Acute myocardial infarction treatment : from prehospital care to secondary prevention

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Chapter 1

General introduction

ACUTE MYOCARDIAL INFARCTION

Coronary artery disease remains the leading cause of mortality in the western world. According to a recent statistics report, in the US alone an estimated 610,000 people will suffer a new myocardial infarction (MI) every year, while 325,000 people will have a recurrent MI.[1] However, there is ample cause for optimism. Following a peak in the mid 1960s, there has been a steady decline in coronary heart disease (CHD) mortality in the United States and in Western Europe.[2-4] In the past 20 years the risk of dying from CHD in the Netherlands was successfully reduced by almost 33%.[5] Treatment and prevention of classic risk factors (hypertension, lipid disorders, and smoking), acute myocardial infarction (AMI) care, and secondary prevention are factors accountable for this pattern.[6-13] In the 1970s, risk factor control and the introduction of specialized coronary care units appeared largely responsible for the declining AMI mortality, but in recent years, short- and long-term care for CHD predominates modeling exercises.[8;14;15] Studies showed that approximately half the decline in U.S. deaths from coronary heart disease from 1980 through 2000 may be attributable to the reduction in major risk factors and approximately half to the introduction of evidence-based medical therapies.[8]

Interestingly over time, the patterns of MI presentation have changed as there is an increasing incidence of myocardial infarction without ST-segment elevation (NSTEMI), with a concurrent decrease in the incidence of ST-segment elevation myocardial infarction (STEMI). In the cardiac catheterization lab, patients with an acute coronary syndrome (ACS) account for almost half of the percutaneous coronary interventions (PCIs) performed annually in the United States, and 40% of ACSs are STEMIs.[16] Both STEMI and NSTEMI are however still associated with higher mortality rates than stable angina on presentation.

It is clear that we are making progress in both the reduction of AMI related mortality and morbidity in the 21st century. However, as mentioned the numbers are still astonishing and force us to focus on the development and implementation of preventive strategies. The organization of care around patients with AMI should be re-structured and focus on rapid intervention in the acute phase and optimization of care during follow-up. The declining mortality and morbidity rates need follow-up to ensure that the reported trends continue. Declining mortality and morbidity figures should also play a role in the planning of healthcare resources allocation. In other words, the "baby-boom" generation may not require additional cardiovascular services which may have an impact on for example the number of coronary care units. On the other hand, as the mainstay of AMI treatment will be rapid intervention it may be necessary to increase the number of interventional facilities in the next decades? Furthermore, as long-term MI care will be provided more and more in an out-patient setting, family physicians play an increasingly important role in initiating and maintaining risk factor modification using evidence-based standards for secondary prevention. Data such as that provided by the work of Chen and colleagues[4], the MISSION

database at the Leiden University Medical Center and other surveillance systems are important to provide guidance to take the correct actions.

GUIDELINES AND IMPLEMENTATION

The number of chronic heart disease patients in North America and Western Europe is increasing rapidly because of better survival after acute myocardial infarction (AMI), improved treatment, and the presence of an aging population. Despite this being a positive development, it also imposes a significant socioeconomic burden on society.[17] To optimize care and outcome of patients with AMI, many organizations, for example, the American College of Cardiology/American Heart Association and the European Society of Cardiology, have published guidelines for treatment of patients with AMI.[18;19] These guidelines advocate early and aggressive reperfusion strategies and recommend the use of a combination of evidence-based medicine (EBM) and support programs to stimulate a healthier lifestyle. Because most of these guidelines are based on large-scale clinical trials, clinical benefit has already been established. Nevertheless, the proven benefit and the endorsement of these guidelines by the scientific society do not seem sufficient to alter well-established daily clinical practice. Consequently, a large gap between EBM and daily practice still exists. Not so long ago, registries showed that only 56% to 76% of the eligible patients actually received reperfusion therapy although reperfusion therapy in the acute phase is known to improve survival of patients with AMI.[20-22] In addition, the National Registry of Myocardial Infarction reported that only 4.2% of patients with AMI transferred for primary percutaneous coronary intervention (PCI) were treated within 90 minutes, which is the benchmark recommended by the international guidelines.[23] After the acute phase modifiable risk factors are often not controlled and prescription medication is often suboptimal.[21;24] Consequently, a significant number of patients with AMI is treated less than optimal.

Schiele et al demonstrated that the degree of guideline compliance is independently correlated with the 1-year mortality after AMI.[25] Various guideline implementation programs, such as Guidelines Applied in Practice, Get With the Guidelines and Crusade, have been successful in improving the quality of care.[26-28] Implementation of this kind of programs resulted not only in better adherence to key indicators, but also in a lower 1-year mortality in patients with AMI.[26;29] Therefore, guideline implementation programs are of paramount importance to optimize AMI care. In order to improve AMI care, investigators of the department of Cardiology at the Leiden University Medical Center in close collaboration with other care providers developed and implemented a pre-hospital, in-hospital and outpatient treatment program in order to standardize evidence-based AMI care in the region "Hollands-Midden," The Netherlands: The MISSION!AMI protocol.[30]

PRE-HOSPITAL CARE

In the acute phase AMI patients require rapid diagnosis and early reperfusion to minimize infarct size and to prevent complications. Measures such as pre-hospital triage by 12-lead electrocardiography (ECG) in the field, thereby allowing early AMI diagnosis and rapid access to an intervention or community center, can reduce the treatment delay significantly.[31] Multiple factors determine treatment delay with its major contributors being patient-delay, physician-delay and in-hospital delay. In order to minimize treatment delay an intensive collaboration is therefore needed between primary care physicians, regional ambulance services, community hospitals (without percutaneous coronary intervention (PCI) facilities), and PCI centers. This has proven to be a complex task not easily achieved, particularly in countries such as the US with large distances between patients' homes and the regional PCI center. Nevertheless, physical distance from the PCI center should not be of influence on in-hospital delays (door-to balloon time). While guidelines recommend having at least 75% of patients treated within 90 minutes of presentation at the hospital, a study using the United States National Registry of Myocardial Infarction led investigators to conclude that this benchmark is rarely achieved for patients undergoing primary PCI in the United States. Only 4.2% of 4278 patients transferred for primary PCI at 419 hospitals were treated within 90 minutes and median door-to-balloon time was 180 minutes.[23] More recently, the reported percentage of patients with door-to-balloon times of <90 minutes in a community-wide surveillance study of patients hospitalized with AMI (in a large central New England community in the United States) was less than 10%.[32] In a Dutch study conducted by Broer et al, investigators reported less dramatic hospital delays of 60-72 min.[33] A major focus of the design of the MISSION! AMI program has been the reduction of such treatment delays in the region Hollands-Midden, regardless of area of residence. The pre-hospital emergency care part of the protocol requires trained ambulance personnel to obtain a 12-lead ECG at patients' home. Suspect ECG's are electronically transmitted to the PCI center. Trained coronary care unit (CCU) nurses determine patient's eligibility for primary PCI and patients found eligible for primary PCI are then transferred directly to the PCI center's coronary care unit. The catheterization room is operational within 20 minutes, 24 hours a day, 7 days a week. In the absence of contraindications, aspirin, clopidogrel and abciximab (a glycoprotein IIb/IIIa inhibitor) are already administered to the patient in the ambulance on the way to the PCI center. The early administration of abciximab in the ambulance has proven to significantly improve early reperfusion in STEMI patients treated with primary PCI.[34] Moreover it was found to be associated with smaller infarct size, improved LV function, a lower risk of heart failure and decreased 1-year mortality on clinical follow-up.[35;36]

IN-HOSPITAL CARE

Primary percutaneous coronary intervention

The principal cause of acute ST segment elevation myocardial infarction (STEMI) is intracoronary plaque rupture with associated occlusive thrombus. Primary percutaneous coronary intervention (PCI) is now established as the optimum treatment for STEMI and for the majority of patients treated in this fashion coronary flow in the infarct-related vessel is restored and myocardial damage limited. Unlike PCI in the setting of stable angina, which reduces anginal symptoms but does not extend life expectancy, PCI in the setting of ACS has proven mortality benefits compared to medical therapy alone.[37-39] In the setting of STEMI, several randomized controlled trials have demonstrated that coronary stenting reduces mortality compared to thrombolysis. In NSTEMI, a meta-analysis of randomized clinical trials (RCTs) has shown a reduction in mortality as well. As a result, PCI has become the preferred treatment for eligible patients with ACS.[40-43]

Drug-eluting stents

Although coronary stents have proven successful, patients treated with bare metal stents (BMS) remain susceptible to restenosis requiring repeat revascularization, which can occur in 14% of patients.[44] Drug-eluting stents (DES) were introduced in the United States in 2003 and have been widely adopted on the basis of profound reductions in restenosis compared with BMS. Randomized trials showed that both sirolimus- and paclitaxel-eluting stents (SES and PES, respectively) reduce in-stent restenosis.[45-50] Over five-year follow-up, these results appear to be durable.[51-53] These trials included patients with unstable angina, but they excluded patients with acute MI (AMI), which remains an "off-label" indication for DES use. Similar results have been published on newer DES, such as everolimus- and zotarolimus-eluting stents.[54-56] AMI, particularly STEMI, has been associated with higher rates of late stent thrombosis (ST).[57-60] Whereas the one-year rate of ST observed in DES or BMS placed for stable angina is 0.6%–0.7%, it has been as high as 3.5% in AMI.[61;62] Whether these rates differ according to stent selection has been a matter of clinical controversy.[63]

The initial report of the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) on BMS- and DES-associated outcomes, published in 2007, reported a significant increase in mortality with DES.[64] Even though a second report extending follow-up and sample size showed no difference in mortality,[65] the findings of the initial study had a substantial impact on clinical practice. First reported in 2007, the GRACE registry, an international study of 5093 patients with STEMI, raised concerns regarding DES safety in AMI in particular. After excluding events of the first six months, the two-year mortality was higher in DES- than in BMS-treated patients (from six months to two years, HR 4.90, p = 0.001).[66] As acknowledged by the authors, the GRACE analysis only adjusted for a limited number of characteristics, and two-year follow-up, based on telephone surveys, was only

completed in 55% of BMS-treated patients and 60% of DES-treated patients. These factors, including the elimination of early events more common in the BMS group, may have introduced bias in this study. Nonetheless, these observations led to a heightened sense of concern regarding the use of DES in AMI.[67] Over longer periods of follow-up, other recently published international registries have not reproduced the results of the GRACE registry. The T-SEARCH and RESEARCH registries have published four-year follow-up data, the longest follow-up in an AMI population. [68]

Among the 1738 consecutive patients with STEMI, despite a higher incidence of late ST (2.7% SES, 0.9% PES, 0 BMS, *p*-value not reported), there was a nonsignificant trend toward improved survival with SES versus BMS (mortality 11.4% SES, 16.4% BMS, adjusted HR 0.63, 95% CI 0.33–1.18).

Through 2008, there have been 14 randomized controlled trials (RCT) of DES in AMI, with >7700 patients, evaluating DES versus BMS in the setting of AMI.[50;62;69-78] These confirm a higher risk of ST in AMI compared to patients with stable angina in similar RCTs. However, in published RCTs to date, rates of ST for BMS and DES in AMI were similar up to one year - approximately 1% when confirmed angiographically, and nearly 2.5%-3.5% in studies using clinical definitions. Most randomized studies, including the MISSION! intervention trial, reported DES to be superior to BMS at 12 months follow-up when comparing DES with BMS treatment for primary PCI in STEMI patients.[50;62;73-76;78;79] In these studies DES mainly reduced the need for repeat revascularization procedures, but with no significant reduction of 12 month rates of death or myocardial infarction.

While randomization is the strongest method to control bias, many of these randomized studies had limitations of lack of follow-up beyond one year or relatively small sample sizes insufficient to detect small differences in ST or mortality. Although the MISSION intervention study found SES implantation in STEMI patients to be associated with a favorable midterm clinical and angiographic outcome compared with BMS treatment, van der Hoeven et al also raised concern about the long-term safety of SES in STEMI patients due to late stent malapposition that was seen more often after SES implantation than after implantation of BMS.[50] The largest RCT comparing DES and BMS in AMI (>3000 patients) showed no difference between BMS and DES rates of death, MI, or ST at one year and longer-term follow-up is in progress.[75]

One of few studies with 5-year follow-up, reported by Goy et al[80], showed durable longer-term results of SES. The authors followed up 344 consecutive patients treated with SES in 2002 (20% of patients were treated for acute coronary syndrome). Over the course of 5-year follow-up, SES appeared to provide durable benefit, particularly with regard to reducing target lesion revascularization (TLR) and the need for repeat procedures. Another 5-year comparison, is the long-term follow-up of the RAVEL study, which randomized 238 patients with stable angina pectoris to either SES or BMS.[52] In the SES group in RAVEL, the 5-year rates of death, MI, and TLR were 12.1%, 8.9%, and 10.3%, respectively (vs 7.1%,

6.9%, and 26.0%, respectively, for BMS). Four-year pooled analysis of 4 major randomized trials of SES (all four studies excluded patients with AMI) reported similar rates.[81] The authors also raised the issue of a late "catch-up" phenomenon of SES. It has been shown that most target lesion-related events in BMS occur within the first year, whereas the risk of TLR among SES appears low but persistent over time.[82] However, although the risk of TLR persists, the low overall risk of TLR at 5 years seemed to argue against a catch-up phenomenon. In addition, 4-year follow-up of the SIRIUS and TAXUS patients notes a persistent reduction in TLR, confirming that a catch-up phenomenon is unlikely within available follow-up to date.[83] Fortunately for those millions of patients treated with DES, these initial 5-year data are reasonably encouraging with regards to DES safety and efficacy in the real world. Nevertheless, more long-term follow-up results on patients treated with DES for AMI is still being eagerly awaited.

Adjunctive medical therapy

The benefit of dual-antiplatelet therapy for 12 months after PCI for ACS has been well established.[84;85] On this basis, the current guidelines of the American College of Cardiology and American Heart Association recommend 12 months of dual-antiplatelet therapy following PCI for ACS with either BMS or DES.[86;87] However, compliance with dual-antiplatelet therapy continues to be a significant challenge. After PCI for STEMI, the rate of noncompliance at 30 days was nearly 14% in one study.[88] Many studies have shown that premature discontinuation of antiplatelet therapy in patients receiving DES is the most important predictor of late ST, particularly in ACS.[88-90] In AMI, patients who stopped thienopyridines within 30 days were more likely to die within the subsequent 11 months (7.5% versus 0.7%, $p < 0.0001$; adjusted HR 9.0; 95% CI 1.3–60.6).[88] Although both DES and BMS require compliance with dual-antiplatelet therapy, and in the setting of ACS for either stent 12 months of treatment is recommended based on large randomized trials, the window of vulnerability to ST resulting from delayed endothelialization is thought to be longer for DES than for BMS, and the ill effects of noncompliance, therefore, greater. Some observational studies indicate that patients with DES may uniquely benefit from dual-antiplatelet therapy beyond 12 months.[91] RCTs that include subjects with and without AMI are under way to determine whether continuation of dual-antiplatelet therapy beyond one year after stent placement will further reduce adverse cardiovascular events or ST.[92]

OPTIMAL TREATMENT AFTER AMI

Secondary prevention

In the outpatient phase the MISSION! AMI program concentrates on active lifestyle improvement and structured medical therapy. [30]

Lifestyle- Regular physical activity is an important component of secondary prevention of CAD; it increases exercise capacity, treats comorbid risk factors, and improves quality of life.[93-95] Exercise-based cardiac rehabilitation has been shown to reduce all-cause and cardiac mortality compared with usual care.[93;94;96-98] The goal for all patients is 30 to 60 minutes of moderate-intensity physical activity (e.g., brisk walking, biking) on most, if not all, days of the week.[93;94;99;100] Consistent physical activity improves cardiovascular risk factors - especially total cholesterol and triglyceride levels - and systolic blood pressure.[99]

Exercise-based cardiac rehabilitation programs may be initiated shortly after an acute coronary syndrome or revascularization procedure.[94;100] The MISSION! AMI protocol offers a standard cardiovascular exercise-based rehabilitation program to each patient, commencing approximately three months after hospital discharge.[30]

Obesity is associated with increased CAD mortality and adversely affects cardiac function and comorbid CAD risk factors.[101] Obesity is classified using the body mass index (BMI). Weight loss is indicated for patients who are classified as overweight or obese according to their BMI. The American Heart Association (AHA) recommends measuring BMI at each office visit, then providing objective feedback and consistent counseling on weight loss strategies.[93;99-101] Improvements in cardiac risk factors are commonly observed with even modest weight loss (i.e., 10 percent of baseline weight).[99;101] Insufficient evidence exists to determine whether weight reduction decreases cardiovascular mortality in persons who are obese.[101]

Smoking cessation has been shown to reduce all-cause mortality in patients with established CAD.[102;103] In a recent Cochrane review, investigators concluded that persons who quit smoking after a myocardial infarction (MI) or cardiac surgery reduce their risk of death by at least one third, and that discontinuing smoking is at least as beneficial as modifying other risk factors.[102;103] In the MISSION AMI protocol physicians are encouraged to ask about tobacco use at each outpatient visit, and to extend a clear recommendation to quit to every patient who smokes. If a patient is willing to try to quit, family physicians can assist with cessation through counseling and pharmacotherapy, which are most effective when combined.[104;105]

Medication- A marked survival advantage in patients with acute coronary syndromes can be achieved, when a combination of evidence-based drugs is prescribed.[106]

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and the AHA recommend treating hypertension (i.e., blood pressure greater than 140/90 mmHg, or greater than 130/80 mmHg for persons with diabetes mellitus or chronic kidney disease) for the secondary prevention of CAD.[107;108] Lifestyle modifications involve weight management, regular physical activity, prudent alcohol consumption, and a low-sodium diet. The JNC 7 and the AHA recommend initial treatment of hypertension after an MI with beta blockers or angiotensin-converting

enzyme (ACE) inhibitors, with additional medications added in a stepwise fashion to achieve goal blood pressure.[107;108]

Antiplatelet agents are recommended in all patients for the secondary prevention of CAD. In a large meta-analysis, antiplatelet therapy reduced recurrent vascular events by one fourth in patients with a previous vascular event.[109] Aspirin treatment should begin immediately after diagnosis of CAD and continued indefinitely unless contraindicated.[93;100;109] Clopidogrel (Plavix) is an effective alternative in patients who cannot take aspirin, and the AHA recommends using clopidogrel in combination with aspirin for up to 12 months after an acute cardiac event or percutaneous coronary intervention (PCI) with stent placement.[109;110] The MISSION! AMI protocol includes standard dual antiplatelet treatment during the initial 12 months and lifelong use of Aspirin thereafter.[30]

Recent clinical trials have demonstrated that reducing cholesterol levels decreases the risk of recurrent coronary events, and evidence-based cholesterol-lowering guidelines have been established by the National Cholesterol Education Program Adult Treatment Panel III (ATP III).[111-113] The AHA and ATP III recommend that all patients with CAD initiate lipid management through therapeutic lifestyle changes.[93;100;111] For the secondary prevention of CAD, ATP III recommends LDL levels of less than 100 mg per dL (2.59 mmol per L), with an optional goal of less than 70 mg per dL (1.81 mmol per L); if the LDL level is greater than 130 mg per dL (3.37 mmol per L), cholesterol-lowering medications are indicated in addition to lifestyle changes.[111]

Statins should be the initial medication choice; however, additional agents may be considered if the LDL goal is not reached through statin therapy alone.[100;111;112] Recent studies have shown intensive statin therapy reduces all-cause mortality in patients after acute coronary syndromes compared with standard therapy; consequently, some have encouraged statin use in all patients who have CAD.[114;115] For every sustained 2 mg per dL reduction in LDL cholesterol, statin therapy has been shown to reduce major coronary events, coronary revascularization, and stroke by 1 percent.[115]

Prevention of sudden cardiac death (SCD)

AMI survivors are at increased risk for sudden death from cardiac causes, in most patients due to a ventricular arrhythmia.[116;117] The Multicenter Automatic Defibrillator Implantation Trial (MADIT) II and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) prospectively tested the hypothesis that implantable cardioverter-defibrillators (ICDs) could reduce mortality in patients at increased risk for sudden death from ventricular tachycardia (VT) or ventricular fibrillation (VF).[118;119] These trials, which demonstrated 5% to 7% absolute mortality reductions over 2 to 4 years, established ICDs as a standard of care for primary prevention of sudden cardiac death. Selection of patients for ICD therapy as primary prevention of sudden cardiac death after AMI depends mainly on the left ventricular ejection fraction (EF). It is now widely accepted that patients who have had an AMI more than 6 weeks previously and have

an EF of 30–35% or less satisfy evidence-based criteria for ICD implantation, without need for further investigation.[120] Most risk stratification efforts to identify candidates for primary prevention ICDs have been based on the hypothesis that patients are likely to benefit if their risk of sudden death is high enough. Various electric measures of arrhythmic risk, such as T-wave alternans, signal-averaged ECG, and electrophysiological study, have not demonstrated adequate or consistent discriminatory power.[121;122] Mortality reduction benefit of primary prevention ICDs was established only when risk stratification was based on measures of left ventricular dysfunction and functional class (left ventricular ejection fraction <30% after myocardial infarction in MADIT II or left ventricular ejection fraction <35% with New York Heart Association class II to III in SCD-HeFT) rather than direct measures of arrhythmic risk.

On the basis of a proportional hazards regression analysis in MADIT II, Goldenberg et al reported a U-shaped curve for efficacy of primary prevention ICDs, in which patients with the lowest and highest risk scores were less likely to benefit.[123] Much attention has been focused on the lowest-risk patients comprising the left arm of this U-shaped curve. It has been motivated by observations that only approximately 20% of patients receive ICD shocks for VT/VF at 3 to 5 years and that this rate of shocks is approximately twice the mortality rate in control groups.[118;124] Thus, only 10% of primary prevention ICD patients receive life-saving therapy, exposing the remaining 90% to all of the risks of ICD implantation and therapy without benefit.[125] However, examination of the mode of death in the low-risk group does not support the concept of patients "too healthy" to benefit from ICD therapy: ICDs reduced the risk of sudden death in this group, but there was a counterbalancing increase in nonarrhythmic death, similar to the findings in the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) of primary prevention ICDs in patients early after myocardial infarction.[123;126] Several cohort analyses have evaluated the right limb of the U-shaped curve of Goldenberg et al, comprising the sickest patients. Investigators have reported that patients with advanced age and chronic renal failure do not benefit from primary prevention ICDs because of imminent, competing causes of death.[127-129]

In summary, both the risk-benefit and cost-benefit ratios of primary prevention ICD therapy would be improved by strategies to exclude presently indicated patients who are unlikely to benefit, if they could be identified accurately. Clinicians fear that the population, eligible for primary prevention ICD treatment, is of such magnitude that provision of ICD therapy will strain financial resources and the pool of trained personnel.[130] As LV function has proven to be a strong indicator for an increased risk of SCD,[131-133] prevention of severe LV dysfunction post-MI should be a priority of AMI care. The MISSION! AMI program attempted to address this problem by focusing on minimal treatment delays, aggressive reperfusion therapy and the use of early and consistent optimal pharmacological therapy.

OBJECTIVES AND OUTLINE OF THIS THESIS

The aim of the main part of this thesis was to evaluate the implementation of the MISSION! AMI protocol in clinical practice at various stages of the program (from pre-hospital care to secondary prevention), to evaluate efficacy and safety of sirolimus-eluting stents at 3-year follow-up, and to study differences in stent edge characteristics in a subgroup of patients by the use of virtual histology-intravascular ultrasound imaging.

In **Chapter 2** the pre-hospital part of the MISSION! AMI program is addressed, with time to treatment delays as particular point of interest. Data collected in a dedicated database show the efficacy of the pre-hospital protocol in achieving predefined targets in all 4 areas of residence in the region "Hollands-Midden".

Chapter 3 describes 3-year clinical outcome of the prospective randomized MISSION! Intervention study. The study compared efficacy and safety of sirolimus-eluting stents with bare-metal stents in eligible patients in the MISSION! AMI program with ST-segment elevation.

In **Chapter 4** the impact of the sirolimus-eluting stent is assessed on plaque composition and morphology at stent edges at 9-month follow-up using Virtual Histology intravascular ultrasound imaging in a subgroup of the MISSION! AMI population. Sirolimus is a potent anti-inflammatory, immunosuppressive and antiproliferative drug effective in inhibiting in-stent neointimal hyperplasia.[134] It was hypothesized that effects of the drug may potentially affect plaque composition at the distal stent edge as part of a downstream effect.

Chapter 5 studies potential advantages of the use of intracoronary aspiration thrombectomy during primary PCI in STEMI patients from the MISSION! AMI program, when used as adjunctive therapy to early abciximab administration. **Chapter 6** briefly describes the frequency and distribution of culprit lesions in patients presenting with ST-segment elevation acute myocardial infarction. In addition, the location of the culprit lesion was related to residual left ventricular function.

Despite the greater incidence and risk of acute myocardial infarction (AMI) among older patients[135;136], there is still a considerable lack of data regarding success of aggressive AMI treatment in this subgroup and factors contributing to clinical outcome. **Chapter 7** aims to provide more insight into the clinical profile, presentation delays, medication compliance and outcome of treatment in the elderly AMI population up to one year post myocardial infarction (MI).

Chapter 8 investigates the clinical relevance of baseline resting heart rate as potential risk factor for adverse outcome in AMI patients with preserved left ventricular function. **Chapter 9** offers suggestions on how to maintain ICD implantation rates within manageable proportions. As it remains difficult to identify patients who will receive ICD therapy in their lifetime, **Chapter 10** offers the right ventricular pacing threshold as a simple parameter to better facilitate evaluation of the prognosis post-implant.

Others:

Chapters 11 and 12 focus on different patient populations and cardiac pathology than the previous Chapters. Catheter ablation has evolved as a possible curative treatment modality for atrial tachyarrhythmias (AT) in patients with congenital heart defects (CHD). However, long-term data on outcome is scarce. **Chapter 11** examines characteristics of recurrent AT after ablation of post-operative AT during long-term follow-up in CHD patients. In **Chapter 12** the long-term success of cavotricuspid isthmus ablation is studied particularly in terms of atrial fibrillation (AF) occurrence in a population of "real-practice" patients with electrocardiographically documented isthmus dependent atrial flutter with and without preablation AF.

Finally, a general summary and conclusions are described.

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