7% vs. 13.7% in E-ZES (HR 0.64, 95% CI 0.42-0.99), primarily driven by reduced TLR rates; 3.4% in EES vs. 7.3% in E-ZES (HR 0.46, 95% CI 0.23-0.92). Definite stent thrombosis rates were low and similar between groups (1.1% in EES vs. 1.9% in E-ZES, p=0.190).

Conclusion: Use of EES led to lower rates of the composite endpoint, driven by reduced TLR. This suggests that EES are more efficacious than Endeavor ZES in STEMI. Definite ST rates were low and the strategy of second generation DES implantation and upfront GPIIb/IIIa inhibitors administration appears to be safe in STEMI.

Introduction

Second generation everolimus-eluting stents (EES) have shown superior results in stable coronary lesions and all-comer patients compared to both bare-metal and first generation paclitaxel-eluting stents (PES).[1-5] Comparison of Endeavor zotarolimus-eluting stents (E-ZES) with bare-metal and PES showed improved outcome after E-ZES implantation in stable coronary lesions.[6-9] Results of these trials have led to widespread use of second generation stents in current clinical practice. Use of drug-eluting stents (DES) in setting of ST-elevation myocardial infarction (STEMI) is however still under investigation. Trials comparing DES in STEMI mainly focused on comparison of bare-metal and first generation DES.[10] Therefore, limited data exist with regard to the performance of different types of second generation DES in patients presenting with STEMI. The current study sought to investigate the long term performance of the second generation EES and Endeavor ZES in an unselected STEMI population.

Methods

Design and patients

The prospective MISSION! registry included all patients treated with primary percutaneous coronary intervention (PCI) for STEMI in a high-volume tertiary center.[11] For the current retrospective analysis, consecutive patients treated between the 1st of January 2007 and the 1st of October 2010 were eligible for inclusion. Patient selection was done according to procedural stent type. All patients treated with either EES (Promus, Boston Scientific, Natick, Massachusetts) or E-ZES (Endeavor, Medtronic Vascular, Santa Rosa, California) were included in the current analysis. E-ZES were implanted in the Leiden University Medical Center from early 2006 and EES were implanted from the beginning of 2007, therefore both stent types were used during the entire inclusion period. Stent choice was left to the discretion of the operator. Patients treated with both stents simultaneously as well as patients treated with other types of drug-eluting or bare-metal stents (BMS) were excluded. Patients were treated and followed according to the institutional STEMI protocol (MISSION!), implemented at Leiden University Medical Center since February 2004.[11] Patients follow a standardized pre-hospital, in-hospital and outpatient clinical framework for decision making and treatment. The pre-hospital protocol included field triage by 12-lead electrocardiogram (ECG) faxed to the operator on call and in-ambulance treatment with loading dose of clopidogrel, aspirin, heparin and intravenous glycoprotein IIb/IIIa inhibitors. Upon arrival at the hospital, patients were transferred directly to the catheterization laboratory or coronary care unit to wait for arrival of the intervention team. Procedures were performed according to current clinical guidelines. If tolerated, patients received beta-blockers, ACE-inhibitors and statins within 24 hours. Additionally, patients were prescribed dual

antiplatelet therapy, consisting of aspirin 100 mg daily for life and clopidogrel 75 mg daily for 12 months. Patients with an indication for a coumadin were subscribed warfarin instead of aspirin.

Following hospital discharge, patients were intensively monitored and managed in the outpatient clinic for one year, after which they were referred back to the general practitioner or referred to a regular, generally regional, cardiological outpatient clinic. Vital status was gathered through municipality records. Follow-up data were adjudicated and prospectively collected in the electronic patient file (EPD Vision version 8.7.0.1.) by independent clinicians; data from patients participating in the out-patient program were gathered by out-patient chart review and follow-up data of patients not participating in the out-patient program were gathered by telephone interviews.

Definitions

STEMI was defined as symptoms of angina lasting longer than 30 minutes along with electrocardiogram demonstrating STEMI (ST-segment elevation ≥0.2 mV in ≥2 contiguous leads in V1 through V3 or ≥0.1 mV in other leads or presumed new left bundle branch block). Recurrent myocardial infarction was defined as symptoms of angina lasting longer than 30 minutes in addition to troponin levels above the ULN (upper limit of normal) or a 25% re-rise of troponin levels in case of re-infarction after index procedure. Peri-procedural infarction was defined as an elevation of troponins 3 times above ULN for PCI and 5 times above ULN for coronary artery bypass grafting (CABG). Target vessel revascularization (TVR) was defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. Target lesion revascularization (TLR) was defined as any repeat PCI or bypass surgery of the target lesion including the 5 mm proximal or distal region of the stented area. Stent thrombosis (ST) was defined according to Academic Research Consortium (ARC) definitions.[12] Furthermore, ARC suggested composite endpoints were defined. The device-oriented endpoint was a composite of cardiac death, MI not clearly related to a non-target vessel and target lesion revascularization (TLR). The patient-oriented endpoint consisted of all-cause mortality, any myocardial infarction and any repeat revascularization procedure.

Statistical analyses

Continuous variables are presented as means with standard deviations (SD) and were compared using Student's t-test. Categorical variables are expressed as counts and percentages and were compared by means of Pearson's χ^2 test. Time to endpoint was analyzed using Kaplan-Meier plots and the log-rank test was applied to compare the cumulative incidences of the endpoints between groups. All statistical tests were 2-tailed and a p-value ≤0.05 was considered statistically significant. Crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI) were calculated using cox proportional hazard regression models.

Univariable predictors of outcome were entered into multivariable models using a cut-off p-value <0.10. In case of limited number of events, selection of variables was based on effect size.

Results

During the inclusion period a total of 1199 patients were treated with primary PCI. Of these patients 931 met the inclusion criteria of this study: 412 patients received at least one EES and 519 patients at least one E-ZES (figure 1). Median follow-up duration was 2.3 years (IQR 1.6-3.0) for EES patients and 2.4 years (IQR 1.6-3.2) for E-ZES patients. Baseline characteristics (table 1) showed that patients treated with E-ZES more frequently had a history of renal insufficiency. Furthermore, patients treated with EES were more frequently discharged with beta-blockers compared to E-ZES patients (table 2). Other baseline and procedural characteristics were balanced.

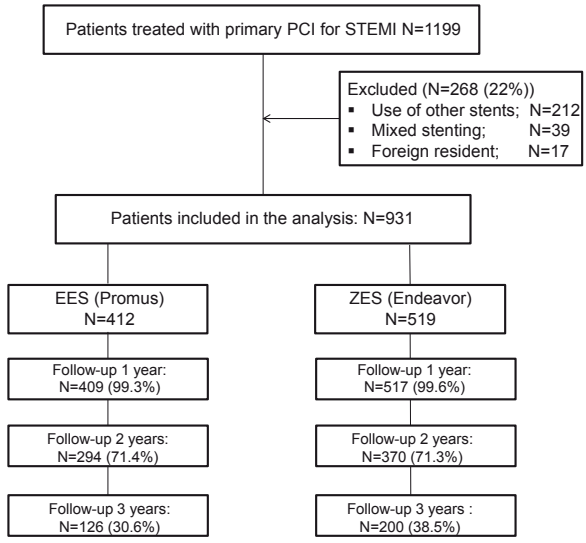

Figure 1. Inclusion and follow-up chart.

Table 3 presents clinical outcomes up to three years. During the first year, the patient-oriented endpoint was balanced between the groups. The device-oriented composite endpoint occurred in 4.7% of EES patients and in 8.7% of E-ZES patients (HR 0.56 in multivariable analysis, 95% CI 0.32-0.97). This was driven by both lower rates of target vessel-related MI (HR 0.27, 95% CI 0.08-0.93) and TLR (HR 0.21, 95% CI 0.06-0.72). In addition, the individual rate of TVR was lower in patients treated with EES compared to E-ZES patients (HR 0.53, 95% CI 0.29-0.98) and definite ST showed a trend toward a lower rate in EES patients (HR 0.16, 95% CI 0.02-1.28).

The rate of the device-oriented endpoint remained significantly lower up to three years follow-up (figure 2A), with 9.7% of EES patients versus 13.7% of E-ZES patients reaching the endpoint (HR 0.64, 95% CI 0.42-0.99). This was mainly driven by TLR (figure 2B), which showed rates of 3.4% in EES patients versus 7.3% in E-ZES patients (HR 0.46, 95% CI 0.23-0.92).

Table 1. Baseline characteristics

	EES (N=412)	**E-ZES** (N=519)	p-Value
Age, years	61.0 ± 12.4	61.9 ± 12.4	0.292
Male	309 (75.0)	378 (72.8)	0.455
Insulin dependent diabetes mellitus	18 (4.4)	18 (3.5)	0.484
Non-insulin dependent diabetes mellitus	35 (8.5)	49 (9.5)	0.607
Hypertension	164 (40.3)	198 (38.6)	0.600
Hypercholesterolemia	86 (21.2)	104 (20.4)	0.758
Family history of cardiovascular disease	169 (41.8)	214 (42.1)	0.929
Current smoker	185 (45.7)	230 (45.0)	0.840
Previous MI	42 (10.2)	50 (9.7)	0.791
Previous PCI	34 (8.3)	42 (8.1)	0.928
Previous CABG	14 (3.4)	14 (2.7)	0.538
History of peripheral vascular disease	17 (4.1)	25 (4.8)	0.605
History of cerebrovascular disease	16 (3.9)	24 (4.7)	0.567
History of malignancy	21 (5.1)	40 (7.7)	0.107
History of renal insufficiency*	7 (1.7)	24 (4.6)	0.013
Symptom to balloon inflation			0.348
0-6 hours	246 (86.0)	328 (85.6)	
6-12 hours	28 (9.8)	44 (11.5)	
12-24 hours	8 (2.8)	10 (2.6)	
>24 hours	4 (1.4)	1 (0.3)	
Diagnosis to balloon inflation, minutes (IQR)	78 (66-98)	80 (67-98)	0.660
Door to balloon inflation, minutes (IQR)	41 (30-63)	40 (32-56)	0.601
Out-of-hospital cardiac arrest	19 (4.6)	34 (6.6)	0.205
Cardiogenic shock	13 (3.2)	21 (4.0)	0.472

* Defined as eGFR<60 ml/min/1.73m^2. Data are expressed as mean ± standard deviation, n (%) or median (interquartile range [IQR]).

Table 2. Procedural characteristics

	EES (N=412)	**E-ZES** (N=519)	p Value
Culprit vessel			0.899
Left main stem	4 (1.0)	7 (1.3)	
Left anterior descending	179 (43.4)	229 (44.1)	
Left circumflex	70 (17.0)	78 (15.0)	
Right coronary artery	154 (37.4)	200 (38.5)	
Bypass graft	5 (1.2)	5 (1.0)	
Pre-dilation	363 (88.1)	470 (90.6)	0.226
Post-dilatation	154 (37.5)	180 (34.7)	0.379
Glycoprotein IIb/IIIa inhibitors	397 (97.3)	501 (96.5)	0.503
Number of vessel disease*			0.944
1	163 (39.6)	211 (40.7)	
2	151 (36.7)	187 (36.0)	
3	98 (23.8)	121 (23.3)	
Pre-procedure TIMI (grade)			0.881
0	251 (61.1)	309 (59.5)	
1	72 (17.5)	88 (17.0)	
2	53 (12.9)	76 (14.6)	
3	35 (8.5)	46 (8.9)	
Post-procedure TIMI 2 or more	406 (98.8)	511 (98.6)	0.857
Stent length culprit vessel, mean ± SD	28 ± 13	29 ± 14	0.792
Stent diameter culprit vessel, mean ± SD	3.3 ± 0.4	3.2 ± 0.4	0.136
Number of stents in culprit, mean ± SD	1.6 ± 0.8	1.6 ± 0.9	0.552
Discharge medication			
Aspirin	397 (99.0)	502 (99.2)	0.741
Clopidogrel	399 (99.5)	505 (99.8)	0.433
ACE-inhibitor	393 (98.0)	492 (97.2)	0.453
Statin	396 (98.8)	499 (98.6)	0.858
Beta-blocker	387 (96.5)	470 (92.9)	0.018

Data are expressed as mean ± standard deviation or n (%). * >50% visual stenosis. TIMI = thrombolysis in myocardial infarction; other abbreviations as in Table 1.

Table 3. Clinical outcomes

	EES (N=412)	**E-ZES** (N=519)	Crude Hazard Ratio (95% CI)	p-Value	Multivariable Hazard Ratio (95% CI)	p-Value
1 year outcomes						
All-cause mortality	17 (4.1)	27 (5.2)	0.84 (0.46-1.53)	0.567	-	
Cardiac mortality	14 (3.6)	26 (5.0)	0.73 (0.39-1.37)	0.325	-	
Myocardial infarction, any	6 (1.5)	17 (3.4)	0.44 (0.17-1.12)	0.084	0.44 (0.17-1.10)	0.080
Target vessel-related MI	3 (0.8)	12 (2.4)	0.27 (0.08-0.93)	0.038	0.27 (0.08-0.93)	0.037
Revascularization, any	44 (11.1)	74 (14.8)	0.73 (0.51-1.07)	0.105	-	
Target vessel revascularization	15 (3.8)	37 (7.4)	0.50 (0.27-0.91)	0.022	0.53 (0.29-0.98)	0.041
Target lesion revascularization	3 (0.8)	17 (3.4)	0.22 (0.06-0.75)	0.015	0.21 (0.06-0.72)	0.013
Definite stent thrombosis	1 (0.3)	8 (1.6)	0.16 (0.02-1.25)	0.080	0.16 (0.02-1.28)	0.084
All-cause mortality, any MI, any revascularization	60 (14.7)	98 (19.0)	0.77 (0.56-1.06)	0.108	-	
Cardiac death, target vessel related MI, TLR	19 (4.7)	45 (8.7)	0.55 (0.33-0.94)	0.028	0.56 (0.32-0.97)	0.037
Up to 3 years						
All-cause mortality	28 (7.6)	39 (8.7)	0.85 (0.52-1.39)	0.512	-	
Cardiac mortality	20 (5.6)	29 (5.7)	0.92 (0.52-1.61)	0.761	-	
Myocardial infarction, any	20 (7.0)	29 (6.7)	0.86 (0.49-1.52)	0.605	-	
Target vessel-related MI	8 (2.7)	19 (4.3)	0.52 (0.23-1.20)	0.124	-	
Revascularization, any	74 (21.5)	108 24.5)	0.84 (0.63-1.13)	0.247	-	
Target vessel revascularization	32 (9.9)	56 (12.9)	0.70 (0.45-1.08)	0.108	-	
Target lesion revascularization	11 (3.4)	31 (7.3)	0.44 (0.22-0.87)	0.019	0.46 (0.23-0.92)	0.027
Definite stent thrombosis	3 (1.1)	9 (1.9)	0.42 (0.11-1.54)	0.190	-	
All-cause mortality, any MI, any revascularization	99 (27.3)	144 (31.4)	0.84 (0.65-1.09)	0.193	-	
Cardiac death, target vessel-related MI, TLR	34 (9.7)	64 (13.7)	0.66 (0.44-0.99)	0.049	0.64 (0.42-0.99)	0.046

Data are n (%). Percentages are cumulative incidences of events from Kaplan Meier analysis. Hazard ratios were calculated using cox proportional hazard models.

The patient-oriented composite endpoint (figure 2C) and cardiac mortality (figure 2D) did not differ during long term follow-up. Moreover, definite ST (figure 3) showed comparable rates. ST occurred sub-acutely (24 hours to 30 days after PCI) in 6 cases, of which 1 in EES and 5 times in E-ZES. Late ST (30 days to 1 year after PCI) occurred in 2 E-ZES patients and very late ST (later than 1 year) occurred in 2 EES patients and 1 E-ZES patient. Dual antiplatelet therapy compliance was similar between the groups, showing a 99% rate for aspirin/coumadin adherence and 98% for clopidogrel adherence at one year. Of the patients suffering from late ST, 2 were using aspirin and one was using both aspirin and clopidogrel at time of ST.

Discussion

The major finding of this observational investigation, comparing long term outcomes of EES and Endeavor ZES in an unselected STEMI population up to three year follow-up, was that EES implantation was independently associated with lower rates of the device-related endpoint of cardiac mortality, target vessel-related MI and TLR compared to E-ZES. This was driven by lower rates of TLR in EES patients. Furthermore, definite ST rates were low and the strategy of second generation DES implantation and upfront GPIIb/IIIa inhibitors administration appears to be safe in STEMI.

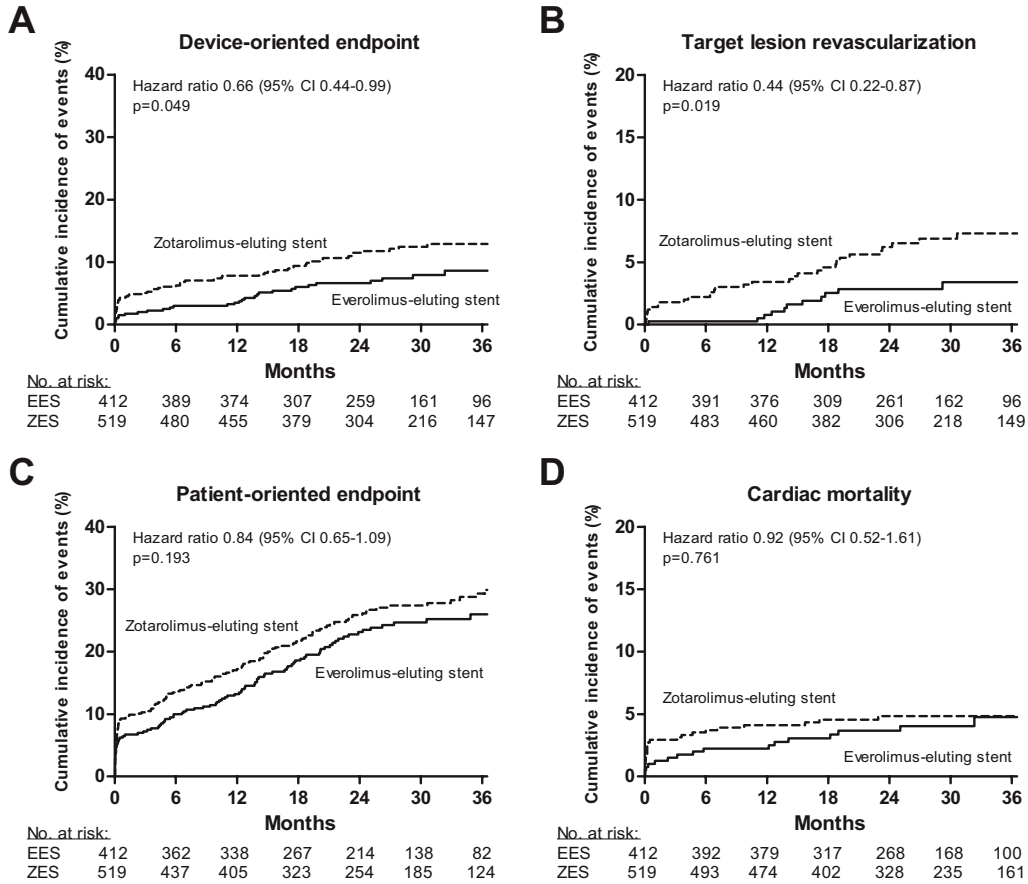

Figure 2: (A) Device-oriented endpoint (composite of cardiac death, target vessel-related MI and target lesion revascularization) up to three year follow-up. **(B)** Target lesion revascularization up to three year follow-up. **(C)** Patient-oriented endpoint (composite of all-cause mortality, any myocardial infarction and any revascularization procedure) up to three year follow-up. **(D)** Cardiac mortality up to three year follow-up. Hazard ratios are calculated using crude cox proportional hazards analyses with E-ZES as reference group.

Myocardial infarction has long been considered an off-label indication for DES. While first generation DES have been shown to reduce revascularization rates in STEMI patients compared to BMS, the benefit is offset by a higher risk of very late ST.[13,14] Stenting in acute coronary syndromes was found to be an independent predictor of ST after DES implantation.[15] Delayed endothelialization, thrombotic burden, stent underexpansion and stent malapposition have been identified as mechanisms for the higher rate of ST after DES implantation in patients with acute coronary syndromes.[16-18] Moreover, evaluation of patient adherence to dual antiplatelet therapy is complicated by the acute setting of myocardial infarction. Second generation stents have been developed to reduce the incidence of ST while attempting to improve the efficacy of DES. In this study, we compared the second generation EES and E-ZES. The EES is a thin strut (81 µm), cobalt-chromium, Multi-Link™ stent with a biocompatible polymer eluting everolimus, a sirolimus-analogue. Eighty percent of the everolimus is eluted in the first 28 days. EES showed faster endothelialization compared to first generation stents in pre-clinical studies.[19] The Endeavor ZES is based on a cobalt-chromium Driver™ platform, consisting of 91 µm struts covered by a biomimetic phosphorylcholine polymer releasing the sirolimus-analogue zotarolimus. The Endeavor stent releases 95% of its inhibitory drug within 28 days, which is the fastest elution of all stents currently in use.

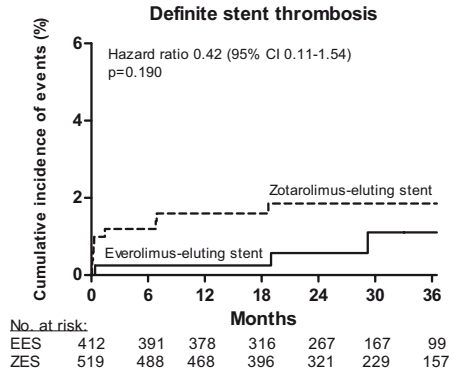

Figure 3. Definite stent thrombosis.

In the current study, patients treated with EES showed lower rates of the composite endpoint of cardiac mortality, target vessel-related MI and TLR compared to E-ZES patients up to three year follow-up. The difference was driven by lower rates of TLR in EES patients. This observation is in line with previous studies demonstrating an association of EES with lower late luminal loss (average 0.14 mm, compared to 0.6mm in E-ZES) which is a strong surrogate endpoint for TLR.[20,21] This indicates that EES have a higher potential for suppressing neointimal growth. It underlines that more aggressive inhibition of intimal hyperplasia is not directly related to a higher risk of ST but that other factors like stent design, polymer properties and release characteristics of the drug also play a role.

Recently, Hannan et al. performed a propensity score matched comparison of EES and E-ZES and found a reduced rate of repeat revascularizations for EES patients during two year follow-up,[22] reflecting the current results. Ten percent of patients included in their registry were treated for MI within 24 hours, however exact diagnosis was not mentioned. Trials or registries focusing on use of EES or E-ZES in STEMI patients specifically are limited. The Evaluation of Xience-V stent in Acute

Myocardial Infarction (EXAMINATION) trial randomized MI patients to EES or BMS and reported lower rates of TVR, TLR and definite ST in the EES group after 1 year.[23] A comparison of EES and SES was made in The XienceV Stent vs. Cypher Stent in Primary PCI for Acute Myocardial Infarction (XAMI) trial, which included 96% STEMI patients, and suggested superior MACE rates in EES compared to SES up to 1 year follow-up, although the trial was not powered for this.[24] Additionally, Kedhi et al.,[25] comparing EES with PES in the indication of STEMI in a post-hoc analysis, observed superior outcomes of EES up to two years of follow-up. Rates of mortality, MI and revascularizations were relatively low compared to the current study. This is most likely due to a higher risk population in the current analysis, since no patients were excluded on account of clinical or angiographic characteristics. In contrast, the HORIZONS-AMI trial reported markedly higher rates of definite ST after PES implantation (4.2% at 3 years) despite inclusion of lower risk patients, indicating that there might be improved safety with use of second generation stents in STEMI.[26]

The ST rates found in the E-ZES group of this study were somewhere in between the results of PES and EES. E-ZES have previously been compared with SES in the setting of STEMI by Kim et al.[27] Up to one year follow-up, E-ZES showed a similar incidence of ST (1.0% vs. 1.8%). Additional studies found no differences in outcome between PES, SES and E-ZES in STEMI patients up to 18 months follow-up.[28-31] In these studies, the E-ZES groups showed variable ST rates ranging from zero to 2.9 percent. Longer term data on the performance of E-ZES in STEMI are lacking.

Recent results from the RESOLUTE all-comers trial showed non-inferiority of the Resolute ZES (R-ZES, characterized by a new biocompatible polymer with a more gradual release of zotarolimus) compared to EES. The 2 year definite ST rate was 2.0% in the R-ZES compared to 1.0% in EES.[32] In contrast, the recent TWENTE trial found a trend toward a reduction in definite/probable ST after 1 year in patients treated with R-ZES compared to EES.[33] These results suggest that improved safety and efficacy outcomes of the R-ZES compared to E-ZES are possibly due to improvements in polymer and elution pattern. However this remains speculation without definitive randomized clinical data. In this study a trend between lower 1 year ST rates in EES was seen, due to differences in the incidence of ST in the early period after stent implantation. From previous studies it is known that acute ST is related to procedure related factors like dissection, undersizing of stent, TIMI flow less than 3 after procedure and lack of glycoprotein IIb/IIIa inhibitors.[34] However, no acute ST were observed in our population. Sub-acute ST, which occurred in 6 instances, is related to a variability of factors, among which diabetes mellitus, left ventricular function under 40%, complex lesions and acuteness of PCI.[35] The role of procedure related factors is smaller in sub-acute ST, suggesting that the higher early rate of ST in E-ZES might be due to differences in stent design. However, long term rates of ST were similar in our population, supporting adequate safety of both second generation stents during long term follow-up.

Study limitations

The current observational cohort included the entire range of STEMI patients encountered in daily practice. Optimal care consisted of low diagnosis- and door-to-balloon times, up-front glycoprotein IIb/IIIa inhibitors and an intensive outpatient management program. There are however several limitations to the current study design. Because the Endeavor ZES is no longer clinically in use, the Resolute ZES might have been a better comparator for EES. Furthermore, results must be interpreted with caution due to the non-randomized, observational nature of the study. Although a wide range of baseline and angiographic characteristics were balanced between the groups, bias could have occurred during the selection of the patients. Multivariable Cox proportional hazards analyses were performed to correct for confounders but unmeasured characteristics may have influenced comparison of the groups. Propensity score matching may have provided more adequate correction for confounding but was not possible due to limitations in population size. The study was underpowered to detect differences in rare events like ST. Additionally, the adjudication of repeat MI events was not performed according to the latest trial protocols and this may have led to underestimation of MI events though there is no reason to suspect that this favored any of the stent types. Moreover, this was a single center investigation and there were no predefined endpoints which may have increased chances of type 2 error, therefore results of this analysis should be considered hypothesis-generating. Whether the advantage of EES in setting of STEMI remains when compared to the newer generation R-ZES is yet to be explored. Large randomized trials with long term follow-up and sufficient power are necessary to decide which newer generation stent is most suitable for STEMI patients.

Conclusions

The current retrospective investigation of EES and Endeavor ZES in setting of STEMI found lower rates of the device-oriented endpoint in EES patients compared to E-ZES patients, driven by lower rates of TLR. This suggests that EES is more efficacious than E-ZES in setting of ST-elevation myocardial infarction up to three years follow-up. Furthermore, definite ST rates were low and the strategy of second generation DES implantation and upfront GPIIb/IIIa inhibitors administration appears to be safe in STEMI.

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CHAPTER 7

Second-generation everolimus-eluting stents vs first-generation sirolimus-eluting stents in acute myocardial infarction: 1-Year results of the randomized XAMI (XienceV stent vs. Cypher stent in primary PCI for Acute Myocardial Infarction) trial

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Abstract

Objectives: The goal of this study was to compare the efficacy and safety of second generation everolimus-eluting stents (EES) with first generation sirolimus-eluting stents (SES) in primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI).

Background: Drug-eluting stents (DES) in AMI are still feared for possible late and very late stent thrombosis (ST). Newer generation DES, with more hemocompatible polymers and improved healing, may show promise to combine the increased efficacy of DES with improved safety. However, no randomized trials in AMI are available.

Methods: A total of 625 patients with AMI were randomized 2:1, EES or SES, in the XAMI trial (Xience vs Cypher in AMI). Primary endpoint was major adverse cardiac events (MACE) at 1 year consisting of cardiac death, non-fatal AMI or any target vessel revascularization (TVR). The study was powered for non-inferiority of EES. Secondary endpoints contain ST rates and MACE rate up to 3 years.

Results: The MACE rate was 4.0% for EES and 7.7% for SES, absolute difference -3.7% [95% CI: - 8.28;-0.03], p = 0.048, RR 0.52, [95% CI: 0.27;1,00]. One year cardiac mortality was low at 1.5% (EES) vs 2.7% (SES) (p=0.36) and one year incidence of definite and/or probable ST 1.2% (EES) vs 2.7% (SES) (p=0.21).

Conclusions: In this all-comer randomized multi-center AMI trial, second generation EES was non-inferior to SES and superiority for MACE was suggested. ST rate in EES at one year was low, but long-term follow-up and larger studies will have to show whether very late ST rates will also be improved in newer DES.

Introduction

The efficacy and safety of drug-eluting stents (DES) in the treatment of coronary artery disease is well established. Restenosis rates have dramatically decreased for both on-label and off-label indications.[1-3] Despite these results the concern for increased (late) stent thrombosis is still present.[3-5] This may be due to delayed vascular healing after DES implantation,[6,7] probably as a result of drug and/or polymer reaction. Late coronary endothelial dysfunction after DES stenting has previously been reported.[8] Because acute myocardial infarction (AMI) presents the highest possible thrombotic coronary lesions, DES implantation during primary percutaneous coronary intervention (PCI) for AMI is still not advocated by many interventional cardiologists. However, even in this challenging population the use of DES has increased over the last few years and several randomized studies and large cohort studies show efficacy and safety.[9-12]

Newer anti-proliferative drugs and more biocompatible polymers have shown promise in reducing further the rate of (late) stent thrombosis in stable patients.[13,14] However, no randomized data is available on the efficacy and safety of newer generation DES in AMI patients.

In our center, Cypher (Cordis, Bridgewater, New Jersey), the sirolimus-eluting Cypher stent (SES) has been the default stent since 2004 in PCI for all indications including acute coronary syndromes. With the emergence of a second generation "limus" DES stent (Xience V [Abbott Vascular, Santa Clara, California], an everolimus-eluting stent [EES]), a multi-center randomized trial was designed to compare both stents in AMI patients (XAMI : Xience vs Cypher in AMI).

Methods

Study design and patient population

Between February 2008 and December 2009 consecutive patients presenting with ST-elevation myocardial infarction (STEMI) treated with primary PCI and fulfilling the inclusion criteria were included in three large interventional centres in the Netherlands. To be included, patients had to have ST-elevation myocardial infarction and be eligible for primary PCI. Patients with Non-ST elevation myocardial infarction (NSTEMI) with emergency indication for PCI at admission were also allowed. Exclusion criteria were as follows: stent thrombosis of previous stent or chronic total occlusion as target lesion, known allergy or intolerance to sirolimus, everolimus, aspirin or clopidogrel, intubated patient after extensive resuscitation or shock patients for whom no informed consent could be obtained, estimated life expectancy < 1 year or stent size required to treat lesion > 3,5 mm (maximum diameter of SES).

The study was approved by the institutional ethics committee at each participating

center, and written informed consent was obtained from all patients.

Randomization and blinding

Patients were randomized 2:1 to EES or SES by sealed envelope, directly after diagnostic angiography and assessment of feasibility for stenting. Operators were not blinded to the allocated stent. An independent Data Safety Monitoring Board (DSMB) evaluated the study safety after 30 day inclusion of 300 patients, blinded to the allocated stent type. At one year, all events were evaluated and adjudicated by an independent Clinical Event Committee (CEC), again blinded to treatment assignment.

Procedure

All patients were pretreated with i.v. aspirin, heparin 5000 IE bolus and received clopidogrel with a loading dose of preferably 600 mg. Interventions were performed according to local practice in three high volume centres by high volume operators. GP IIb/IIIa receptor blocker use, thrombus aspiration and balloon predilatation were left up to the operator. Aspirin was recommended for life and clopidogrel for a minimum of one year. The study has a planned follow-up of 3 years.

Study Endpoints and Definitions

The primary endpoint was major adverse cardiac events (MACE) at 12 months consisting of any event during follow-up in hierarchical order: cardiac death, non-fatal re-infarction or any target vessel revascularization (TVR). The secondary endpoints were (sub)-acute stent thrombosis (SAT) at 30 days and late stent thrombosis (LST) at 1, 2 and 3 year, MACE at 30 days and 2 and 3 years and all-cause mortality at 1, 2 and 3 year. Reinfarction was defined by recurrent symptoms and/or new electrocardiographic changes, with re-elevation of the creatine kinase (CK) of > 1.5 times the previous value with elevation of CK-MB, if within 48 h, or > 3 times the upper normal limit, if after 48 h from the index AMI. More than 5 times the upper limit of normal CK was required for the diagnosis of AMI after bypass surgery. TVR was defined as any repeat percutaneous intervention or by-pass grafting of the target vessel and Target Lesion Revascularization (TLR) as any repeat percutaneous intervention or by-pass grafting of the target lesion or the 5 mm proximal or distal to the initial stent. Definite and probable stent thrombosis was defined according to the Academic Research Consortium criteria (ARC).[15]

Statistical analysis

Data collection, handling and statistical analyses were performed by an independent Core Lab, Diagram b.v., Zwolle, The Netherlands. This trial was based on the notion that the performance of EES would not be inferior to SES in relation to the primary outcome, MACE at 1 year, with the use of a pre-specified non-inferiority margin and a 95% confidence interval. We calculated that a sample size of 600

patients (2:1 randomisation) would give a power of 80% (Farrington and Manning method). This sample size took into account an expected one year MACE rate of 8% and a non-inferiority margin of 6%, and a two sided risk of 0.05. Sample size was increased to 625 patients (after the pilot phase without any unblinding of data) to compensate for a small pilot phase of 80 patients, randomized 1:1, to maintain adequate power of the trial. Study outcomes were assessed by both intention-to-treat and per-protocol analyses. The intention-to-treat population included all patients who were randomized. These results are reported in this paper. The per-protocol population included all patients who fulfilled the inclusion and exclusion criteria and in which the randomized stent was placed. A second per-protocol analysis also excluded the included NSTEMI patients in the trial to check consistency of the trial results in true STEMI patients. Data are reported as percentages for discrete variables. Continuous variables are reported as mean with standard deviation or median with 25th and 75th percentiles. Categorical variables were compared with the chi-square test or Fisher's exact test. Continuous variables were compared with the nonparametric Mann Whitney U test. Kaplan-Meier survival estimates were used to compare time to the first occurrence of MACE, with pair-wise differences tested using the log rank test.

Results

Patients and baseline characteristics

A total of 625 consecutive patients with AMI were included in three large referral interventional clinics in The Netherlands. Four percent of patients were included with NSTEMI, treated with emergency PCI at presentation. All other patients presented with STEMI. Baseline characteristics are shown in Table 1. Seven percent of patients presented with Killip class > 1. Diabetes was present in 10 % of patients. In the Netherlands, a dedicated infrastructure is present to directly refer AMI patients to the catheterization suite of an interventional center without any interference of a local hospital, general practitioner or even the emergency department. First medical contact is typically at the patient's home and median time from this first contact to balloon inflation was only 75 minutes in this study. At diagnosis, the ambulance personnel immediately administer both high dose acetylsalicylic acid and heparin intravenously and in some regions clopidogrel orally.

Procedure

Angiographic and procedural characteristics are shown in table 2. More than 50% of patients had TIMI 0 flow at presentation and single vessel disease. Compared with previous AMI studies, a high percentage of radial access of >50% was used. High dose clopidogrel loading was administered in most patients; there was also a high percentage of Glycoprotein IIb/IIIa receptor blocker use and thrombus aspiration catheter use. No significant differences were seen in all parameters except

Table 1. Baseline Characteristics of the Patients

	EES (n= 404)	SES (n = 221)	p-value
Male gender - no. (%)	295 (73.0)	167 (75.1)	0.57
Age (mean) – yr ± SD	61.2 ± 11.3	62.0 ± 11.4	0.39
Killip class I - no. (%)	377 (93.3)	206 (92.8)	0.79
STEMI - no. (%)	387 (95.8)	213 (96.4)	0.72
NSTEMI - no. (%)	17 (4.2)	8 (3.6)	0.72
History			
Previous Q wave MI - no. (%)	6 (1.5)	7 (3.2)	0.24
Previous non Q wave MI - no. (%)	17 (4.2)	7 (3.2)	0.52
Previous PCI - no. (%)	17 (4.2)	6 (2.8)	0.34
Previous CABG - no. (%)	1 (0.2)	4 1.8)	0.06
Previous stroke - no. (%)	10 (2.5)	12 (5.4)	0.06
Risk factors			
Smoking - no. (%)	220 (54.5)	122 (55.2)	0.86
Diabetes Mellitus - no. (%)	36 (8.9)	25 (11.3)	0.33
Hypertension - no. (%)	119 (29.5)	66 (29.9)	0.92
Family history - no. (%)	172 (42.6)	99 (44.8)	0.59
Renal failure - no. (%)	4 (1.0)	4 (1.8)	0.46
Time (median in minutes)			
symptoms to first medical contact	94 (60 – 180)	97.5 (60 – 186)	0.92
First medical contact to balloon	75 (60 – 103)	75 (61 – 100)	0.58
Infact size (peak in U/l; mean ± SD)			
CPK	1831 ± 1816	1923 ± 1994	0.93
CPK-MB	205 ± 180	216 ± 219	0.96
Pre hospital anticoagulation/antithrombotics			
Aspirin - (%)	85.3	83.1	0.47
Unfractionated heparin - (%)	74.6	71.7	0.43
Clopidogrel loading - (%)	37.3	34.2	0.45
GP 2b/3a blocker iv - (%)	5.2	6.8	0.41
Access site (%)			0.27
Radial	52.0	56.6	
Femoral	48	43.4	
IABP (%)	1.5	1.4	1.00

CABG:Coronary artery bypass grafting; CPK:Creatinin phosphokinase; EES: Everolimus-eluting stent; GP:Glycoprotein; MI:Myocardial infarction; NSTEMI:Non-ST-elevation myocardial infarction; PCI:Percutaneous coronary intervention; SES: Sirolimus-eluting stent; STEMI: ST-elevation myocardial infarction.

Table 2. Angiographic and Procedural Characteristics

	EES (n=404)	SES (n=221)	p-value
Target vessel (%)			0.43
RCA	42.3	36.7	
LAD	38.6	43.0	
RCX	18.8	19.5	
Left main	0	0.5	
Graft	0.2	0.5	
Lesion type (%)			0.44
A	1.2	0	
B1	31.4	32.6	
B2	34.7	34.9	
C	32.7	32.6	
Heavy calcification (%)	5.7	11.0	0.02
Severe tortuosity (%)	11.2	9.5	0.52
Ostial lesion (%)	3.5	5.4	0.24
Bifurcation (%)	11.4	15.8	0.12
Visible Thrombus (%)	85.1	86.4	0.67
TIMI flow (%)			0.74
0	54.5	57.2	
1	6.7	5.0	
2	17.8	15.8	
3	21.0	22.1	
Extend of coronary artery disease (%)			0.54
One vessel	54.2	49.8	
Two vessels	32.7	36.7	
Three vessels	13.1	13.6	
Clopidogrel 300 mg loading (%)	3.2	2.3	0.62
Clopidogrel 600 mg loading (%)	96.0	97.2	0.46
Overall GP2b/3a blocker (%)	74.5	77.8	0.36
Thrombus aspiration (%)	61.9	63.8	0.64
Stent placement (%)	99.5	99.5	1.00
TIMI flow 0-2 (%)	5.0	6.3	0.47
Total stent length target segment (mm)	25.1 ± 13.5	27.9 ± 17.0	0.09
Max stent diameter target segment (mm)	3.1 ± 0.4	3.1 ± 0.4	0.54
Additional treatment other vessel than target (%)	5.2	5.9	0.72
Number of stents per patient	1.3 ± 0.6	1.4 ± 0.7	0.45

GP:Glycoprotein; IABP:Intra-aortic balloon pump; TIMI:Thrombolysis in myocardial infarction.

Table 3. Medication at discharge

	EES (n= 404)*	SES (n=221)*	p-value
ASA	98.5	98.2	0.75
Clopidogrel	98.5	98.6	1.00
Beta blocker	83.7	81.9	0.57
Ace inhibitor	45.8	47.1	0.76
AT II Blocker	5.2	5.9	0.72
Statin	90.6	90.0	0.82
Diuretics	8.9	14.5	0.03
Insulin	3.5	3.6	0.92
Oral antidiabetic	5.7	6.8	0.58
Calcium antagonist	4.0	5.9	0.28
Anticoagulation	2.5	6.8	0.01
Nitrate	4.5	2.3	0.16
Spironolacton	2.2	5.4	0.03
Digoxin	0	0.5	0.35

*: in case of in-hospital mortality, medication was checked at time of death. ASA: acetylsalicylic acid; AT: Angiotensin.

for more heavy calcification in the SES group. Medication at discharge is shown in table 3.

30 day outcome

One patient was excluded because of withdrawal of informed consent. Results can be seen in table 4. Mortality was low and consisted entirely of cardiac mortality. Acute stent thrombosis was seen in 1 patient of each group and definite and/or probable stent thrombosis at 30 day was low at 1.3%. Subacute stent thrombosis was higher with SES though not statistically significant.

1 Year outcome

At 1 year, 1 additional patient withdrew informed consent and was excluded. This withdrawal resulted in a clinical follow-up at 1 year of 99.7%. One year results are listed in table 4. The primary endpoint of MACE, consisting of cardiac death, non-fatal MI or any TVR at 1 year was 4.0 % for EES and 7.7% for SES. The non-inferiority criterion for EES was met with an absolute difference of -3.7% (95% CI: -8.28; -0.03). MACE rate was significantly reduced for EES with a p-value of 0.048 and a relative risk (RR) of 0.52 (95% CI: 0.27; 1.00). Diverging of the MACE-free survival curves can be seen in figure 1. The cardiac death rate was 1.9 % for the total group. Individual endpoints of all-cause mortality, cardiac death, AMI and TVR all showed a consistently slightly higher event rate in the SES group, but this was not statistically significant.

Table 4. Clinical results at 30 days and one year follow-up

	Total	EES	SES	p-
	(n=624) *	(n=403)	(n=221)	value
30 day follow-up - no. (%)				
Death	10 (1.6)	4 (1.0)	6 (2.7)	0.18
Cardiac death	10 (1.6)	4 (1.0)	6 (2.7)	0.18
Non fatal MI	1 (0.2)	0	1 (0.5)	0.35
TVR	7 (1.1)	5 (1.2)	2 (0.9)	1.00
TLR	2 (0.3)	1 (0.2)	1 (0.5)	1.00
Stent thrombosis (definite, probable)	8 (1.3)	3 (0.7)	5 (2.3)	0.14
Acute	2 (0.3)	1 (0.2)	1 (0.5)	1.00
Sub acute	6 (1.0)	2 (0.5)	4 (1.8)	0.19
One Year follow-up- no. (%)	(n=623) †	(n=402)	(n=221)	
MACE ‡	33 (5.3)	16 (4.0)	17 (7.7) §	0.048
Death	15 (2.4)	8 (2.0)	7 (3.2)	0.36
Cardiac death	12 (1.9)	6 (1.5)	6 (2.7)	0.36
Non fatal MI	5 (0.8)	2 (0.5)	3 (1.4)	0.35
TVR	19 (3.0)	10 (2.5)	9 (4.1)	0.27
TLR	7 (1.1)	5 (1.2)	2 (0.9)	1.00
Stent thrombosis (definite, probable)	11 (1.8)	5 (1.2)	6 (2.7)	0.21
Late (30-365 days)	3 (0.5)	2 (0.5)	1 (0.5)	1.00

*: One patient is excluded, withdrawal informed consent. †: In total by 1 year two patients excluded because of withdrawal of consent ‡: MACE is primary endpoint: Cardiac Death, Non fatal MI, any TVR §:Non-inferiority criterion was met, absolute difference -3.7% (95% CI: -8.28; -0.03); p value: 0.048 with RR 0.52 (95% CI: 0.27; 1.00).

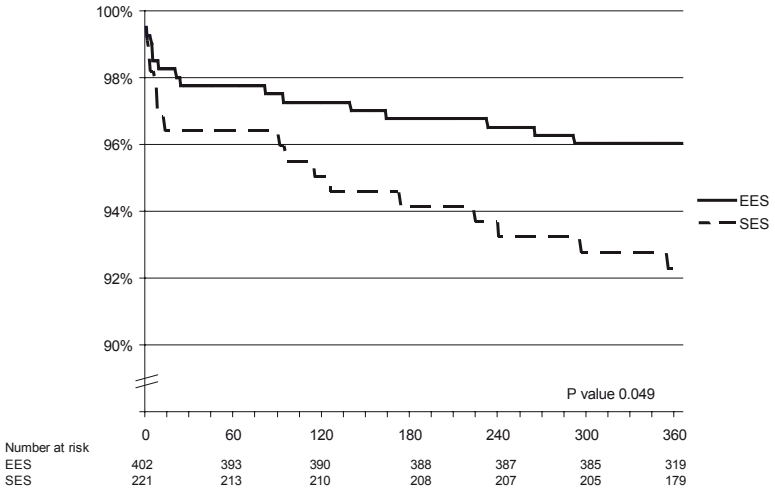

Figure 1. Kaplan-Meier estimates of MACE-free survival at one year of infarct patients randomized to EES and SES.

The overall one year definite and/or probable stent thrombosis rate was 1.8%. The difference between EES (1.2%) and SES (2.7%) could be attributed to an early difference at 30 days. Late stent thrombosis rate beyond 30 day and up to 1 year was identical and 0.5% in each group. At 1 year, 94% of patients were still using clopidogrel, together with ASA or with oral anticoagulants. No significant difference between both groups was seen (data not shown).

Additional "per-protocol analysis", including NSTEMI patients, confirmed robustness of the outcome of the primary endpoint, with a MACE rate of 3.3% (EES) vs 7.8% (SES), p= 0.01; RR 0.43 (95% CI: 0.21; 0.86). Per protocol analysis, excluding the 4% NSTEMI patients which were included in the trial, also revealed a clear benefit of the EES with a MACE rate of 3.5 % vs 7.6 % for SES, p= 0.027, RR 0.46 (95 % CI: 0.22; 0.93).

Discussion

In this randomized trial, the first generation drug-eluting stent, the SES Cypher stent was compared with the second generation EES Xience V stent in patients with AMI. The results show very low MACE rates and low percentages of stent thrombosis at one year in these very thrombotic lesions. Superiority of the EES was shown for the primary endpoint and MACE-free survival curves are still diverging at one year follow-up. Robustness of outcome was confirmed with additional per-protocol analysis.

Study Population

The current study represents a medium mortality risk all-comer AMI population. This is illustrated by the mean peak infarction enzyme levels and comparable to other trials.[12,16] Diabetes was present in only 10 % of patients, which is almost identical to findings from several other Dutch AMI trials.[16,17] Patient characteristics were comparable to other AMI trials like the large HORIZONS-AMI trial[12] and the PASSION trial,[16] and higher risk than the Typhoon trial,[10] in which sirolimus-eluting stents were compared to BMS in AMI patients. In this study, mortality was low and quite similar to our study, but extensive exclusion criteria made this a low mortality risk population.

Event Rates

All-cause mortality and cardiac mortality rates at 1 year were very low in both arms of our study. This may also reflect the progress over the last few years in patient treatment. Pre-medication with aspirin and heparin at the patient's home and direct referral to interventional centers leading to a short " first contact to balloon" times will undoubtedly have an effect on final infarct size and mortality. The use of radial access in over 50 % of cases impacts the risk of bleeding and the morbidity and

mortality related to bleeding complications.[18,19] The benefit of thrombus aspiration was demonstrated in the TAPAS study.[17] Thrombus aspiration was used in almost 63% of cases in the XAMI trial. For comparison, in the HORIZONS-AMI study thrombus aspiration was used in only 11 % of patients. Using these contemporary interventional techniques, DES was associated with a low re-intervention rate at 1 year. Overall TLR rate in this trial was only 1.1 % at 1 year. In-stent restenosis, as seen in BMS in 20% to 23% of patients in TYPHOON and HORIZONS-AMI, may not be benign[20] and reintervention for in–stent restenosis is also associated with complication risks.

The entire cohort of patients in our trial was not treated for STEMI. The inclusion criteria allowed NSTEMI patients to be randomized under strict conditions of indication for emergency PCI at presentation. The pathophysiology of these very unstable lesions will barely differ and frequently also reflect a totally thrombotic occluded vessel in NSTEMI. In our trial only 4% of patients with NSTEMI were included and will not preclude comparison of our event rates with other STEMI trials. Per protocol analysis, excluding the 4% NSTEMI patients, confirmed this hypothesis, showing a clear benefit for EES in MACE rate at 1 year, with a p-value of 0.027.

Stent Thrombosis

The event rate was accompanied by a low rate of definite and/or probable stent thrombosis. The rate for sirolimus-eluting stent was 2.7 % and for everolimus-eluting stent even only 1.2 %. In comparison, rates were 3.1 % for paclitaxel-eluting stents in the largest randomized AMI trial with DES so far, the HORIZONS-AMI. In that trial the bare metal stent thrombosis rate (definite or probable) was 3.4 %. Pre-randomization heparin and a 600 mg clopidogrel loading dose were independent predictors of reduced acute and subacute stent thrombosis in HORIZONS-AMI, respectively.[21] In the XAMI trial a very high percentage of patients received both. The difference in stent thrombosis rates at 30 days was mainly responsible for the difference at one year. Though the influence of procedural and patient characteristics cannot be excluded, it has been suggested that the newer polymer coatings used in second generation DES, like the EES, may have anti-inflammatory properties and may be partly responsible for reduction in early stent thrombosis. Emerging data on delayed healing[6,7] and late endothelial dysfunction after stenting with SES,[8,22] possibly involved in (very late) stent thrombosis, has hampered the use of DES, especially in patients with acute coronary syndromes as their highly thrombotic lesions are more prone to stent thrombosis. Despite this, randomized trials and large risk-adjusted retrospective studies have shown superiority of first generation DES over bare metal stents (BMS) up to several years follow-up.[23,24] Next to a significant decrease in re-interventions, some studies also indicate decreased mortality,[23] although randomized trials have not confirmed this. Despite the promising low percentage of stent thrombosis, long-term follow-up will have to demonstrate safety, as continuing rates of late stent thrombosis have been reported in first generation DES during the first few years.[5,25] Data on improved vascular healing and endotheliali-

zation of second generation DES[7,26] provide some incentive for the hypothesis that in these newer generation DES incremental rates of (very) late stent thrombosis may be ameliorated, even in this highly thrombotic subset of patients. Recently, 2 year follow-up data of large randomized all-comer trials including 20-30 % of AMI patients were presented. Very few additional stent thromboses were seen between one and two year in the EES stent arms,[27-29] as well as in a (not separately randomized) subgroup analysis of AMI patients.[30] The XAMI trial will conduct a follow-up up to 3 years to investigate the incidence of very late ST.

Study Limitations

Despite the fact that this was an all-comer trial and infarct enzymes do not reflect a low-risk population, clinically unstable shock patients were less likely to be enrolled and only 7% of patients were in Killip class > 1. The low MACE rate cannot be extended to the general total AMI population, but patient characteristics were very comparable to most other reported clinical AMI trials comparing DES and BMS as discussed previously. The lesions in the SES group were more calcified and despite comparable peak enzymes in both groups, medication at discharge shows a higher percentage of diuretics and oral anticoagulation use in the SES patients. A small imbalance between groups with lower ejection fraction in the SES group at presentation cannot be excluded, but quantified data on left ventricular function at presentation or follow-up were not collected. The primary objective of the XAMI trial was to demonstrate non-inferiority of the EES for MACE. The trial was not powered for superiority, but at one year follow-up a marginally significant better outcome was seen for EES. According to several statistical papers,[31,32] superiority may be claimed in this case, but a definite verdict is questionable. As MACE curves diverge at one year, longer follow-up may answer this question in the coming years. The trial is not powered to detect significant differences in adverse events like stent thrombosis, which has a low incidence. Very large trials are necessary to be adequately powered for these events. However, our trial has a planned follow-up of three years and continuing trends towards differences in incidence of very late stent thrombosis may be seen at longer follow-up. The cardiologists performing the primary PCI were not blinded to the allocated stent type. This would also not be ethical as each stent type has its own typical behaviour and handling. Despite the higher profile of the sirolimus-eluting stent, only once the operator had to cross over from the SES to EES to cross the lesion. Four times the EES was crossed over to a non-study stent. However, analysis of MACE was performed on “intention to treat” basis and performed by a blinded independent CEC.

Conclusions

In this contemporary all-comer randomized multi-center AMI trial, low MACE rates were seen at 1 year with the use of DES in primary PCI in AMI. Although not pow-

ered for superiority, the second generation everolimus-eluting DES displayed a significantly lower MACE rate than the first generation sirolimus-eluting stent, at least proving non-inferiority and even suggesting superiority. Stent thrombosis rate in EES was very low, but long-term follow-up and larger scale studies will have to show whether the reported continuing stent thrombosis rates beyond one year as shown in first generation DES will also be improved in EES.

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CHAPTER 8

Two-year results of an open-label randomized comparison of everolimus-eluting stents and sirolimus-eluting stents

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Abstract

Background: Second generation drug-eluting stents were developed to improve the safety and efficacy of first generation stents. So far, limited long term randomized data exist comparing the second generation everolimus-eluting stents (EES) with first generation sirolimus-eluting stents (SES).

Methods: A prospective, open-label, randomized, single center trial comparing EES and SES in all-comer patients. The primary endpoint was a composite of cardiac mortality, myocardial infarction and target vessel revascularization. Secondary endpoints included individual components of the composite, along with target lesion revascularization and stent thrombosis.

Results: In total, 977 patients were randomized, of which 498 patients to EES and 479 to SES. Average age was 65.2 ± 11.2 years and 71.6% of the population was male. Fifty percent of patients were treated for acute coronary syndrome, more often for ST-elevation myocardial infarctions in EES patients (13.7% vs. 9.2% in SES). In contrast, SES patients more often had prior interventions and showed more calcified lesions. Two-year follow-up was available in 98% of patients. The primary endpoint occurred in 10.7% of EES patients compared to 10.6% of SES patients (HR 1.00, 95% CI 0.68-1.48). Additionally, secondary endpoints were similar between groups. The rate of stent thrombosis was low for both stent types.

Conclusion: In this all-comer population, there were no differences in endpoints between EES and SES during two-year follow-up. Stent thrombosis rates were low, supporting the safety of drug-eluting stent appliance in clinical practice.

Introduction

First generation drug-eluting stents (DES) have reduced the need for revascularization procedures compared to bare-metal stents.[1] However, introduction of DES did not lead to reductions in mortality and re-infarctions but instead was associated with a higher incidence of late stent thrombosis (ST).[2,3] In order to improve the safety and efficacy of DES, second generation stents were developed. Everolimus-eluting stents (EES) have shown superior outcomes compared to first generation paclitaxel-eluting stents in a wide range of coronary lesions.[4,5] Data is starting to accumulate for the comparison of EES with first generation and previous golden standard sirolimus-eluting stent (SES) but randomized data with long term follow-up are limited.[6,7]

Our goal was to compare the safety and efficacy of the second generation EES with first generation SES in all-comer patients undergoing percutaneous coronary intervention (PCI) during two year follow-up.

Methods

The APPENDIX-AMI trial was a single center, prospective, open-label, randomized clinical superiority trial (NTR3170, http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3170) comparing EES (Xience V [Abbott Vascular, Santa Clara, California]) and SES (Cypher [Cordis, Bridgewater, New Jersey]) in patients treated with PCI for any indication. APPENDIX-AMI was a sub-study of the XAMI trial,[8] and was designed to evaluate the superiority of EES over SES in all-comer patients up to two year follow-up. The protocol for this trial and supporting CONSORT checklist are available as supporting information; see Checklist S1 and Protocol S1. Inclusion ran between 18 September 2007 and 27 May 2010 in the Medical Center Leeuwarden, the Netherlands. Patients had to be eligible for coronary revascularization by PCI and willing to sign informed consent to be entered in the trial. Exclusion criteria were: minor patients, intravenous drug or alcohol abusers, patients unable to give informed consent, patients with a known allergy for everolimus or sirolimus, patients with known intolerance or contra-indications for acetylsalicylic acid or clopidogrel and finally patients in whom stent implantation was not deemed technically possible. Also, patients included in XAMI were not eligible for inclusion in APPENDIX-AMI. Patients were randomized in a 1:1 fashion to EES or SES directly after angiography using sealed envelopes by research nurses. The randomization sequence was based on date of birth, resulting in different stent allocation between uneven and even dates. Operators were not blinded to the allocated stent.

In the power analysis performed for the XAMI trial, a primary endpoint rate of 8 % in both stent groups at 1-year follow-up was assumed. An absolute difference in the primary endpoint between the two stents of 6 % at 1 year was accepted, which

required in total 600 patients when assuming a power of 80%, an alpha of 0.05 and 2:1 randomization to EES versus SES (Farr. & Mann testing method). The population size of 2000 in APPENDIX-AMI was deduced from the power analysis of the XAMI study and was estimated to be able to show a relevant difference in the rate of the primary endpoint between the groups. Inclusion was stopped before reaching 2000 patients after exceeding the planned inclusion period due to a slower than anticipated inclusion.

Ethics statement

The study protocol was approved by the local ethics committee of the Medical Center Leeuwarden and the trial was conducted according to the principles of the Declaration of Helsinki. All patients gave oral consent before enrollment and written informed consent after procedure. Note: APPENDIX-AMI was primarily registered as a sub-study under XAMI (NTR1123, http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1123). Because enrollment for APPENDIX-AMI started earlier than for XAMI, the start of the inclusion period pre-dated the registration of the XAMI study by 1 month.

Procedure

Patients were pretreated with loading doses of aspirin and clopidogrel, in addition to intravenous heparin bolus of 5.000 IE in case of acute myocardial infarction. Interventions were performed according to local practice by high-volume operators. The use of glycoprotein IIb/IIIa inhibitors, thrombus aspiration and balloon pre-dilatation were left up to the discretion of the operator. Aspirin was recommended for life and clopidogrel for a minimum of 1 year.

Follow-up

Protocol-defined follow-up was performed after thirty days, one year and two years by either questionnaires or phone contact. Follow-up was gathered by research nurses in a blinded fashion. Final event adjudication was performed between physicians on a consensus-basis in an unblinded fashion. No routine angiographic follow-up was scheduled. Information about in-hospital outcome was obtained from the institutional clinical database and by review of hospital records of those discharged to referring hospitals. Patient data were collected on case report forms and entered into an online database. Follow-up was planned for three years.

Study endpoints and definitions

The primary endpoint was a composite of cardiac death, myocardial infarction (MI) and target vessel revascularization (TVR). MI was defined as a rise of creatine kinase (CK) more than 3 times the upper limit of normal along with a rise in CK-MB with recurrent symptoms and/or new electrocardiographic changes. In acute coronary syndrome patients, re-infarction within 48 hours after index procedure was

defined as a re-elevation of CK of >1.5 times the previous value with elevation of CK-MB, along with recurrent symptoms and/or new electrocardiographic changes. MI around CABG required a CK rise of >5 times the upper limit or normal. TVR was defined as any repeat percutaneous or surgical intervention on any segment of the target vessel. Secondary endpoints included the individual components of the primary endpoint (cardiac mortality, MI or TVR), in addition to all-cause mortality, target lesion revascularization (TLR) and definite or probable ST. TLR was defined as any repeat intervention or bypass grafting of the target lesion previously treated with stenting along with the 5 mm proximal or distal vessel. ST was defined in accordance with the Academic Research Consortium definitions.[9]

Statistical analyses

Study outcomes were analyzed using both intention-to-treat and per-protocol principle. Continuous variables are presented as means with standard deviations or medians with interquartile range (IQR) and were compared using Student's t-test. Categorical variables are expressed as counts and percentages and were compared by means of Pearson's χ^2 test. All statistical tests were 2-tailed and a p-value <0.05 was considered statistically significant. Time-to-event analyses were performed using Kaplan Meier curves and survival curves were compared using log-rank tests. Finally, cox proportional hazards analyses were performed to calculate unadjusted and adjusted effect sizes. Adjustment for misbalance between the arms was done through multivariable models which included clinical characteristics that significantly differed at baseline. In case of limited events, the clinical characteristics with the strongest effect size were entered into the multivariable models to avoid over-adjustment.

Results

In total, 977 patients were included in the intention-to-treat analysis; 498 patients were randomized to EES and 479 patients to SES. The study flowchart is shown in Figure 1. Baseline characteristics (Table 1) showed that the average age was 65.2 ± 11.2 years and 71.6% of the population was male. Patients in the EES arm less commonly suffered a history of hypertension and also less frequently had undergone previous PCI or coronary artery bypass grafting compared to SES patients. Furthermore, indication for PCI was more commonly ST-elevation myocardial infarction in EES patients, balanced by a higher percentage of PCI for stable angina in patients included in the SES arm. Angiographic and procedural characteristics are shown in Table 2. EES patients showed a lower percentage of heavily calcified coronary lesions compared to SES patients. Also, the vascular access site differed significantly, with slightly more radial access in the EES arm. Finally, EES patients were treated more frequently with glycoprotein IIb/IIIa inhibitors compared to patients in the SES arm.

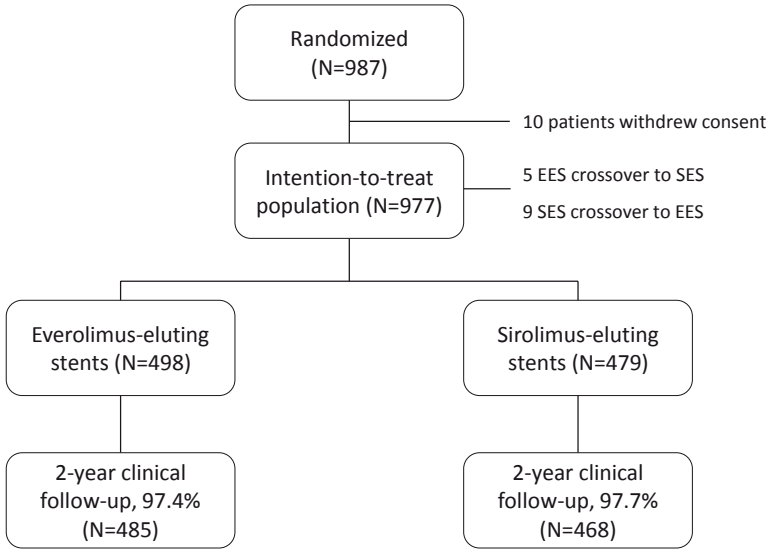

Figure 1. Study flowchart.

Table 1. Baseline characteristics

	EES (N=498)	**SES** (N=479)	p Value
Age, years	65.3 ± 11.3	65.0 ± 11.2	0.688
Male	353 (70.9)	347 (72.4)	0.589
Risk factors			
Insulin dependent diabetes mellitus	22 (4.6)	29 (6.3)	0.248
Non-insulin dependent diabetes mellitus	28 (5.8)	41 (8.9)	0.072
Hypertension	208 (42.8)	238 (51.0)	0.012
Hypercholesterolemia	249 (53.7)	251 (54.9)	0.701
Family history of cardiovascular disease	263 (55.3)	256 (55.9)	0.843
Current smoker	133 (27.4)	107 (23.2)	0.137
Previous myocardial infarction	109 (22.1)	108 (22.7)	0.829
Previous percutaneous coronary intervention	83 (16.8)	108 (22.5)	0.023
Previous coronary artery bypass grafting	50 (10.1)	72 (15.0)	0.019
Renal insufficiency	53 (11.6)	45 (10.3)	0.542
Indication for percutaneous coronary intervention			
Stable angina	251 (50.4)	275 (57.4)	0.028
Non ST-segment elevation myocardial infarction or unstable angina	179 (35.9)	160 (33.4)	0.404
ST-segment elevation myocardial infarction	68 (13.7)	44 (9.2)	0.028

Table 2. Angiographic and procedural characteristics

	EES (N=498)	**SES** (N=479)	p Value
Target vessel location			0.109
Left main artery	26 (5.3)	15 (3.2)	
Left anterior descending artery	214 (43.4)	184 (38.7)	
Left circumflex artery	106 (21.5)	131 (27.5)	
Right artery	145 (29.4)	144 (30.3)	
Bypass graft	2 (0.4)	2 (0.4)	
Lesion type			0.251
A	24 (4.9)	35 (7.4)	
B1	192 (39.1)	173 (36.5)	
B2	176 (35.8)	158 (33.3)	
C	99 (20.2)	108 (22.8)	
Heavy calcification	65 (13.2)	89 (18.7)	0.019
Chronic total occlusion	18 (3.7)	25 (5.3)	0.229
Bifurcation lesion	116 (23.7)	100 (21.1)	0.338
Visible thrombus	89 (18.1)	72 (15.2)	0.221
Thrombus aspiration	11 (2.3)	7 (1.5)	0.379
Extent of coronary artery disease			0.688
1-vessel	227 (45.7)	208 (43.4)	
2-vessel	171 (34.4)	166 (34.7)	
3-vessel	99 (19.9)	105 (21.9)	
Access site			0.019
Radial	302 (61.1)	255 (53.7)	
Femoral	192 (38.9)	220 (46.3)	
Rotablation	8 (1.6)	4 (0.8)	0.271
Glycoprotein IIb/IIIa blocker	143 (29.2)	106 (22.3)	0.015
Total stent length (mm)	28.1 ± 19.2	28.1 ± 15.8	0.942
Max stent diameter (mm)	3.1 ± 0.6	3.1 ± 0.5	0.199
Multivessel intervention	95 (19.3)	94 (19.7)	0.851
Number of stents/patients	1.50 ± 0.76	1.47 ± 0.76	0.477

Clinical outcomes at two years (Table 3, Figure 2) were balanced between patients treated with EES and SES, resulting in a HR of 1.00 (95% CI 0.68-1.48) for the primary endpoint rate. This did not change after adjustment for potential misbalance between the two groups: EES showed a HR of 1.02 (95% CI 0.68-1.53) compared to SES for the primary endpoint rate. Furthermore, per-protocol analysis showed identical results: implantation of EES resulted in a HR of 0.99 (95% 0.81-1.20) for

the primary endpoint compared to SES.

During follow-up, use of dual antiplatelet was similar between the groups. Aspirin (or coumadin when indicated) was used for at least 1 year in 97.8% of EES and 99.3% of SES patients (p=0.053), while 97.7% of EES and 97.8% of SES patients used aspirin for at least 2 years (p=0.943). Clopidogrel was used for at least 1 year in 97.3% of EES and 97.3% of SES patients (p=0.977), while 12.6% of EES and 11.0% of SES patients used clopidogrel at the 2-year follow-up moment (p=0.445).

Table 3. Clinical outcomes at 2 years

	EES (N=498)	**SES** (N=479)	p Value	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Major adverse cardiac events*	52 (10.7)	50 (10.6)	0.990	1.00 (0.68-1.48)	1.02 (0.68-1.53)
Mortality					
All-cause	28 (5.7)	22 (4.7)	0.453	1.24 (0.71-2.16)	1.28 (0.72-2.27)
Cardiac	18 (3.7)	12 (2.6)	0.309	1.46 (0.70-3.03)	1.52 (0.72-3.22)
Myocardial infarction	4 (0.9)	8 (1.7)	0.224	0.48 (0.15-1.60)	0.52 (0.16-1.74)
Revascularizations					
Any	57 (11.8)	58 (12.4)	0.768	0.95 (0.66-1.36)	0.92 (0.62-1.35)
Target vessel revascularization	35 (7.3)	34 (7.3)	0.998	0.99 (0.62-1.60)	1.05 (0.65-1.69)
Target lesion revascularization	20 (4.1)	18 (3.9)	0.818	1.08 (0.57-2.04)	1.09 (0.57-2.08)
Definite stent thrombosis	2 (0.4)	4 (0.9)	0.395	0.49 (0.09-2.66)	0.56 (0.10-3.07)
Early (0 to 30 days)	0 (0.0)	1 (0.2)	0.308		
Late (30 days to 12 months)	0 (0.0)	1 (0.2)	0.308		
Very late (>12 months)	2 (0.4)	2 (0.4)	0.971		
Definite/probable	3 (0.6)	6 (1.3)	0.295	0.49 (0.12-1.94)	0.52 (0.13-2.09)

Percentages are cumulative incidences of events based on survival tables.
*Cardiac mortality, myocardial infarction and target vessel revascularization
CI = confidence interval; HR = hazard ratio.

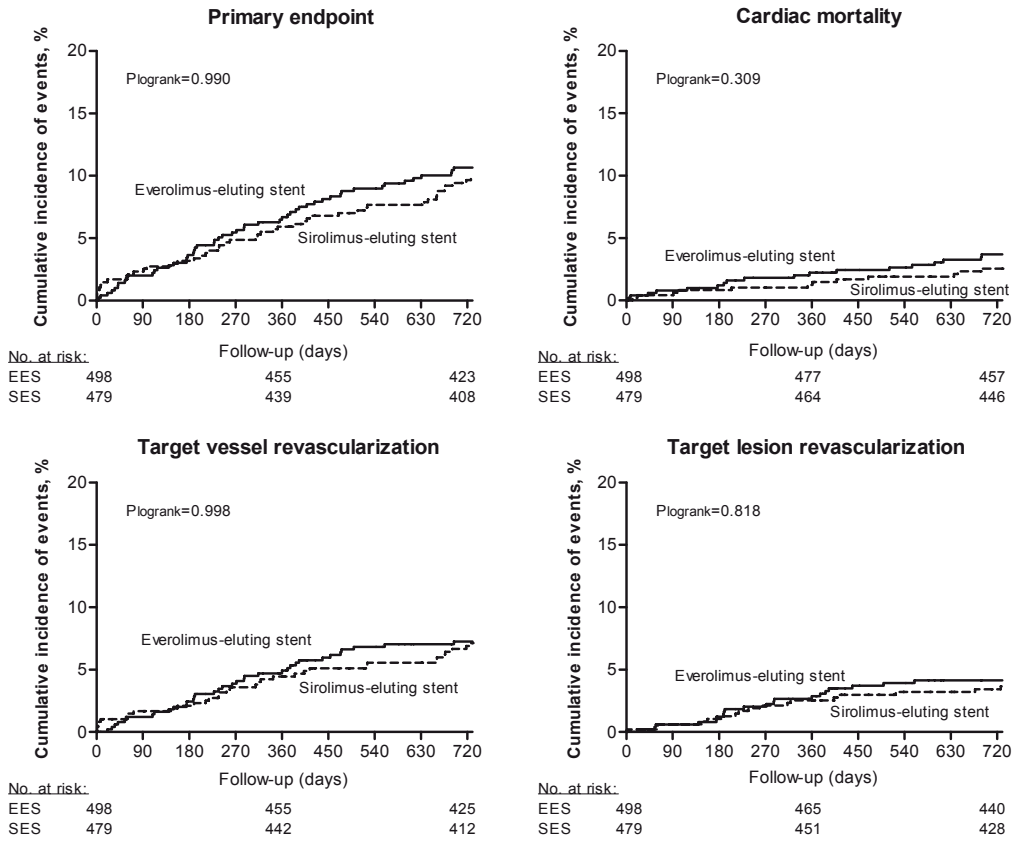

Figure 2. Two-year clinical outcomes. Primary endpoint = composite of cardiac mortality, MI and target vessel revascularization.

Discussion

In the present open-label, randomized clinical trial, the primary endpoint was comparable between EES and SES during 2-year follow-up. Moreover, secondary endpoints were balanced and definite ST was low in both groups, supporting the safety of DES appliance in clinical practice.

The heightened occurrence of late ST in first generation DES compared to bare-metal stents led to the development of next generation stents in attempt to improve the safety and efficacy of DES.[2,3] The COMPARE and SPIRIT trials established the superiority of EES over first generation paclitaxel-eluting stents.[4,5] Major trials comparing EES with SES, the previous golden standard DES, are on-going but so far mostly limited to 1-year follow-up. The current trial compared EES and SES in an all-comer population, which included a high percentage of acute coronary syndromes and complex lesions such as bifurcations and chronic total occlusions. No differences in the primary and secondary endpoints between the 2 limus-based stents were

observed during 2-year follow-up.

The findings of this single-center trial are in accordance with the results of the SORT OUT IV (Scandinavian Organization for Randomized Trials with Clinical Outcome IV) Trial.[6] The Danish investigators found no differences in clinical endpoints during 2-year follow-up, with the exception of a lower rate of definite ST in EES patients. ST rates found in SORT OUT IV mirror our results, albeit that the current study was underpowered to detect a difference in ST rates. The largest follow-up available to date exists in the ISAR-TEST-4 (Intracoronary Stenting and Angiographic Results: Test Efficacy of 3-Limus-Eluting Stents-4) trial, showing no differences in outcome up to 3 years.[7] As both arms of the permanent polymer part of the trial consisted of approximately 650 patients, this trial was most likely also underpowered to detect differences in ST. Consistent among all previous trials was the similar efficacy of both stent types. The RESET (Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial) and the EXCELLENT (Efficacy of Xience/Promus Versus Sirolimus-Eluting Stents in Patients Undergoing Percutaneous Coronary Intervention) trials further support this by showing comparable rates of late luminal loss in these stents during 1-year follow-up.[10,11] The comparable efficacy is explained by the chemically similar antirestenotic drugs with a virtually identical elution pattern applied in these stents, albeit that the total dose is lower in the EES. The characteristics that set EES apart from SES are the slim 81µm struts covered with biocompatible fluoropolymer. Compared to the 140 µm struts with polyethylene-co vinyl acetate + poly n-butyl methacrylate polymer used in SES, endothelialization is faster after EES implantation. This possibly explains the slight safety benefit of EES over SES as incomplete endothelialization of strut surface is a substrate for stent thrombosis.[12] The important influence of polymer on ST was further emphasized in the LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial, which showed an improvement of (very) late ST rates after implantation of stents with a biodegradable polymer compared to conventional SES.[13] The question whether the final solution of long term safety issues will be provided by complete disappearance of the stent structure is currently under investigation in the ABSORB II trial.[14]

Additional studies focused on comparison of EES with second generation Resolute zotarolimus-eluting stents. In both the RESOLUTE All Comers trial and the TWENTE trial, no differences in outcome between EES and zotarolimus-eluting stents were observed.[15,16] Importantly, both stents showed low rates of ST during follow-up, supporting the safety of DES appliance in clinical practice.

Limitations

There are several limitations that apply to the current study. The randomization sequence was based on date of birth, which may have been the cause of the partial misbalance between the groups, theoretically influencing the outcomes. However, adjustment for baseline differences using cox proportional hazards analyses resulted in only marginal changes in the effect sizes for the individual endpoints, sug-

gesting that the misbalance between the arms was of little influence. Furthermore, the required population size was deduced from the power analysis of the primary study, the XAMI trial. An independent power analysis may have been more accurate. Moreover, the final number of patients was not reached due to inclusion that was slower than anticipated and therefore, the trial was underpowered to discriminate between rare events such as ST. Operators were not blinded to the allocated stent and event adjudication was performed in an unblinded fashion. This reduced the objectivity of the results although the adjudication on consensus basis makes it unlikely that one of the stent types would have been favored. Finally, SES are no longer in clinical use. However, monitoring clinical outcomes of current and previously used stents is necessary to provide further evidence for existing devices and guide future developments of newer generation stents.

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CHAPTER 9

Everolimus- and sirolimus-eluting stent implantation in patients with and without ST-segment elevation myocardial infarction

Submitted.

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Abstract

Background: Everolimus-eluting stents (EES) were superior to sirolimus-eluting stents (SES) in a dedicated myocardial infarction trial, a finding that was not observed in trials with low percentages of ST-elevation myocardial infarction (STEMI). Therefore, this study sought to investigate the influence of clinical presentation on outcome after EES and SES implantation.

Methods: A pooled population of 1602 randomized patients was formed from XAMI (acute MI trial) and APPENDIX-AMI (all-comer trial). Primary outcome was cardiac mortality, MI and target vessel revascularization at 2-years. Secondary endpoints included definite/probable stent thrombosis (ST). Adjustment was done using cox regression.

Results: In total, 902 EES and 700 SES patients were included, of which 44% STEMI patients (EES 455;SES 257) and 56% without STEMI (EES 447;SES 443). In the pooled population, EES and SES showed similar outcomes during follow-up. Moreover, no differences in the endpoints were observed after stratification according to presentation. Although a trend toward reduced early definite/probable ST was observed in EES compared to SES in STEMI patients, long term ST rates were low and comparable.

Conclusions: EES and SES showed similar outcome during two-year follow-up, regardless of clinical presentation. Long term safety was excellent for both devices, despite wide inclusion criteria and a large sub-population of STEMI patients.

Introduction

Drug-eluting stents (DES) were designed to reduce the in-stent neointimal hyperplasia that commonly occurred in bare-metal stents (BMS). Indeed, first generation DES (i.e. paclixatel-eluting stents (PES) and sirolimus-eluting stents (SES)) reduced the need for revascularization procedures compared to BMS but were associated with higher rates of late stent thrombosis (ST), especially in complex patients such as those presenting with myocardial infarction (MI).[1-3]

Delayed arterial healing and stent malapposition were found to play a role in the higher ST rates after DES implantation in setting of MI.[4-5] Second generation DES were designed to be safer and more effective through changes in stent alloy, strut configuration, polymer and anti-restenotic drugs. So far, second generation everolimus-eluting stents (EES) have shown superior results to PES in a wide range of indications.[6] Compared to SES, EES have mostly shown comparable outcomes but improvements in ST rates have been observed.[7-10] In contrast, one dedicated trial of predominantly ST-segment elevation myocardial infarction (STEMI) patients showed superiority of EES over SES during short term follow-up.[11] Long term randomized data are scarce, especially in setting of STEMI.

This study sought to investigate the influence of clinical presentation on outcome of EES and SES during two-year follow-up.

Methods

Patient-level data from the randomized XAMI and APPENDIX-AMI trials were pooled to form the patient population. The design and results of these trials have been published previously.[11,12] In short, XAMI (NTR1123, http://www.trialregister.nl/trialreg/admin/ctview.asp?TC=1123) was a multicenter, clinical non-inferiority trial randomizing 625 acute MI patients to EES (Xience V [Abbott Vascular, Santa Clara, California]) or SES (Cypher [Cordis, Bridgewater, New Jersey]) in a 2:1 ratio. To be enrolled, patients had to have STEMI or non-STEMI with an emergency indication for percutaneous coronary intervention (PCI). Exclusion criteria were: chronic total occlusion as target lesion; known allergy to sirolimus, everolimus, aspirin or clopidogrel; inability to obtain informed consent; life expectancy <1 year or stent size required to treat lesion >3.5 mm.

APPENDIX-AMI (NTR3170, http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3170) was a single center open-label trial randomizing 977 all-comer patients to EES and SES (ratio 1:1). The trial included all patients eligible for coronary revascularization by PCI for any indication. Exclusion criteria were: minor patients; intravenous drug or alcohol abusers; patients unable or unwilling to give informed consent; known allergy for everolimus or sirolimus; known intolerance or con-

tra-indications for acetylsalicylic acid or clopidogrel and anatomy in which stent implantation was not deemed technically possible.

Patients were pretreated with loading doses of aspirin and clopidogrel, in addition to intravenous heparin bolus of 5.000 IE in case of acute MI. Interventions were performed according to local practice by high-volume operators. Use of glycoprotein IIb/IIIa inhibitors, thrombus aspiration and balloon pre-dilatation were left up to the discretion of the operator. Aspirin was recommended for life and clopidogrel for a minimum of 1 year. Protocol-defined follow-up was performed after thirty days, one year and two years by questionnaires and phone contact. Follow-up was gathered by research nurses in a blinded fashion. Event adjudication was performed by a blinded clinical event committee in XAMI. In APPENDIX-AMI, event adjudication was performed between physicians on a consensus-basis in an unblinded fashion. The study protocols were approved by the local ethics committees of the participating centers and the trials were conducted according to the principles of the Declaration of Helsinki. All patients gave oral consent before enrollment and written informed consent after procedure.

Definitions

The primary endpoint was a composite of cardiac death, MI and target vessel revascularization (TVR). MI was defined as a rise of creatine kinase (CK) more than 3 times the upper limit of normal along with a rise in CK-MB with recurrent symptoms and/or new electrocardiographic changes. In acute coronary syndrome patients, re-infarction within 48 hours after index procedure was defined as a re-elevation of CK of >1.5 times the previous value with elevation of CK-MB, along with recurrent symptoms and/or new electrocardiographic changes. MI around coronary artery bypass grafting required a CK rise of >5 times the upper limit or normal. TVR was defined as any repeat percutaneous or surgical intervention on any segment of the target vessel. Other secondary endpoints included the individual components of the composite endpoint, target lesion revascularization (TLR) and definite or probable ST. TLR was defined as any repeat intervention or bypass grafting of the target lesion previously treated with stenting along with the 5 mm proximal or distal vessel. ST was defined in accordance with the Academic Research Consortium definitions.[13]

Statistical analyses

Comparisons were made according to randomized treatment and presentation with or without STEMI. Continuous variables are presented as means with standard deviations or medians with interquartile range (IQR) and were compared using Student's t-test. Categorical variables are expressed as counts and percentages and were compared by means of Pearson's χ^2 test. All statistical tests were 2-tailed and a p-value <0.05 was considered statistically significant. Time-to-event analyses were performed using Kaplan Meier curves, which were compared using log-rank tests. To adjust for unbalanced baseline characteristics, cox proportional hazards analy-

ses were performed. The proportional hazards assumption was investigated visually. Adjusted effect sizes were calculated for primary and secondary endpoints with a p-value less than 0.10 as judged by log rank test. Adjustment was performed for characteristics significantly differing between groups ($p<0.05$), which were incorporated in the multivariable models. Analyses were repeated with a variable stating the trial the patient originated from, to evaluate the influence of individual trials on the results.

To avoid dropping of events due to missing baseline information, multiple imputation was performed for the baseline variables that were included in the multivariable models: presence of heavy calcification was unknown in 4 patients (3 EES and 1 SES) and total stent length was unknown in 4 patients (3 EES and 1 SES). Reasons for missing data were unknown and assumed to be random. Total stent length was log transformed to meet the assumption for normal distribution. Missing data values were imputed for heavy calcification and total stent length using the following predictors: age, gender, cardiac risk factors, cardiac history, renal insufficiency, indication for PCI, target lesion, lesion type, number of vessel disease, heavy calcification, total stent length, max stent diameter, number of stents per patient. Twenty imputed datasets were created and cox proportional hazards analyses were performed on the pooled datasets.[14] Analyses were performed using IBM SPSS version 21.

Results

In total, 1602 patients were randomized in the XAMI and APPENDIX-AMI trials, of which 902 to EES and 700 to SES. Two year follow-up data was available for 1575 patients (98.3%). The presenting diagnosis was stable angina in 526 patients (32.8%), unstable angina or non-STEMI in 364 patients (22.7%) and STEMI in 712 patients (44.4%). After pooling of the 2 trials, the primary endpoint occurred in 8.8% of EES patients vs. 10.2% of SES patients during 2-year follow-up in the overall population, HR 0.86 (95% CI 0.62-1.18), p=0.347. Secondary endpoints were also balanced between the groups.

Stratification on presenting diagnosis

STEMI patients were younger than patients without STEMI and more likely to smoke but had lower rates of comorbidity and other risk factors (Table 1). Coronary thrombus was more common in STEMI, but rates of heavy calcification, bifurcations and multivessel disease were lower. Stent length and number of stents used were also lower in STEMI, but stent diameter was slightly larger. Finally, glycoprotein IIb/IIIa inhibitor use was more common in STEMI while TIMI 3 flow after procedure was less often achieved. During 2 year follow-up, STEMI patients showed lower rates of the primary endpoint (7.2% vs. 11.2%, p=0.007) and TLR (1.4% vs. 4.1%, p=0.001) compared to patients without STEMI.

Table 1. Baseline characteristics

Variable	STEMI			Other indications		
	EES (N=455)	SES (N=257)	p Value	EES (N=447)	SES (N=443)	p Value
Age, years	61.8 ± 11.4	62.4 ± 11.5	0.501	65.2 ± 11.3	65.1 ± 11.1	0.868
Male	329 (72.3%)	194 (75.5%)	0.356	319 (71.4%)	319 (72.0%)	0.831
Diabetes mellitus	41 (9.1%)	26 (10.2%)	0.612	73 (16.9%)	80 (18.6%)	0.492
Hypertension*	136 (30.1%)	81 (31.8%)	0.643	191(43.6%)	223 (51.5%)	0.020
Hypercholesterolemia†	124 (27.8%)	60 (23.8%)	0.250	242 (57.5%)	246 (57.9%)	0.906
Current smoker	232 (51.3%)	135 (53.1%)	0.642	121 (27.6%)	94 (21.9%)	0.051
Prior myocardial infarction	32 (7.0%)	19(7.4%)	0.858	100 (22.6%)	102 (23.2%)	0.844
Prior PCI	19 (4.2%)	9 (3.5%)	0.653	81 (18.2%)	105 (23.7%)	0.046
Prior CABG	4 (0.9%)	5 (1.9%)	0.221	47 (10.5%)	71 (16.0%)	0.016
Prior renal insufficiency	8 (1.8%)	6 (2.4%)	0.596	49 (11.8%)	43 (10.6%)	0.598
Presenting diagnosis						0.072
Stable angina	0 (0.0%)	0 (0.0%)	-	251 (56.2%)	275 (62.1%)	
Unstable angina or Non-STEMI	0 (0.0%)	0 (0.0%)	-	196 (43.8%)	168 (37.9%)	
STEMI	455 (100%)	257(100%)	-	0 (0.0%)	0 (0.0%)	-
Symptoms to first medical contact (min)	90 (60-170)	100 (60-185)	0.419	-	-	
First medical contact to balloon inflation (min)	75 (60-100)	75 (60-100)	0.937	-	-	

Data are expressed as mean ± SD, as number (percentage), or as median (interquartile range). CABG = Coronary artery bypass grafting. * Blood pressure 140/90 mm Hg or previous pharmacologic treatment. † Total cholesterol 190 mg/dl or previous pharmacologic treatment.

Table 2. Procedural characteristics

Variable	STEMI			Other indications		
	EES (N=455)	SES (N=257)	p Value	EES (N=447)	SES (N=443)	p Value
Target coronary lesion			0.651			0.108
Left main artery	0 (0.0%)	1 (0.4%)		26 (5.9%)	15 (3.4%)	
Left anterior descending artery	175 (38.5%)	104 (40.5%)		195 (44.0%)	175 (39.8%)	
Left circumflex artery	86 (18.9%)	50 (19.5%)		96 (21.7%)	124 (28.2%)	
Right coronary artery	192 (42.3%)	101 (39.3%)		124 (28.0%)	124 (28.2%)	
Bypass graft	1 (0.2%)	1 (0.4%)		2 (0.5%)	2 (0.5%)	
Multivessel disease	206 (45.3%)	130 (50.6%)	0.173	249 (55.8%)	252 (56.9%)	0.751
Bifurcation intervention	55 (12.1%)	37 (14.4%)	0.390	107 (24.4%)	98 (22.4%)	0.496
Heavy calcification	26 (5.8%)	28 (10.9%)	0.013	62 (14.0%)	85 (19.4%)	0.032
Lesion type B2/C	300 (66.7%)	171 (67.6%)	0.803	245 (55.4%)	241 (55.0%)	0.903
Visible thrombus	383 (84.5%)	223 (87.1%)	0.352	49 (11.1%)	39 (8.9%)	0.276
Thrombosuction	250 (54.9%)	142 (55.3%)	0.937	11 (2.5%)	6 (1.4%)	0.222
Total stent length (mm)	25.3 ± 14.7	27.7 ± 16.5	0.046	28.2 ±18.9	28.2 ±16.0	0.986
Max stent diameter (mm)	3.1 ± 0.4	3.1 ± 0.3	0.676	3.1 ± 0.6	3.1 ± 0.5	0.436
No. of stents/patients	1.4 ± 0.7	1.4 ± 0.7	0.396	1.5 ± 0.7	1.5 ± 0.8	0.475
Glycoprotein IIb/IIIa inhibitor treatment	346 (76.0%)	196 (76.3%)	0.947	98 (22.3%)	82 (18.7%)	0.181
Postprocedural TIMI flow grade 3	431 (94.9%)	238 (92.6%)	0.206	428 (98.2%)	420 (97.0%)	0.262

Data are expressed as number (percentage) or as mean ± SD. TIMI = thrombolysis in myocardial infarction.

In the STEMI population, EES patients less frequently showed heavily calcified lesions and total stent length was shorter compared to SES (Table 2). During two-year follow-up, randomization to EES resulted in a similar primary endpoint rate (unadjusted HR 0.63, 95% CI 0.36-1.09, p=0.097, adjusted HR 0.66, 95% CI 0.38-1.15, p=0.141) compared to SES (Table 3, Figure 1). A trend was observed for a reduction in early definite/probable ST in EES. However, long term ST rates were low and similar (Figure 2). At 1-year, aspirin (or coumadin) compliance was 94.8% in EES versus 91.5% in SES (p=0.092). Thienopyridine compliance was 95.6% in EES versus 91.8% in SES (p=0.040). Two patients were not on dual antiplatelet therapy at the time of ST, 1 EES and 1 SES patient, both suffering probable ST.

Table 3. Clinical endpoints at 2-year

	STEMI			**Other indications**		
Variable	EES	SES	p	EES	SES	p
	(N=450)	(N=257)	Value	(N=436)	(N=432)	Value
Primary composite endpoint*	27 (6.0)	24 (9.3)	0.099	51 (11.7)	46 (10.6)	0.624
Mortality						
All-cause	15 (3.3)	14 (5.4)	0.173	25 (5.7)	19 (4.4)	0.370
Cardiac	10 (2.2)	8 (3.1)	0.470	16 (3.7)	10 (2.3)	0.242
Myocardial infarction	6 (1.3)	5 (1.9)	0.527	6 (1.4)	8 (1.9)	0.578
Target vessel revascularization	15 (3.3)	13 (5.1)	0.258	33 (7.6)	32 (7.4)	0.928
Target lesion revascularization	7 (1.6)	3 (1.2)	0.674	19 (4.4)	17 (3.9)	0.755
Stent thrombosis						
Definite	3 (0.7)	0 (0.0)	0.190	3 (0.7)	4 (0.9)	0.695
Definite/probable	6 (1.3)	7 (2.7)	0.186	4 (0.9)	5 (1.2)	0.727
Early	3 (0.7)	6 (2.3)	0.057	1 (0.2)	2 (0.5)	0.558
Late	2 (0.4)	1 (0.4)	0.913	0 (0.0)	1 (0.2)	0.315
Very late	1 (0.2)	0 (0.0)	0.449	3 (0.7)	2 (0.5)	0.661

Values are expressed as number (percentage). *Cardiac mortality, myocardial infarction and target vessel revascularization.

In the population without STEMI, EES patients showed lower rates of hypertension, prior PCI, bypass grafting and heavy calcification compared to SES patients (Table 1, Table 2). At 2-years, EES and SES showed similar rates of the primary endpoint (HR 1.10, 95% CI 0.74-1.64, p=0.637) (Table 3, Figure 3). Other secondary endpoints were also balanced. Definite/probable ST rates were low and similar between the groups (Figure 4). Aspirin compliance during 1-year was 97.6% in EES and 99.3% in SES (p=0.047). Thienopyridine compliance was 96.8% in EES and 97.5% in SES (p=0.518).

The p-value for interaction between randomized stent and presenting diagnosis (STEMI vs. other) was 0.104 (HR 1.76, 95% CI 0.89-3.46) for the primary endpoint.

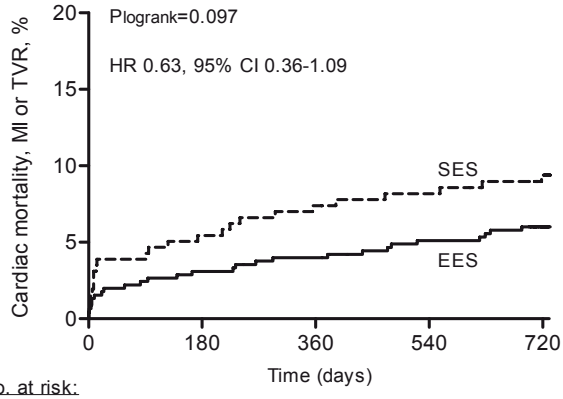

Figure 1. Two-year primary outcome according to randomized stent in STEMI patients. Primary composite endpoint = cardiac mortality, MI, TVR.

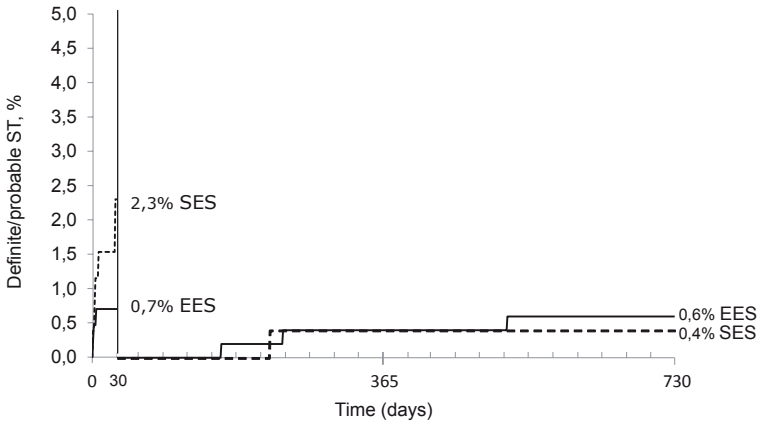

Figure 2. Definite/probable stent thrombosis with landmark analysis at 30-days in STEMI population.

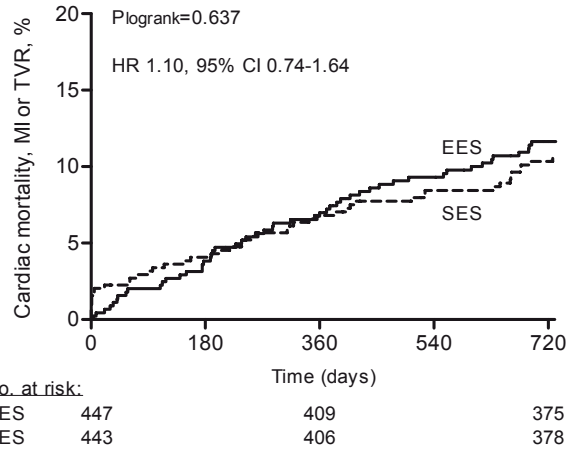

Figure 3. Two-year primary outcome according to randomized stent in patients without STEMI. Primary composite endpoint = cardiac mortality, MI, TVR.

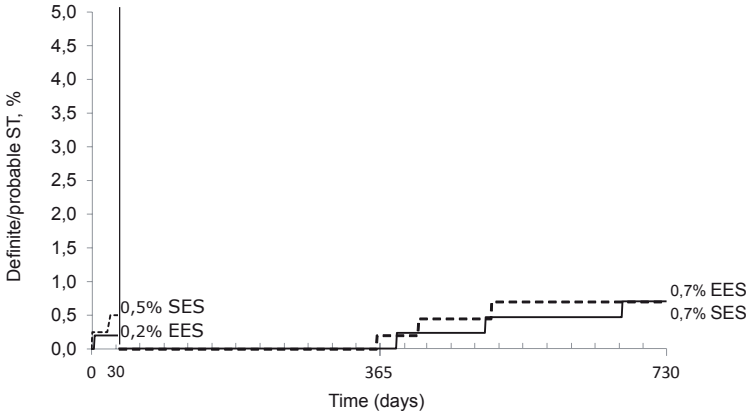

Figure 4. Definite/probable stent thrombosis with landmark analysis at 30-days in population without STEMI.

Discussion

The present pooled analysis of the randomized XAMI and APPENDIX-AMI trials provided 2-year outcome data of EES and SES according to clinical presentation. The performance of the first and second generation DES was found to be similar and independent of clinical presentation. Importantly, despite wide inclusion criteria and a large sub-population of STEMI patients, both devices showed a comparable safety at long term follow-up.

Implantation of first generation DES in the previously off-label indication of acute MI was controversial until publication of the HORIZONS-AMI trial, which confirmed the safety and efficacy of PES compared to BMS in primary PCI.[15] Supe-

riority of second generation EES over PES in acute coronary syndromes has been established but data comparing EES with previous golden standard SES are less abundant, especially in setting of STEMI.[16] In SORT OUT IV, EES and SES showed comparable outcomes up to 2 years, with the exception of a lower rate of definite ST in EES patients.[7] However, only 10% of patients presented with STEMI. The other major trials that compared EES and SES showed no differences in outcome up to 3-year follow-up.[8-10] Also in these trials, the STEMI population was strongly underrepresented, making randomized data of EES and SES in STEMI patients scarce beyond 1-year. In contrast, almost half of patients included in the current study presented with STEMI.

In the STEMI population of the present study, event rates were lower than in the population without STEMI, likely explained by the more complex coronary artery disease in an all-comer population compared to the usually less complex thrombotic lesions of STEMI patients. Although EES appeared to perform slightly better than SES, no significant differences in the primary outcome measure were observed. Nonetheless, a strong trend toward reduced early definite/probable ST hinted at a possible advantage of EES over SES in the early phase after MI. In contrast, clinical outcomes were balanced between EES and SES in patients presenting with a diagnosis other than STEMI, which is in accordance with previous trials.[8-10]

Findings observed in the STEMI population were comparable to reports of the EXAMINATIONS trial, in which EES use resulted in a lower rate of early definite/probable ST compared to BMS in STEMI patients.[17] At 1-year, the definite/probable ST rate was 0.9% in the EES group; comparable to the 1.1% rate observed in this study. Additionally, Kalesan et al. performed a propensity matched comparison of EES and SES in ACS patients and found a reduction in both the primary endpoint and ST during 3-year follow-up.[18]

Important differences of EES compared to SES are the thin strut design (81 μm vs. 140 μm) and the biocompatible polymer. In ex-vivo and in-vivo models, thin struts were less thrombogenic and the slim design of EES has been associated with faster endothelialization compared to SES.[19,20] Also, the biocompatible polymer of EES may be associated with a reduced long term inflammatory response. While the current study found reassuringly low rates of ST in both DES up to 2-year follow-up, very long term monitoring is necessary to establish a potential benefit of EES over SES. This is relevant because in the TYPHOON trial, SES showed a late 'catch-up' phenomenon for ST, i.e. the relatively low early ST rates were abolished by higher very late ST rates compared to BMS in STEMI patients during 4 year follow-up.[21]

Although the polymer applied in EES is more biocompatible than the SES polymer coating, additional improvement may be achieved with a biodegradable polymer coating. The COMFORTABLE AMI trial compared biolimus-eluting stents with BMS in STEMI patients but did not find a reduction in 1-year definite/probable ST.[22] However, long term follow-up will have to show if STEMI patients benefit from DES with

biodegradable polymer, as the main effect of a biodegradable polymer in reducing ST becomes evident after 1 year.[23]

Limitations

Our study is limited by its post hoc nature and therefore findings should be considered hypothesis-generating. XAMI included patients with STEMI or NSTEMI with emergency indication, while APPENDIX-AMI included all-comer patients. Furthermore, the randomization rate differed between XAMI (2:1) and APPENDIX-AMI (1:1) which created baseline misbalance between the groups, although multivariable corrections were performed to correct for these differences. Also, the analysis was underpowered to detect differences in the ST rates.

Conclusions

The present pooled analysis of the XAMI and APPENDIX-AMI trials found similar outcomes between EES and SES during 2-year follow-up, regardless of presenting diagnosis. Long term ST rates were reassuringly low in both stent types.

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CHAPTER 10

Summary, conclusions and future perspectives

Samenvatting, conclusies en toekomstperspectieven

Summary

The general introduction of this thesis (**Chapter 1**) provided an overview of the epidemiology, pathophysiology, risk factors and diagnosis of coronary heart disease with a focus on ST-elevation myocardial infarction (STEMI). Additionally, a historical background of STEMI treatment was provided, with an extensive overview on coronary stenting. The final section discussed risk stratification of STEMI patients.

The identification of patients at risk for recurrent events is more important than ever, in the current era of increasingly limited health care budgets and growing global burden of coronary heart disease. **The first part** of this thesis aimed to improve the care and risk stratification of STEMI patients, through identification of high risk sub-populations.

Additionally, novel technological developments in coronary stenting may proof beneficial for reducing patient morbidity and mortality and its associated health care costs. **The second part** of this thesis focused on the optimization of treatment of coronary heart disease by appliance of second generation drug-eluting stents (DES).

Part 1

Chapters 2, 3 and 4 were based on data provided by a collaboration of 3 Dutch tertiary centers (the Leiden University Medical Center, the Medical Center Alkmaar and the Medical Center Leeuwarden), which supply STEMI care for a total area of approximately 1.85 million inhabitants. During a 4 year inclusion period, all patients treated with primary percutaneous coronary intervention (PCI) for STEMI were prospectively registered and pooled in a large patient-level database. Data on pre-hospital delay were collected through cooperation with local emergency medical systems and vital status was obtained through municipality records. **Chapter 2** investigated the influence of gender on delay to treatment and outcome after STEMI. In total, 3483 patients were included in the multicenter registry, among which 868 women (25%). At baseline, women were older, showed a higher risk factor burden and were more frequently known with non-cardiac comorbidity compared to men. In contrast, men showed higher rates of atherosclerosis-related disease. Median time between onset of symptoms and reperfusion therapy was almost 20 minutes longer in women. However, this delay could be explained by comorbidity and age. During 1-year follow-up, mortality was significantly higher in women (9.9% vs. 6.6% in men), due to higher mortality in the first 7 days after primary PCI. After adjustment for confounders, female gender was found to predict early but not long term mortality. The reasons for the higher early mortality in women remain speculative, as none of the measured confounders could explain the effect on adverse outcome. In **chapter 3**, we sought to identify angiographic factors related to the occurrence and prognosis of a devastating complication of STEMI; out-of-hospital cardiac arrest (OHCA). OHCA patients were included in the registry if spontaneous circulation had returned on arrival at the catheterization laboratory. OHCA had occurred in

6.4% (N=224/3483) of patients undergoing primary PCI for STEMI. Cardiogenic shock was common in OHCA patients (30.8% vs. 4.8% in patients without OHCA). In two thirds of patients, OHCA had occurred before arrival of emergency medical systems and ventricular fibrillation was most commonly the first observed rhythm. Angiographic culprit lesion was associated with risk of OHCA: left coronary culprit lesions showed the highest risk of OHCA, with proximal lesions resulting in higher risk than non-proximal lesions. Risk was lowest for right coronary culprit lesions. In-hospital neurological outcome and 1-year survival did not differ according to culprit lesion. However, culprit location was associated with success of reperfusion and risk of cardiogenic shock, both of which were driving factors of prognosis after OHCA. **Chapter 4** investigated the influence of cancer on the prognosis after STEMI. During the inclusion period, 208 patients had a known history of cancer (6.0%). In (previous) cancer patients, the last diagnosis was made ≤6 months ago in 20.7%, 6 months-3 years ago in 21.7% and >3 years ago in 57.6% of patients. Patients with a history of cancer were older, more often female and more frequently known with hypertension and prior myocardial infarction. Additionally, comorbidity such as peripheral vascular disease, cerebrovascular disease, renal insufficiency and anemia were more common. During PCI, cancer patients were treated less often with coronary stents, but procedural success was comparable to patients without cancer. As anticipated, cancer patients showed higher all-cause mortality during follow-up. However, also cardiac mortality was higher compared to patients without cancer, which was due to especially high early cardiac mortality in the population with a recent cancer diagnosis (HR 3.34, 95% CI 1.57-7.08). The effect on prognosis was partly explained by anemia and development of cardiogenic shock during PCI, while previous treatment with chemotherapy did not influence prognosis. Because part of the effect of cancer on STEMI prognosis remained unexplained, a cancer specific influence on prognosis was suspected.

Chapter 5 described a study based on SCAAR (the Swedish Coronary Angiography and Angioplasty Registry), a nationwide registry for angiography and PCI in Sweden. Using SCAAR, consecutive elderly patients (aged≥80 years) undergoing primary PCI for STEMI during a 10-year inclusion period were identified. Temporal trends in presentation, care and 1-year prognosis were investigated, as well as long term outcome compared to a control group of patients aged 70-79 years. Relative survival was calculated by dividing the observed survival rate with the expected survival rate of the general population. In total, 4876 elderly patients were included. Average age was observed to increase over time, and the share of nonagenarians more than doubled. Also, risk factor burden and comorbidity increased, while the rate of patients with prior MI decreased. Total ischemic time was found to improve markedly during the inclusion period, and also use of antithrombotic therapy before and during PCI increased. One-year rates of mortality, myocardial infarction and heart failure generally remained stable during the inclusion period, although a significant difference in mortality between the earliest and latest cohort was observed. Additionally, stroke and bleeding risk were similar over time. Higher age

was associated with increased risk of adverse events such as stroke and bleeding after primary PCI. Nevertheless, elderly patients surviving the early phase after primary PCI showed a slightly higher survival compared to the general population up to 3-year follow-up.

Part 2

Part 2 focused on the comparison of drug-eluting stents using observational and randomized designs. In **chapter 6**, the long term performance of the second generation everolimus-eluting stents (EES) and Endeavor zotarolimus-eluting stents (E-ZES) were compared in 931 STEMI patients. In this observational study, consecutive patients treated in the Leiden University Medical Center between January 2007 and October 2010 were stratified according to stent type, and followed up to 3 year post-PCI. Adjusted endpoints were calculated using cox proportional hazards analyses. The two groups were largely comparable at baseline. At 1 year follow-up, EES patients showed lower rates of the device-oriented composite endpoint of cardiac death, target vessel-related MI and target lesion revascularization compared to E-ZES patients; adjusted HR 0.56 (95% CI 0.32-0.97). This reduction was sustained up to 3-year follow-up (adjusted HR 0.64, 95% CI 0.42-0.99), and was mainly driven by reduced target lesion revascularization. Stent thrombosis (ST) rates were low and did not differ between the groups, supporting the safety of second generation DES in setting of STEMI.

Chapter 7 described the results of the XAMI trial, a multicenter randomized clinical non-inferiority trial comparing EES and sirolimus-eluting stents (SES) in patients with acute MI (STEMI or Non-STEMI with emergency indication for PCI). The pre-defined non-inferiority margin was 6%. In total, 625 patients were randomized in a 2:1 ratio, of which 404 to EES and 221 to SES. STEMI was the indication for PCI in 96% of cases. The primary endpoint of cardiac death, non-fatal MI and target vessel revascularization occurred in 4.0% of EES patients and 7.7% of SES patients at 1-year, meeting the non-inferiority criterion. Moreover, superiority of EES over SES was suggested (RR 0.52, 95% CI 0.27-1.00, p=0.048) and primary endpoint curves were still diverging at one year follow-up.

The evaluation of EES and SES was extended to the entire spectrum of coronary heart disease in **chapter 8**, which reported the results of the APPENDIX-AMI trial. This single center, all-comer, open-label trial randomized 977 patients to treatment with EES or SES. Initially aimed to include 2000 patients, this number was not reached due to slower than expected inclusion. At baseline, approximately half of the patient population presented with an acute coronary syndrome, with a slightly higher percentage of STEMI patients in the EES arm. Hypertension, prior cardiac interventions and heavy calcifications were more common in SES patients. Cox proportional hazards analyses were performed to correct for these differences. During 2-year follow-up, EES and SES showed no differences in the unadjusted and adjusted primary endpoint of cardiac mortality, MI and target vessel revascularization.

Moreover, individual end points were balanced between the groups.

The final chapter explored the response of second and first generation DES implantation in different clinical settings, to investigate the potential differences in outcome in patients with and without STEMI (**chapter 9**). To achieve this, the patient populations of XAMI and APPENDIX-AMI were pooled and followed for 2 years for the occurrence of events. After combination of the trials, a patient-level pooled population of 1602 patients was formed. Overall, EES and SES showed similar outcome up to two-year follow-up. Subsequently, stratification was performed according to clinical presentation. Almost half of the pooled population presented with STEMI, of which 455 EES patients and 257 SES patients. The rest of the population presented without STEMI (447 EES and 443 SES). Minor differences in baseline characteristics were corrected using cox proportional hazards analysis. At 2-year follow-up, the primary endpoint of cardiac death, MI and TVR occurred in a similar rate between EES and SES, regardless of clinical presentation. A trend for reduced early definite/probable ST was observed in EES compared to SES in STEMI patients, but long term ST rates were low and comparable between the two devices. This analysis suggests that EES and SES are equally safe and efficacious in patients from the entire range of clinical practice, with no influence of clinical presentation.

Conclusions and future perspectives

The rapid development of STEMI care has been one of the most impressive feats in medical history. Nevertheless, the global burden of coronary heart disease is increasing and continuous scientific effort is required to reduce the load. The first part of this thesis identified several high-risk sub-populations to improve the care and risk stratification of STEMI patients. It was observed that common patient characteristics such as female gender, cancer and old age have a strong impact on the delay to reperfusion therapy and prognosis of STEMI patients. The distinct nature of increased risk among these sub-populations indicates the need for further research on care tailored toward these high-risk individuals. Furthermore, the historically devastating complication of out-of-hospital cardiac arrest continues to have an impact of the STEMI population. Angiographic determinants of the occurrence and prognosis of out-of-hospital cardiac arrest were identified, which may improve the care of these high-risk patients.

The second part of this thesis investigated the use of second generation drug-eluting stents for the treatment of coronary heart disease. Among the second generation DES, EES showed superior results compared to E-ZES in a real world cohort of STEMI patients. A randomized acute MI trial subsequently established the non-inferiority of EES to the first generation SES, with results suggesting superiority. In contrast, EES and SES performed similarly in an all-comer trial, which prompted a pooling of the two trials to investigate the influence of clinical presentation on

outcomes. EES and SES were found to perform similarly during 2-year follow-up, regardless of clinical presentation. The low rates of stent thrombosis and the similar efficacy confirmed the usefulness of both stents in the entire range of patients with coronary heart disease, most notably those with STEMI.

Despite these promising results, concerns remain about the effect of the permanent polymer layer on the coronary environment. Novel generation DES designs include polymer free stents and stents with biodegradable polymer. Theoretically, these stents offer the antirestenotic benefit of DES with a similar long term safety profile as bare-metal stents. Biodegradable scaffolds further extent this concept, leading to complete absorption of the stent within years after implantation. Future trials should explore the value of these promising devices in STEMI patients.

Samenvatting

De introductie van dit proefschrift (**Hoofdstuk 1**) geeft een overzicht van de epidemiologie, pathofysiologie, risicofactoren en diagnostiek van coronaire hartziekten, met speciale aandacht voor het ST-elevatie myocard infarct (STEMI). Daarnaast werd een historisch overzicht van de STEMI-zorg gegeven, met uitgebreide achtergrondinformatie over coronary stents. Tot slot is ingegaan op de risicostratificatie van STEMI patiënten.

Het identificeren van patiënten met risico op herhaling van events is belangrijker dan ooit, in de huidige tijd van financiële beperkingen in de gezondheidszorg en de toenemende last van coronaire hartziekten wereldwijd. **Deel 1** van dit proefschrift heeft als doel de zorg en risicostratificatie van STEMI patiënten te verbeteren, door middel van de identificatie van hoog-risico subpopulaties.

Daarnaast bieden nieuwe technologische ontwikkelingen op het gebied van coronary stents mogelijk voordelen voor het verminderen van morbiditeit en mortaliteit en de daarmee geassocieerde kosten voor de gezondheidszorg. **Deel 2** van dit proefschrift richt zich op de optimalisatie van de behandeling van coronaire hartziekten door middel van tweede generatie drug-eluting stents.

Deel 1

De **hoofdstukken 2,3 en 4** zijn gebaseerd op gegevens die verzameld werden via een samenwerking van 3 Nederlandse tertiaire ziekenhuizen (het Leids Universitair Medisch Centrum, het Medisch Centrum Alkmaar en het Medisch Centrum Leeuwarden). Deze ziekenhuizen voorzien gezamenlijk een gebied van 1.85 miljoen inwoners van STEMI zorg. Alle patiënten die gedurende een periode van 4 jaar een primaire percutane coronaire interventie (PCI) voor STEMI ondergingen werden prospectief geregistreerd en samengevoegd in een database. Gegevens over het voortraject werden verzameld door samenwerking met lokale ambulancediensten en overlevingsstatus werd verkregen door middel van de gemeentelijke basisadministratie. **Hoofdstuk 2** onderzocht de invloed van geslacht op ischemietijden en de prognose na STEMI. In totaal werden er 3483 patiënten geïncludeerd in de multicenter registratie, waarvan 868 vrouwen (25%). Vrouwen waren ouder, toonden meer risicofactoren en waren vaker bekend met niet-cardiale comorbiditeit vergeleken met mannen. Mannen hadden daarentegen vaker een voorgeschiedenis van atherosclerose-gerelateerde aandoeningen. De mediane tijd tussen het ontstaan van de klachten en reperfusie therapie was bijna 20 minuten langer bij vrouwen. Deze vertraging kon echter verklaard worden door hogere leeftijd en aanwezigheid van comorbiditeit. Mortaliteit was significant verhoogd bij vrouwen gedurende 1-jaars follow-up (9.9% vs. 6.6% bij mannen), door een hogere sterfte in de eerste 7 dagen na primaire PCI. Na correctie voor confounders bleek vrouwelijk geslacht een onafhankelijke voorspeller voor vroege maar niet late sterfte. De oorzaak van de hogere vroege sterfte in vrouwen blijft speculatief, omdat geen van

de gemeten confounders het effect op de uitkomsten kon verklaren. In **hoofdstuk 3** onderzochten we angiografische determinanten van het ontstaan en de prognose van een ernstige complicatie van STEMI: een acute hartstilstand buiten het ziekenhuis, ook bekend als out-of-hospital cardiac arrest (OHCA). OHCA patiënten werden geïncludeerd in de registratie indien herstel van spontane circulatie was opgetreden bij aankomst op het katheterisatie laboratorium. STEMI werd gecompliceerd door OHCA in 6.4% (N=224/3483) van de met primaire PCI behandelde patiënten. Cardiogene shock was veelvoorkomend in OHCA patiënten (30.8% vs. 4.8% in patiënten zonder OHCA). OHCA vond plaats vóór aankomst van ambulance personeel in twee derde van de gevallen, en ventrikelfibrilleren was het meest geobserveerde eerste ritme. Angiografische culprit laesie was gerelateerd aan risico op OHCA: het hoogste risico op OHCA bestond bij culprit locaties in de linker coronairarterie. Dit risico steeg naarmate de culprit laesie zich meer proximaal in de arterie bevond. Risico op OHCA was het laagst voor patiënten met een culprit laesie in de rechter coronairarterie. Neurologisch herstel in het ziekenhuis en 1-jaars overleving verschilden niet tussen de verschillende culprit laesies. Locatie van de culprit laesie was echter wel gerelateerd aan het succes van reperfusie therapie en het risico op cardiogene shock, welke drijvende factoren waren voor de prognose na OHCA. **Hoofdstuk 4** onderzocht de invloed van kanker op de prognose na STEMI. Gedurende de inclusie periode hadden 208 STEMI patiënten een voorgeschiedenis van kanker (6.0%). De meest recente diagnose van kanker was ≤6 maanden geleden in 20.7%, 6 maanden – 3 jaar geleden in 21.7% en meer dan 3 jaar geleden gemaakt in 57.6% van deze patiënten. Patiënten met een verleden van kanker waren ouder, vaker van het vrouwelijk geslacht en vaker bekend met hypertensie en eerdere hartinfarcten. Daarnaast kwamen comorbiditeit zoals perifeer vaatlijden, cerebrovasculaire ziekte, nierinsufficiëntie en anemie vaker voor. Tijdens primaire PCI werden patiënten met een verleden van kanker minder vaak behandeld met coronary stents, maar procedureel succes was vergelijkbaar met patiënten zonder kanker. Zoals verwacht was de 'all-cause' mortaliteit hoger in patiënten met een kanker diagnose. Maar daarnaast was ook de cardiale mortaliteit hoger in deze patiënten, als gevolg van een hogere vroege cardiale sterfte in patiënten met een recente kanker diagnose (HR 3.34, 95% CI 1.57-7.08). Het effect van kanker op de prognose kon deels verklaard worden door anemie en het ontwikkelen van cardiogene shock, terwijl eerdere behandeling met chemotherapie geen invloed had op de prognose. Een kanker-specifieke invloed op de cardiale prognose werd vermoed, omdat een deel van het effect van kanker op de prognose van STEMI onverklaard bleef.

Hoofdstuk 5 beschrijft een studie die gebaseerd was op gegevens van SCAAR (the Swedish Coronary Angiography en Angioplasty Registry), het nationale Zweedse register voor angiografie en PCI. Door middel van SCAAR werden alle STEMI patiënten van 80 jaar en ouder geïdentificeerd die gedurende een periode van 10 jaar met primaire PCI waren behandeld. Naast trends in veranderingen van presentatie, zorg en 1-jaars prognose werden de lange-termijn resultaten van de ouderen verge-

leken met een controle groep van patiënten tussen de 70 en 80 jaar oud. Relatieve overleving werd berekend door de geobserveerde overleving te delen door de verwachtte overleving van de algemene populatie. In totaal werden er 4876 oudere STEMI patiënten geïncludeerd. De gemiddelde leeftijd liep op tijdens de observatie periode, en het aandeel patiënten van 90 jaar of ouder verdubbelde. Daarnaast namen risicofactoren en comorbiditeit toe, terwijl het aantal patiënten met een eerder hartinfarct af nam. De totale ischemie tijd verbeterde sterk tijdens de inclusie periode, en het gebruik van antitrombotische therapie voor en tijdens PCI nam toe. Sterfte, myocardinfarcten en opnames voor hartfalen in het eerste jaar na PCI ble-ven vergelijkbaar tijdens de inclusie periode, al werd er wel een significant verschil in sterfte tussen het eerste en het meest recente cohort gezien. Daarnaast bleef het percentage patiënten met beroertes en bloedingen gelijk. Hogere leeftijd was geassocieerd met een sterk toegenomen risico op adverse events na primaire PCI. Desondanks was de langetermijnoverleving voor de ouderen STEMI populatie hoger vergeleken met de algemene populatie, indien de vroege fase na primaire PCI overleefd werd.

Deel 2

Deel 2 richtte zich op de evaluatie van drug-eluting stents (DES) in zowel observationele als gerandomiseerde setting. **Hoofdstuk 6** beschrijft de vergelijking van twee tweede generation DES, de everolimus-eluting stent (EES) en de Endeavor zotarolimus-eluting stent (E-ZES). Het observationele onderzoek includeerde 931 STEMI patiënten die werden behandeld met primaire PCI tussen januari 2007 en oktober 2010 in het Leids Universitair Medisch Centrum. Stratificatie vond plaats op basis van stent type en patiënten werden gevolgd tot 3 jaar na PCI. Gecorrigeerde eindpunten werden berekend door middel van cox proportional hazards analyses. De groepen waren grotendeels vergelijkbaar op baseline. Het gecombineerde eindpunt van cardiale sterfte, target-vessel gerelateerde MI en target lesion revascularization kwam significant minder voor in de EES groep vergeleken met E-ZES na 1-jaar follow-up; gecorrigeerde HR 0.56 (95% CI 0.32-0.97). Deze vermindering werd doorgezet tot 3 jaar na PCI (gecorrigeerde HR 0.64, 95% CI 0.42-0.99), wat met name werd veroorzaakt door een vermindering in target lesion revascularization. De veiligheid van tweede generatie DES in STEMI werd gesteund door de lage incidentie van stent trombose (ST).

De resultaten van XAMI werden besproken in **hoofdstuk 7**. XAMI was een multicenter, klinische non-inferiority trial waarin patiënten met een acuut hartinfarct (STEMI of non-STEMI met een indicatie voor spoed PCI) gerandomiseerd werden naar behandeling met de eerste generatie sirolimus-eluting stents (SES) of de EES. De van te voren gedefinieerde non-inferiority grens lag op 6%. In totaal werden 626 patiënten in een 2:1 ratio gerandomiseerd naar EES (N=404) of SES (N=221). In 96% van de gevallen was STEMI de indicatie voor PCI. Het primaire eindpunt van cardiale sterfte, niet-fatale MI en target vessel revascularization vond plaats in 4.0% van de EES patiënten en 7.7% van de SES patiënten na 1-jaar follow-up, de non-

inferiority van EES bevestigend. Daarnaast suggereerden de resultaten superioriteit van EES over SES voor het primaire eindpunt (RR 0.52; 95% CI 0.27-1.00, p=0.048), en bleven de event curves verder uiteenlopen gedurende follow-up.

Hoofdstuk 8 beschrijft de resultaten van de APPENDIX-AMI studie, een single-center, all-comer, open-label trial waarin 977 patiënten vanuit het gehele spectrum van coronaire hartziekten werden gerandomiseerd naar behandeling met EES of SES. Initieel had APPENDIX-AMI het doel om 2000 patiënten te includeren maar dit aantal werd niet gehaald als gevolg van een inclusie die langzamer verliep dan verwacht. Ongeveer de helft van de studiepopulatie presenteerde zich met een acuut coronair syndroom, waarvan een licht hoger percentage patiënten met STEMI in de EES groep. Daarnaast waren hypertensie, eerdere cardiale ingrepen en calcificaties vaker voorkomend in de SES groep. Cox proportional hazards analyses werden uitgevoerd om te corrigeren voor deze baseline verschillen. Er werden geen verschillen tussen EES en SES in de primaire uitkomstmaat van cardiale sterfte, MI en target vessel revascularization gezien gedurende 2 jaar follow-up. Daarnaast waren individuele uitkomsten vergelijkbaar tussen de groepen.

Het laatste hoofdstuk (**hoofdstuk 9**) onderzocht de response op eerste en tweede generatie DES implantatie in verschillende klinische settings, om potentiële verschillen in uitkomsten bij patiënten met en zonder STEMI te onderzoeken. Om dit te bewerkstelligen werden de patiëntenpopulaties van de XAMI en APPENDIX-AMI trials gecombineerd en gevolgd gedurende 2 jaar follow-up. Na combinatie van de trials onderstond een populatie van 1602 patiënten. In de gecombineerde populatie toonden EES en SES geen verschillen in uitkomsten na 2 jaar. Vervolgens werden patiënten gestratificeerd op basis van klinische presentatie. Bijna de helft van de populatie presenteerde zich met STEMI, waarvan 455 EES patiënten en 257 SES patiënten. De rest van de populatie presenteerde zich zonder STEMI (447 EES en 443 SES). Beperkte verschillen op baseline werden gecorrigeerd door middel van cox proportional hazards analyses. Twee jaar follow-up liet geen verschillen in het primaire eindpunt van cardiale sterfte, MI en target vessel revascularization zien tussen EES en SES, ongeacht de klinische presentatie. Alhoewel een trend tot een verlaging van definite/probable ST met EES werd gezien, kwam ST zelden voor in de beide groepen op de lange termijn. Deze analyse suggereerde dat EES en SES even veilig en werkzaam zijn voor de behandeling van de gehele breedte van patiënten, zonder beïnvloed te worden door klinische presentatie.

Conclusies en toekomstperspectieven

De opkomst van de STEMI zorg is een van de meest indrukwekkende ontwikkelingen in de medische geschiedenis geweest. Desondanks blijft de wereldwijde last van coronaire hartziekten toenemen en bestaat er een continue noodzaak voor wetenschappelijk onderzoek om deze last te verlichten. Het eerste deel van dit

proefschrift identificeerde hoog-risico subpopulaties van STEMI om de zorg en risicostratificatie van STEMI patiënten te verbeteren. Hierin werd duidelijk dat veel voorkomende patiëntkenmerken zoals vrouwelijk geslacht, voorgeschiedenis van kanker en hoge leeftijd een sterke impact op de tijd tot ondergaan van reperfusie therapie en de prognose van STEMI patiënten hebben. De sterk wisselende aard van risicotoename in de verschillende subpopulaties toont het belang van onderzoek naar tailored care, zorg op maat ingericht op de specifieke behoeftes van het hoog-risico individu. Daarnaast blijft de historische ernstige complicatie van STEMI, out-of-hospital cardiac arrest, een negatieve invloed houden op de prognose van STEMI patiënten. Angiografische determinanten van het optreden en de prognose van out-of-hospital cardiac arrest werden geïdentificeerd, wat mogelijk kan leiden tot verbetering van de zorg van deze hoog-risico patiënten.

Het tweede deel van dit proefschrift onderzocht de waarde van tweede generatie drug-eluting stents voor de behandeling van coronaire hartziekten. De tweede generatie EES verbeterde de lange termijn resultaten vergeleken met E-ZES na primaire PCI in een real world observationeel cohort. Een gerandomiseerde non-inferiority myocardinfarct studie toonde vervolgens de gelijkwaardigheid van EES met de eerste generatie SES aan, met veelbelovende resultaten die superioriteit suggereerden. EES en SES toonden daarentegen vergelijkbare uitkomsten in een all-comer trial. De 2 trials werden gecombineerd om de invloed van klinische presentatie op de uitkomsten na percutane interventie verder te onderzoeken. Daaruit bleek dat EES en SES vergelijkbare uitkomsten hebben na 2-jaar follow-up, ongeacht de klinische presentatie. Stent trombose kwam zelden voor op de lange termijn in beide stent groepen, en de werkzaamheid van de stents was vergelijkbaar, wat het nut van de beide devices voor patiënten uit de gehele breedte van coronaire hartziekten steunt. Ondanks deze gunstige resultaten blijven er zorgen bestaan over de lange termijn effecten van de permanente polymeer op de coronaria. Nieuwe DES met biologisch afbreekbare of polymeer-vrije ontwerpen bieden in potentie het anti-restenotische voordeel van DES in combinatie met het gunstige langetermijn veiligheidsprofiel van bare-metal stents. Volledig biologisch afbreekbare stents, welke binnen enkele jaren volledig geabsorbeerd zijn, gaan nog een stap verder met het concept van resorptie. Toekomstig onderzoek zal moeten aantonen wat de aanvullende waarde van deze veelbelovende devices in STEMI is.

CHAPTER 11

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Dankwoord / Acknowledgements

Curriculum Vitae

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Sara, this small page can't hold all the reasons why you are important to me, let's disappear together for a few months and I will tell you all about it!

Curriculum vitae

Matthijs Alexander Velders was born on the 5th of March 1986 in Sneek, the Netherlands. After graduating from the RSG Magister Alvinus in 2004, he started studying Medicine at the University of Groningen. As part of his internships, he stayed for 3 months in Tanzania studying tropical medicine. His final internship in cardiology was performed at the Medical Center Leeuwarden, the Netherlands. After receiving his medical degree in 2010, he started a research fellowship at the Department of Cardiology of the Leiden University Medical Center under the supervision of Prof.dr. M.J. Schalij, in cooperation with the Medical Center Leeuwarden. During this period, he was involved in a working group of the Netherlands Society of Cardiology, concerning the nationwide optimization of care for patients with ST-elevation myocardial infarction. In 2013, he spent 8 months in Sweden to do research at the Uppsala Clinical Research Center under the supervision of Dr. S.K. James and Prof. L. Wallentin. He will be continuing his medical career in Sweden in summer 2014.