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# Acute myocardial infarction treatment : from prehospital care to secondary prevention

Atary, J.Z.

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# Acute Myocardial Infarction Treatment

## From Prehospital Care to Secondary Prevention

Jael Z. Atary

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# **Acute Myocardial Infarction Treatment:**
From Prehospital Care to Secondary Prevention

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Ter verkrijging van
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Jael Z. Atary
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Promotores:
Prof. dr. Martin J. Schalij, verbonden aan de afdeling cardiologie, LUMC, Leiden.
Prof. dr. Ernst E. van der Wall, verbonden aan de afdeling cardiologie, LUMC, Leiden.

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Dr. N.M.S. de Groot, verbonden aan de afdeling cardiologie, Erasmus MC, Rotterdam.

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# Table of contents

# 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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# Chapter 2

## Standardized pre-hospital care of acute myocardial infarction patients: MISSION! guidelines applied in practice.

Jael Z. Atary[1], Matthijs de Visser[2], Rene van den Dijk[1], Jan Bosch[2], Su San Liem[1], M. Louisa Antoni[1], Marianne Bootsma[1], Eric P. Viergever[3], Charles J. Kirchhof[4], Iman Padmos[5], Meredith I. Sedney[6], Henk J. van Exel[7], Harriette F. Verwey[1], Douwe E. Atsma[1], Ernst E. van der Wall[1], J. Wouter Jukema[1], Martin J. Schalij[1]

[1]Department of Cardiology, Leiden University Medical Center, The Netherlands,
[2]Regional Ambulance Service Hollands-Midden, Leiden, The Netherlands,
[3]Groene Hart Hospital, Gouda, The Netherlands,
[4]Rijnland Hospital, Leiderdorp, The Netherlands,
[5]Diaconessenhuis, Leiden, The Netherlands,
[6]Bronovo Hospital, The Hague, The Netherlands,
[7]Rijnlands Rehabilitation Center, Leiden, The Netherlands

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## ABSTRACT

### Background

To improve acute myocardial infarction (AMI) care in the region "Hollands-Midden" (the Netherlands), a standardized guideline based care program was developed (MISSION!). This study aimed to evaluate outcome of the pre-hospital part of the MISSION! program and to study potential differences in pre-hospital care between four areas of residency.

### Methods

Time to treatment delays, AMI risk profile, cardiac enzymes, hospital stay, in-hospital mortality, and pre-AMI medication was evaluated in consecutive AMI patients (n=863, 61±13years, 75% male) transferred to the Leiden University Medical Center for primary percutaneous coronary intervention (PCI).

### Results

Median time interval between onset of symptoms and arrival at the catheterization laboratory was 150(101-280)minutes. The alert of emergency service to arrival at the hospital time was 48(40-60)minutes and the door to catheterization laboratory time was 23(13-42)minutes. Despite significant regional differences in ambulance transportation times no difference in total time from onset of symptoms to arrival at the catheterization room was found. Peak troponin T was 3.33(1.23-7.04)µg/L, hospital stay was 2(2-3)days and in-hospital mortality was 2.3%.

Twelve percent had 0 known risk factors, 30% had 1 risk factor, 45% 2-3 risk factors and 13% had ≥4 risk factors. No significant differences were observed for AMI risk profiles and medication pre-AMI.

### Conclusions

This study shows that a standardized regional AMI treatment protocol achieved optimal and uniformly distributed pre-hospital performance in the region "Hollands-Midden", resulting in minimal time delays regardless of area of residence. Hospital stay was short and in-hospital mortality low. Eighty-eight percent of patients had ≥1 modifiable risk factor.

## INTRODUCTION

Coronary heart disease (CHD) is the leading cause of death in the western world. Current guidelines are therefore aimed at optimizing care and outcome of patients with acute myocardial infarction (AMI).[1;2] In the past 20 years the risk of dying from CHD in the Netherlands was successfully reduced by almost 33%.[3] This was in part the result of increased efforts to improve acute treatment and secondary prevention strategies.[3-5]

In the acute phase AMI patients require rapid diagnosis and early reperfusion to minimize infarct size and to prevent complications. Several 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.

A regional AMI guideline implementation program (MISSION!) was developed to optimize the use of evidence-based medicine in practice.[6] MISSION! contains a pre-hospital, in-hospital and out-patient clinical framework for decision making and treatment of AMI patients. The main goal of this study was to study the outcome of the pre-hospital part of MISSION! and to evaluate and identify potential regional differences in multidisciplinary performance and related patient factors in the region "Hollands-Midden".

## METHODS

### Patients

The geographical region studied (Hollands Midden = "Center of Holland") spans an area of 875 $km^2$ with a population of approximately 750.000 inhabitants. Patients included in this study were all living in the region and were admitted with the diagnosis of AMI in the years 2006-2008 at the Leiden University Medical Center for primary PCI. The study population was partitioned into four areas of residency within Hollands-Midden, classified as "Duin & Bollen" (region 1), "Leiden" (region 2), "Alphen" (region 3) and "Gouda" (region 4) (Fig. 1). AMI patients admitted for primary PCI living outside of the region Hollands-Midden were excluded.

### Clinical protocol

To align AMI care, an intensive collaboration was established among primary care physicians, the regional ambulance services, three community hospitals without PCI facilities, three cardiac rehabilitation centers and the Leiden University Medical Center, serving as primary PCI facility. The MISSION! protocol was developed based on the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for AMI.[2;7]

The pre-hospital emergency care required trained ambulance personnel to obtain a 12-lead ECG at patients' home. In the case of suspect characteristics, the ECG was electronically transmitted to the PCI center. Trained coronary care unit (CCU) nurses determined patient's eligibility for primary PCI. Patients not eligible for PCI, were transferred to a community hospital for further assessment. Patients eligible for primary PCI, were transferred directly to the PCI center's Cardiac Care Unit. In the ambulance aspirin, abciximab and clopidogrel was administered to the patient. The catheterization room was operational within 20 minutes, 24 hours a day, 7 days a week. After discharge, patients were offered a cardiac rehabilitation program and benefited from intensive out-patient follow up for the period of 1 year.

The current study focused on the pre-PCI phase of the MISSION! protocol.

## Data collection

Data was recorded by ambulance personnel and medical staff at the hospital. All the data was registered in a departmental electronic patient system (EPD-Vision, LUMC, Leiden, The Netherlands).

## Endpoints

Pre-clinical performance in the four residence areas was measured by the following time intervals (minutes): Onset of Symptoms to Alert of Emergency Services (patient delay), Onset of Symptoms to Arrival at Catheterization Room (Cath-Lab), Door to Cath-Lab (hospital delay) and Interval between the Alert of Emergency Services to Arrival at the Hospital. Additional endpoints of interest were peak Troponin T and peak Creatine Phosphokinase (CPK) levels.

Furthermore, risk profile for CHD was compared between the 4 areas of residency within Hollands-Midden, including risk factors like smoking, hypertension, hyperlipidemia, positive family history, diabetes mellitus and prior myocardial infarction. Lastly, drug treatment before occurrence of AMI was studied. Pre-admission medication use of interest was beta-blockers, statins, aspirin, ACE-inhibitors, angiotensine II (AT2)-antagonists, diuretics and calcium-antagonists.

## Statistical Analysis

Sample comparisons were made with a Pearson $\chi^2$ test for categorical variables using Yate's correction where appropriate. A Kruskal-Wallis one-way analysis of variance was employed for the comparison of not normally distributed continuous variables such as time intervals. All tests were two-sided, a p-value of $< 0.05$ was considered significant (using Bonferroni correction where appropriate). All data were analyzed with SPSS 16.0.02.

## RESULTS

### Study population

A total of 1002 consecutive AMI patients were admitted at the PCI center between 2006 and 2008. Of these patients, 863 (86%) were Hollands-Midden residents and included in the final study population. Baseline characteristics are shown in Table 1. The majority of patients was male (75%) and the mean age was 61 ± 13 years. The distribution of patients from the areas of residence 1, 2, 3 and 4 was 31%, 29%, 21% and 19%, respectively (Fig. 1).

**Table 1.** Patient characteristics.

| Patient Characteristics (n=863) | |
|---|---|
| Male (%) | 646 (74.9) |
| Age (years) | 61 ± 13 |
| BMI (kg/m$^2$) | 28.4 (24.9-41.1) |
| BMI ≥30 kg/m$^2$ (%) | 374 (43.3) |
| Region of residency (%) | |
| 1 | 265 (30.7) |
| 2 | 253 (29.3) |
| 3 | 185 (21.4) |
| 4 | 160 (18.5) |
| Risk factors for coronary diseases (%) | |
| Smoking | 462 (53.5) |
| Hypertension | 307 (35.6) |
| Hyperlipidemia | 167 (19.4) |
| Family History | 358 (41.5) |
| Diabetes Mellitus | 108 (12.5) |
| Prior Myocardial Infarction | 90 (10.4) |
| Median time intervals in minutes (IQR) | |
| Onset Symptoms - Arrival at Cath-Lab | 150 (101-280) |
| Door - Arrival at Cath-Lab | 23 (13-42) |
| Onset Symptoms – Alert of Emergency Services | 61 (25-158) |
| Alert of Emergency Services – Arrival at Hospital | 48 (40-60) |
| Hospitalization | |
| Days hospitalized (median [IQR]) | 2 (2-3) |
| In-hospital mortality (%) | 20 (2.3) |

Values expressed as n (%), normally distributed data as mean ± standard deviation, otherwise as median (interquartile range [IQR]: 25$^{th}$-75$^{th}$ percentile).
BMI = Body Mass Index, Cath-Lab = Catheterization Room.
Hyperlipidemia= Total cholesterol ≥190 mg/dl or previous pharmacological treatment.
Hypertension = Blood pressure ≥140/90 mm Hg or previous pharmacological treatment.

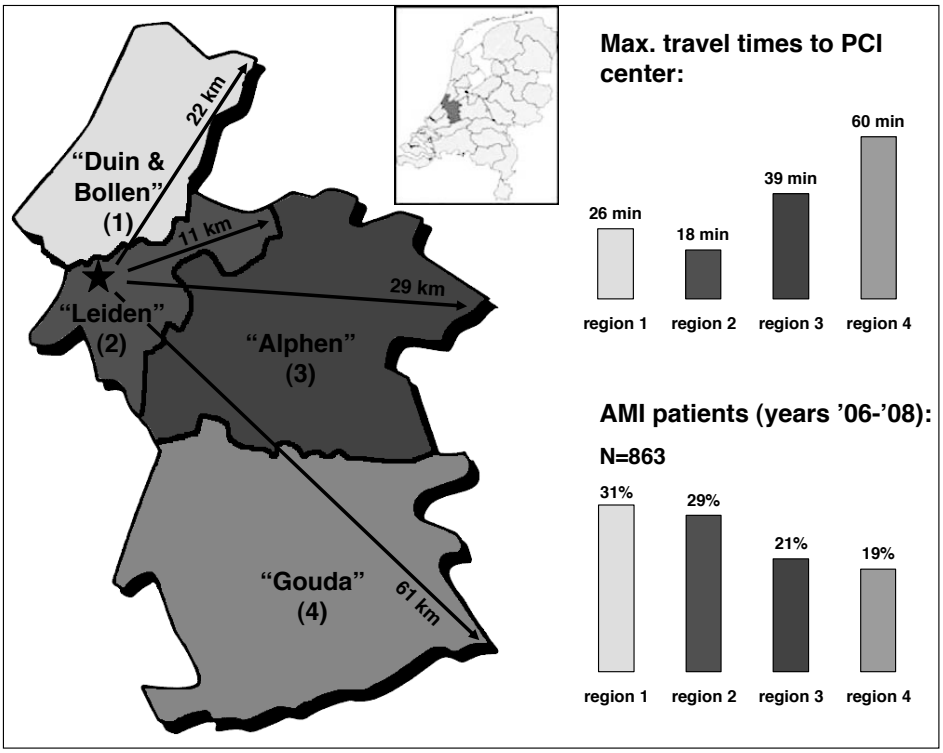


**Figure 1.** The region of "Hollands-Midden" as divided into four areas of residency.
Schematic map of the region "Hollands-Midden" (The Netherlands) further subdivided into the four areas of residency: "Duin & Bollen" (region 1), "Leiden" (region 2), "Alphen" (region 3), "Gouda" (region 4). The star within "Leiden" (region 2) represents the location of the PCI center. Maximal travel time to each area of residency (minutes) and percentage of patients per area are shown in the bar graphs on the right.
AMI = acute myocardial infarction, KM = kilometers, Max. = maximal, PCI = percutaneous coronary intervention.

The four most common risk factors were smoking (54%), a family history of coronary artery disease (CAD) which was present in 42% of patients, a Body Mass Index (BMI) ≥30 kg/m$^2$ (43%) and hypertension in 36% of patients.

Median duration from onset of symptoms to arrival at the Cath-Lab was 150 minutes (101-280 min). Median patient delay, measured as time between the onset of symptoms and the moment of alerting the emergency service, was 61 minutes (25-158 min), whereas the median time between the alert of emergency services and the arrival at the hospital was 48 minutes (40-60 min). Median Door to Cath-Lab time was 23 minutes (13-42 min). Hospital stay was only 2 (2-3) days and in-hospital mortality was 2.3% (20/863). Total 30 day mortality was 3.5% (30/863, including in-hospital mortality).

## Clinical characteristics per area of residency

Clinical characteristics according to the area of residency are shown in Table 2. In summary, comparisons revealed a similar age and gender distribution between the 4 areas and similar

**Table 2.** Patients' medical history per region of residency.

| | Region 1 n = 265 | Region 2 n = 253 | Region 3 n = 185 | Region 4 n = 160 | p-value |
|---|---|---|---|---|---|
| Patient Characteristics | | | | | |
| Male (%) | 203 (76.6) | 190 (75.1) | 130 (70.3) | 123 (76.9) | 0.415 |
| Age (years) | 61 ± 13 | 61 ± 13 | 61 ± 13 | 62 ± 12 | 0.931 |
| Body Mass Index (kg/m$^2$) | 28.7 (25.5-42.6) | 28.4 (25.0-40.4) | 27.5 (24.5-39.6) | 27.8 (24.7-42.3) | 0.466 |
| Risk factors (%) | | | | | |
| Smoking | 151 (57.0) | 128 (50.8) | 105 (57.1) | 78 (49.1) | 0.239 |
| Hypertension | 102 (38.5) | 86 (34.3) | 68 (37.0) | 51 (32.1) | 0.540 |
| Hyperlipidemia | 50 (18.9) | 49 (19.4) | 35 (19.0) | 33 (20.8) | 0.969 |
| Family History | 115 (43.4) | 99 (39.3) | 81 (44.0) | 63 (39.6) | 0.658 |
| Diabetes Mellitus | 29 (11.0) | 36 (14.3) | 26 (14.1) | 17 (10.7) | 0.533 |
| Prior Myocardial Infarction | 24 (9.1) | 34 (13.5) | 16 (8.7) | 16 (10.1) | 0.304 |
| Prior PCI | 21 (8.0) | 22 (8.7) | 10 (5.4) | 9 (5.7) | 0.471 |
| CABG in past | 6 (2.3) | 8 (3.2) | 3 (1.6) | 3 (1.9) | 0.724 |
| History of Angina Pectoris | 33 (12.6) | 43 (17.5) | 28 (15.6) | 25 (15.8) | 0.498 |
| Nr. of risk factors | | | | | |
| 0 | 39 (14.7) | 31 (12.3) | 12 (6.5) | 20 (12.5) | 0.063 |
| 1-2 | 139 (52.5) | 145 (57.3) | 119 (64.3) | 97 (60.6) | 0.076 |
| 3-4 | 73 (27.5) | 63 (24.9) | 45 (24.3) | 37 (23.1) | 0.747 |
| ≥ 4 | 36 (13.6) | 39 (15.4) | 23 (12.4) | 15 (9.4) | 0.352 |
| Medication before MI (%) | | | | | |
| Beta-blocker | 67 (25.4) | 45 (18.0) | 41 (22.4) | 27 (17.0) | 0.104 |
| Aspirin | 51 (19.2) | 52 (20.8) | 33 (18.0) | 20 (12.6) | 0.195 |
| Statin | 52 (19.7) | 48 (19.2) | 34 (18.6) | 21 (13.2) | 0.354 |
| ACE-inhibitor | 35 (13.2) | 33 (13.2) | 20 (10.9) | 17 (10.7) | 0.779 |
| Angiotensine II-antagonist | 15 (5.7)* | 16 (6.4) | 25 (13.7)* | 10 (6.3) | 0.008* |
| Diuretic | 31 (11.7) | 25 (10.0) | 22 (12.0) | 23 (14.5) | 0.598 |
| Ca-antagonist | 30 (11.3) | 25 (10.0) | 21 (11.5) | 15 (9.4) | 0.893 |
| Peak troponin T (µg/L) | 3.45 (1.28-7.14) | 2.81 (0.92-6.39) | 3.34 (1.24-6.68) | 3.95 (1.98-7.87) | 0.083 |
| Peak CPK (U/L) | 1388 (587-2618) | 997 (448-2165) | 1323 (522-2727) | 1586 (755-3146) | 0.008* |
| LVEF 3 months post-MI (%) | 56 (47-64) | 56 (47-64) | 55 (49-63) | 55 (47-63) | 0.887 |

Values expressed as n (%), normally distributed data as mean ± standard deviation, otherwise as median (interquartile range [IQR]: 25$^{th}$-75$^{th}$ percentile). * p<0.05

ACE = Angiotensin-Converting Enzyme, Ca = Calcium, CABG = coronary artery bypass surgery, CPK = Creatine Phosphokinase, LVEF = Left ventricular ejection fraction, MI = myocardial infarction, PCI = percutaneous coronary intervention.

risk profiles for CHD. Medication prior to AMI was similar between the 4 patient groups except for a significantly larger percentage of patients using AT2-antagonist living in region 3 when compared to patients living in the region 1 (13.7% versus 5.7%, respectively).

## Pre-hospital care

Pre-hospital time delays per area of residency are illustrated in Fig. 2. Patient delays were similar between the four areas of residency as revealed by the median time between onset of symptoms to alert of emergency services (Panel A: range of a median 51 min for region 2 to a median 74 min for region 1; p=0.796).

In addition, total time elapsing between the onset of symptoms and the arrival at the catheterization laboratory was also similar for patients of all four areas of residency (Panel B: median 148 min for region 3 to median 165 min for region 4; p=0.809). Panel C furthermore shows that median in-hospital delay was relatively short (median 17 min for region 4 to median 28 min for region 2) and comparable between the patient groups (p=0.056).

Fig. 3 shows that significant differences were present between the four areas of residence in the total time needed for emergency services to arrive at the patient (from the moment



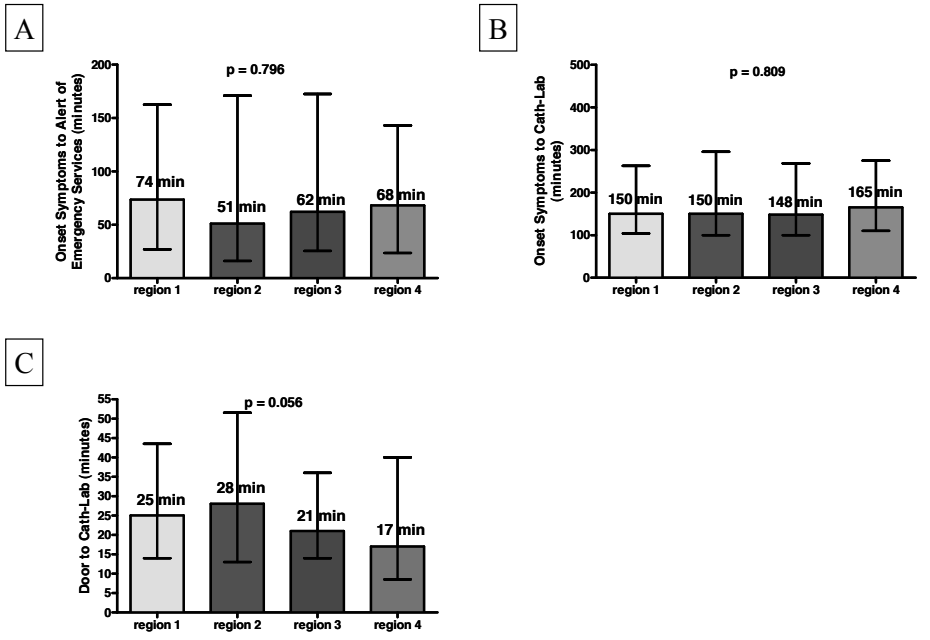


**Figure 2.** Time to treatment delay.
Bar graphs showing: (Panel A) patient delay defined as time from onset of symptoms to alert of emergency services, (Panel B) time interval from symptom onset to arrival at the catheterization room ("cath-lab"), and (Panel C) hospital delay expressed as time from arrival at the hospital to arrival at the cath-lab. Top of bar represents median time (minutes). Error bars indicate 25$^{th}$ and 75$^{th}$ percentile (minutes). Abbreviations as in figure 1.

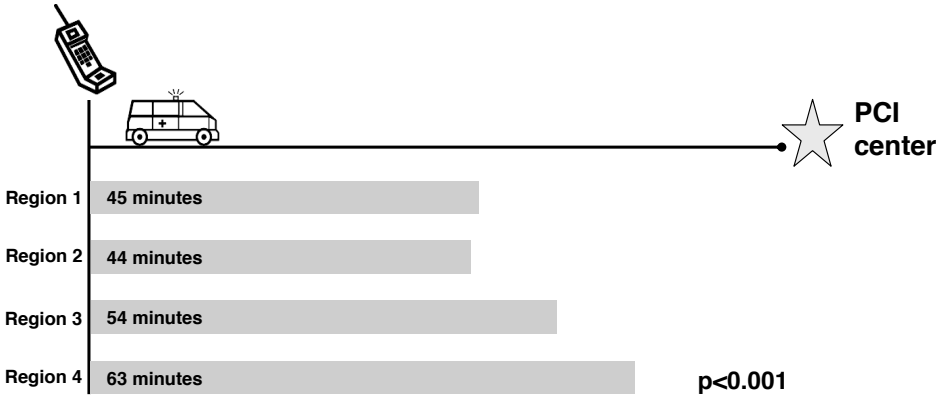


**Figure 3.** Time from alert of emergency services to arrival at PCI center.
Bars represent time interval (median minutes) from 911 call to the arrival at PCI center (represented by star) per region of residency. Abbreviations as in figure 1.

of the 911 call) in addition to the amount of time needed to transport the patient to the PCI center ($p<0.001$). Only two areas of residency did not differ significantly: Region 1 and region 2 (median of 45 min and 44 min respectively). Patients living outside of this area all needed significantly more time to reach the PCI center (≥50 min). Transportation time of patients from region 4 was the longest (median of 63 min). Of interest, these patients had the shortest door to Cath-Lab time (17 min) when compared to patients from other areas.

## DISCUSSION

The main findings of this study were: (1) the pre-hospital MISSION protocol succeeded in achieving equally high quality pre-hospital performance in all areas of the region Hollands-Midden regardless of the distance from the PCI center, (2) time delay due to geographical distance ("Gouda"[region 4] patients) was counterbalanced by a short in-hospital delay, and (3) there was no significant difference in pre-AMI medication use and risk profile of patients between the four areas of residency.

### Structured care for AMI patients

Previous reports demonstrated that a standardized guideline-based treatment system can improve the quality of AMI care and can even result in a lower in-hospital and 1-year mortality.[8-11] Collaboration between general practitioner, ambulance services and hospital is essential in prevention, acute care and rehabilitation of (potential) AMI patients. Results of this study demonstrate the efficacy of the pre-hospital MISSION! protocol in achieving predefined targets.[6] Furthermore despite significant differences in transportation time (due to differences in distance from the PCI center) similar time intervals between the onset

of symptoms to arrival at the Cath-Lab in all 4 areas of residence demonstrate that the multidisciplinary pre-hospital care is uniformly distributed and well organized in the region Hollands-Midden. Furthermore, even though physical distance was of influence on the time needed to get the patient to the hospital (from the start of symptoms), the short door to Cath-Lab time (median 23 min) leveled out these differences.

Benefits of the standardized pre-hospital care program are also reflected in short admission duration (median 2 days) and low in-hospital mortality (2.3%). Peak cardiac enzyme levels per area of residency, such as troponin T levels demonstrated that final infarct size was similar, regardless of the geographical distance. Moreover, it corresponded well with left ventricular ejection fraction of patients as measured 3 months post myocardial infarction by stress/rest myocardial perfusion scanning (Table 2).

Hardly any significant differences were observed in medications prescribed by general practitioners prior to AMI and in risk factors for CHD between the four areas of residence within Hollands Midden. Investigators of the EUROASPIRE Study investigated risk factor control in several countries in Europe.[12] Compared with their most recent data, risk factors for CHD were less prevalent in our study population, except for smoking (this study: 54.0% vs. EUROASPIRE: 18.3%) and BMI $\geq$30 kg/m$^2$ (43% vs. 38.0%).[13] Lower prevalence of hypertension (35.6% vs. 60.9%), hyperlipidemia (19.4% vs. 46.2%) and diabetes (12.5% vs. 28.0%) point to a relatively successful risk factor control in the region 'Hollands Midden'. Possibly, greater attention for modifiable lifestyle factors, particularly smoking and obesity, may facilitate in further improving prevention of AMI in the region Hollands-Midden in the future.



## Inconsistency of guideline implementation

Many organizations have recommended early reperfusion strategies and use of evidence-based medicine, together with long-term support programs to stimulate healthier lifestyle for the treatment of patients with AMI.[1;2] Although benefit of these guidelines has already been established, their implementation in the treatment of AMI patients is still inconsistent. Broer et al. showed that there were regional differences in pre-hospital time delays for AMI patients in the Netherlands.[14] The EURASPIRE survey showed that there were significant differences in risk factor control and cardioprotective drug prescription between European countries.[13]

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-ballon time was 180 minutes.[15] 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%.[16] In another Dutch study conducted by Broer et al, investigators reported hospital delays of 60-72 min.[14] In contrast, the present study achieved a median door-to-Cath-Lab time of 23 minutes, with 90% of patients reaching the Cath-Lab in <90 minutes.

### Clinical implications

Standardized protocols like MISSION! contribute to improved adherence to evidence-based medicine in routine clinical practice and to the uniform implementation of structured care for patients with AMI, stressing the importance of close collaboration with all partners.

### Limitations

No comparisons could be made between the current study population and a population not treated according to the MISSION! protocol in the region Hollands-Midden. Nevertheless, compared to previous studies, the MISSION! protocol performed well in the care of AMI patients.[14-16]

As this was a single center, single region study conclusions may not pertain to larger regions. Furthermore, as data on prevalence of risk factors and medication use was derived in part from patient self-report, it should be considered with the necessary caution.

## CONCLUSION

This study shows that a standardized regional AMI treatment protocol achieved optimal and uniformly distributed pre-hospital performance in the region Hollands-Midden, resulting in minimal time delays to treatment regardless of the area of residence. Furthermore hospital stay was short and in-hospital mortality low. Eighty-eight percent of patients had 1 or more modifiable risk-factors.

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# Chapter 3

## Three-year outcome of sirolimus-eluting versus bare-metal stents for the treatment of ST-segment elevation myocardial infarction (From the MISSION! intervention study)

Jael Z. Atary[1], Bas L. van der Hoeven[1], Su-San Liem[1], J. Wouter Jukema[1], Johanna G. van der Bom[2], Douwe E. Atsma[1], Marianne Bootsma[1], Katja Zeppenfeld[1], Ernst E. van der Wall[1], Martin J. Schalij[1]

[1]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands.
[2]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.

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## ABSTRACT



In order to compare long-term efficacy and safety of sirolimus-eluting stents (SES) to bare-metal stents (BMS) for ST-segment elevation myocardial infarction (STEMI), outcome was assessed in patients (n=310, age 59±11years, 78% male) included in the randomized MISSION!-intervention study after a median follow-up of 38 months. All patients were treated with aspirin (lifelong) and clopidogrel for 1 year after stent implantation. Except for a significant difference between reference vessel diameters (SES: 2.76mm vs. BMS: 2.92mm, p=0.02), there were no significant differences in baseline and angiographic characteristics between the treatment groups (158 SES, 152 BMS). A significant difference between SES and BMS patients for all revascularization endpoints was found after the first year of follow-up. However, at 3 years of follow-up, although there was still a trend towards a better clinical outcome in SES treated patients, differences were no longer significant [death (4.4% vs. 6.6%; p=0.41), target vessel related myocardial infarction (2.5% vs. 4.6%; p=0.32), target vessel revascularization (8.9% vs. 15.8%; p=0.06), target lesion revascularization (6.3% vs. 12.5%; p=0.06) and target vessel failure (12.0% vs. 19.7%; p=0.06)]. Three cases of very late (definite) stent thrombosis were observed in the SES group (1.9%) versus 0 in the BMS group (p=0.14).

In conclusion, the significant SES benefit (compared to BMS) in STEMI patients at 1 year follow-up in terms of target vessel revascularizations declined to some extent due to more similar target vessel revascularization rates during the 2 subsequent years. Rates of death and nonfatal recurrent MI remained comparable. (Current controlled trials number, ISRCTN628258620.)

## INTRODUCTION

This randomized prospective study was designed to evaluate angiographic outcome and clinical efficacy of third-generation bare-metal stents (BMS) compared with that seen in sirolimus-eluting stents (SES) in ST-segment elevation myocardial infarction (STEMI) patients. Following the mid-term (12 months) angiographic and clinical results [1], the present study evaluated clinical outcome after 3 years of follow-up from the index event.

## METHODS

### Study design

The MISSION! intervention study (Current Controlled Trials number, ISRCTN62825862 [1]) was a single-center, single-blind, randomized prospective study to evaluate clinical and 9-month angiographic results in STEMI patients treated with either BMS or SES. The study protocol was approved by the institutional ethical committee. Written informed consent was obtained from all patients before enrollment and before the follow-up catheterization. Patients and operators performing the follow-up were blinded to the treatment assignment. During the study period, all patients were treated according to the institutional STEMI protocol, which included standardized outpatient follow-up [2].

The study design, and methods have been described in detail previously [1]. In brief, consecutive patients with de novo coronary lesions were eligible for participation if symptoms of STEMI started <9 hours before arrival at the catheterization laboratory and the ECG demonstrated a STEMI. Exclusion criteria were detailed previously,[1] but in summary consisted of any "off-label" indication other than STEMI. Randomization to treatment with a BMS (Vision, Guidant Corp. Indianapolis, Indiana) or SES (Cypher, Cordis Corp., Miami Lakes, Florida) was performed in a 1:1 ratio.

Before the procedure all patients received 300 mg of aspirin, 300 to 600 mg of clopidogrel, and an intravenous bolus of abciximab (25 µg/kg), followed by a continuous infusion of 10 µg/kg/min for 12 h. At start of the procedure, 5,000 IU of heparin was given. Lesions were treated according to current interventional practice.

### Follow-up and data collection

Both treatment groups received dual antiplatelet therapy for an equal treatment duration. Aspirin (100 mg/day) was prescribed indefinitely and clopidogrel (75 mg/day) for 12 months. Patients were seen at the outpatient clinic at 30 days, 3, 6, and 12 months according to the MISSION care program [2]. During follow-up, patients were treated with beta-blocking agents, statins, and angiotensin-converting enzyme inhibitors or angiotensin II blockers. Follow-up angiography was performed at 9 months. Long-term follow-up data of each patient was

documented prospectively in an electronic patient file and data management system (EPD-VISION 6.01) of the Leiden University Medical Center. Data was recorded after 3 years by patient visits at the out-patient clinic, or if not possible, by telephone inquiry. When a patient visit took place at another hospital, specific data inquiry was performed after written consent of the patient.

## Endpoint definition

Endpoints of the current study were death, myocardial infarction (MI), target vessel revascularization, target lesion revascularization, target vessel failure and stent thrombosis. All deaths were defined as cardiac, unless it was unequivocally proven noncardiac. Myocardial infarction during follow-up was defined as a troponin-T rise >0.03 µg/l with symptoms or PCI, a rise of troponin-T >0.15 µg/l after coronary artery bypass grafting, or a rerise of troponin-T >25% after recent MI in the presence of symptoms or re-PCI, or the development of new Q waves on ECG [3;4]. Infarctions were categorized as spontaneous or procedure related (non-index procedure)[3], [4].

Target vessel and target lesion revascularization were defined as any revascularization procedure of the target vessel or target lesion, respectively. Target vessel failure was defined as the composite of cardiac death or recurrent nonfatal MI attributable to the target vessel or any revascularization procedure of the target vessel. If events could not unequivocally be attributed to a nonculprit vessel, they were considered culprit vessel related.

Stent thrombosis was defined as definite, probable and possible stent thrombosis (the composite of these being total stent thrombosis), further subdivided into acute (≤1day), subacute (>1day - ≤1month), late (>1month - ≤1year) and very late (>1year) stent thrombosis, according to the Academic Research Consortium definition [5]. All clinical events were adjudicated by a clinical events committee whose members were blinded for the assigned stent type.

## Statistical Analysis

Since this study was planned as follow-up investigation of the MISSION! intervention study, sample size calculations were done for the original purpose only. Analyses were conducted according to the intention-to-treat principle. Continuous data are expressed as mean (±standard deviation) or as median (interquartile range (IQR) $25^{th}/75^{th}$ percentile); dichotomous data are presented as numbers and percentages. All continuous variables were compared between the treatment groups with a *t* test or, in the case of a non-Gaussian distribution, with a nonparametric test. Categorical variables were compared with Pearson's chi-square test or Fisher exact test as appropriate. Event rates over time were analyzed by method of Kaplan-Meier with corresponding log-rank test for differences in distribution between the curves.

Effect of a reference diameter ≥3mm on the risk of stent thrombosis was estimated by multivariate Cox regression analysis with treatment group as sole covariate. The rational to conduct analysis this way was as follows: Other potential (known and unknown) confounders have already been accounted for due to the randomized design of this study. Adding variables to the multivariate analysis after randomization may reduce comparability between the treatment groups. Therefore, only variables that were known to be different from baseline, such as stent type and (see also baseline characteristics table) reference vessel diameter were entered into the multivariate model. All p values were 2-sided, and a p value < 0.05 was considered statistically significant. All analyses were conducted with SPSS version 16.0 statistical analysis software (SPSS Inc., Chicago, Illinois).

## RESULTS

### Baseline characteristics

A total of 316 STEMI patients were enrolled in the study (Figure1). Six patients were subsequently excluded because the assigned study stent was not available, and 310 patients (152 assigned to BMS and 158 assigned to SES) were included in the analysis [1]. Baseline characteristics of the study population are reported in Table 1.

With exception of a slightly larger reference diameter in the BMS group, the groups were comparable. One patient crossed over from SES to BMS because of the inability to cross

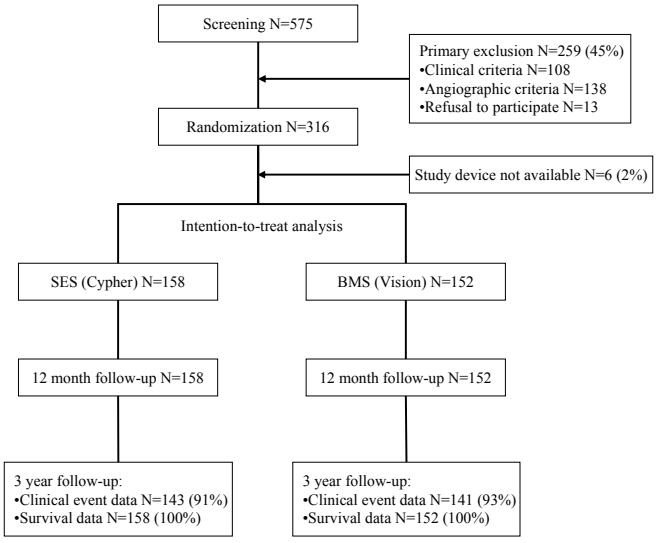


**Figure 1.** Patient Flow Chart, Enrollment and Follow-up.
BMS = bare-metal stent; SES = sirolimus-eluting stent.

the lesion with the SES. No patients were lost for follow-up and all patients were contacted (Figure 1). Complete clinical data were available for 91% of the patients assigned to the SES group and for 93% of the patients assigned to the BMS group.

**Table 1.** Clinical and angiographic characteristics

| Characteristics | SES (n = 158) | BMS (n = 152) | p value |
|---|---|---|---|
| Age (mean years ± SD) | 59.2 ± 11.2 | 59.1 ± 11.6 | 0.99 |
| Men | 118 (74.7%) | 123 (80.9%) | 0.19 |
| Diabetes mellitus | 20 (12.7%) | 10 (6.6%) | 0.07 |
| Current smoker | 84 (53.2%) | 85 (55.9%) | 0.63 |
| Hypercholesterolemia† | 37 (23.4%) | 25 (16.4%) | 0.13 |
| Hypertension‡ | 48 (30.4%) | 39 (25.7%) | 0.36 |
| Family history of coronary artery disease | 73 (46.2%) | 60 (39.5%) | 0.23 |
| Prior myocardial infarction | 7 (4.4%) | 5 (3.3%) | 0.60 |
| Prior percutaneous coronary intervention | 4 (2.5%) | 1 (0.7%) | 0.37 |
| Prior coronary artery bypass grafting | 1 (0.6%) | 1 (0.7%) | 1.00 |
| Symptoms onset to first electrocardiogram (median min [interquartile range]) | 88 (47–153) | 106 (71–151) | 0.11 |
| Symptoms onset to balloon inflation (median min [interquartile range]) | 183 (133–258) | 195 (153–257) | 0.19 |
| Target coronary artery | | | |
| Left | 87 (55.1%) | 83 (54.6%) | |
| Right | 40 (25.3%) | 51 (33.6%) | 0.09 |
| Left circumflex | 31 (19.6%) | 18 (11.8%) | |
| Multivessel disease | 56 (35.4%) | 50 (32.9%) | 0.64 |
| TIMI flow grade before | | | |
| 0 | 96 (60.8%) | 90 (59.2%) | |
| 1 | 18 (11.4%) | 15 (9.9%) | 0.87 |
| 2 | 20 (12.6%) | 24 (15.8%) | |
| 3 | 24 (15.2%) | 23 (15.1%) | |
| Maximal creatinine phosphokinase (U/l) | | | |
| Median | 1,844 | 2,079 | 0.25 |
| Interquartile range | 863–3,413 | 1,012–3,792 | |
| Quantitative coronary angiography pre-procedure | | | |
| Lesion length (mean mm ± SD) | 13.9 ± 5.6 | 15.0 ± 8.6 | 0.47 |
| Reference diameter (mean mm ± SD) | 2.76 ± 0.54 | 2.92 ± 0.56 | 0.02* |
| Minimal luminal diameter (mean mm ± SD) | 0.21 ± 0.35 | 0.27 ± 0.41 | 0.19 |
| Stenosis (mean % of luminal diameter ± SD) | 91.0 ± 13.6 | 92.5 ± 12.4 | 0.35 |

*p <0.05

† Total cholesterol ≥190 mg/dl or previous pharmacological treatment.

‡ Blood pressure ≥140/90 mm Hg or previous pharmacological treatment.

## Long-term follow-up

Clopidogrel was used up to 12 months by 93% (147/158; with 156 patients alive at follow-up) of patients in the SES group and by 96% (146/152; 148 patients alive at follow-up) of patients in the BMS group (p = 0.24). Aspirin treatment was continued by all patients during the entire follow-up of 3 years except when oral anticoagulation was indicated (n=39). Twenty-one patients (11 BMS, 10 SES) used clopidogrel >1 year. Reasons for prolongation of clopidogrel treatment were in most cases (n=17) the occurrence of an in-stent restenosis or stent thrombosis, and in 4 cases because of patient/doctor miscommunication. All patients who experienced target lesion revascularization and/or stent thrombosis <1year post-MI used clopidogrel at the time the first event took place. This was true for patients of both treatment groups.

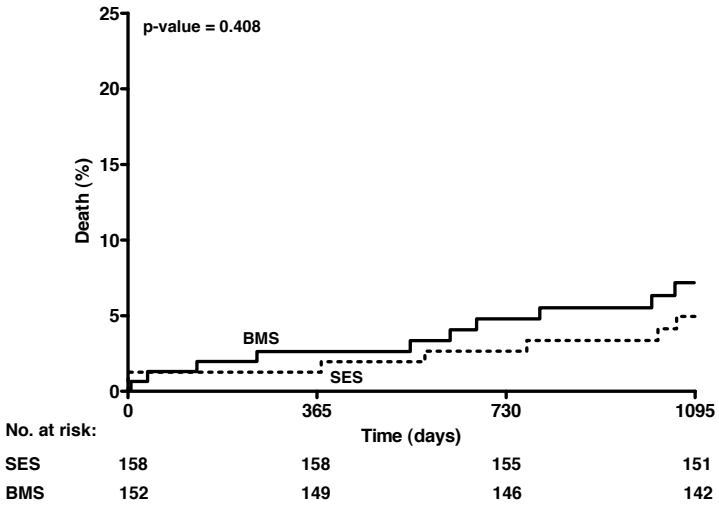


**Figure 2.** Kaplan-Meier estimates of the cumulative incidence of all-cause death. Abbreviations as in figure 1.

## Deaths

Clinical outcome data at long-term follow-up are reported in Table 2. As compared to the previously reported mid-term results [1], 11 additional deaths occurred of which 5 in the SES group and 6 in the BMS group (p=NS). About half of these additional deaths were noncardiac (6/11, 55%, all cancer related). A Kaplan-Meier estimates of the cumulative incidence of all-cause death for the SES and BMS group is shown in Figure 2. Both treatment groups demonstrate a similar probability of all-cause death over the years (log-rank test p=0.41).

## Myocardial infarction

Table 2 furthermore shows that most of the (6/7) additional recurrent spontaneous myocardial infarctions after the first year were target vessel related. There was no significant difference

**Table 2.** Clinical outcome at 12 months and at 3-year follow-up.

| Event | 12-month outcomes | | | 3-year outcomes | | |
|---|---|---|---|---|---|---|
| | SES (n = 158) | BMS (n = 152) | p value | SES (n = 158) | BMS (n = 152) | p-value |
| Death | 2 (1.3%) | 4 (2.6%) | 0.44 | 7 (4.4%) | 10 (6.6%) | 0.41 |
| Noncardiac | — | 2 (1.3%) | 0.24 | 3 (1.9%) | 5 (3.3%) | 0.68 |
| Cardiac | 2 (1.3%) | 2 (1.3%) | 1.00 | 4 (2.5%) | 5 (3.3%) | 0.95 |
| Recurrent myocardial infarction† | 9 (5.7%) | 14 (9.2%) | 0.24 | 12 (7.6%) | 17 (11.2%) | 0.28 |
| Spontaneous | 2 (1.3%) | 3 (2.0%) | 0.68 | 5 (3.2%) | 7 (4.6%) | 0.51 |
| Target vessel related | 2 (1.3%) | 3 (2.0%) | 0.68 | 4 (2.5%) | 7 (4.6%) | 0.32 |
| Procedure related | 7 (4.4%) | 11 (7.2%) | 0.29 | 7 (4.4%) | 11 (7.2%) | 0.29 |
| Target vessel related | 2 (1.3%) | 6 (3.9%) | 0.17 | 2 (1.3%) | 6 (3.9%) | 0.17 |
| Revascularization procedure† | 19 (12.0%) | 35 (23.0%) | 0.01* | 28 (17.7%) | 39 (25.7%) | 0.09 |
| PCI | 17 (10.8%) | 30 (19.7%) | 0.03* | 26 (16.5%) | 33 (21.7%) | 0.24 |
| CABG | 2 (1.3%) | 5 (3.3%) | 0.28 | 3 (1.9%) | 8 (5.3%) | 0.11 |
| Target vessel revascularization† | 8 (5.1%) | 20 (13.2%) | 0.01* | 14 (8.9%) | 24 (15.8%) | 0.06 |
| PCI | 6 (3.8%) | 17 (11.2%) | 0.01* | 11 (7.0%) | 20 (13.2%) | 0.07 |
| CABG | 2 (1.3%) | 3 (2.0%) | 0.68 | 3 (1.9%) | 6 (3.9%) | 0.46 |
| Target lesion revascularization† | 5 (3.2%) | 17 (11.2%) | 0.006* | 10 (6.3%) | 19 (12.5%) | 0.06 |
| PCI | 3 (1.9%) | 14 (9.2%) | 0.005* | 7 (4.4%) | 15 (9.9%) | 0.06 |
| CABG | 2 (1.3%) | 3 (2.0%) | 0.68 | 3 (1.9%) | 6 (3.9%) | 0.46 |
| Clinically driven | 4 (2.5%) | 12 (7.9%) | 0.03* | 9 (5.7%) | 14 (9.2%) | 0.28 |
| Target vessel failure | 11 (7.0%) | 23 (15.1%) | 0.02* | 19 (12.0%) | 30 (19.7%) | 0.06 |
| Stent thrombosis | | | | | | |
| Definite | 1 (0.6%) | 1 (0.7%) | 1.00 | 4 (2.5%) | 1 (0.7%) | 0.39 |
| Probable | 1 (0.6%) | 2 (1.3%) | 0.97 | 1 (0.6%) | 2 (1.3%) | 0.97 |
| Possible | — | — | — | 1 (0.6%) | 1 (0.7%) | 1.00 |

*p <0.05. † The first event per patient was counted.
CABG = Coronary artery bypass grafting; PCI = percutaneous coronary intervention.

in the number of patients with spontaneous target vessel related myocardial infarction at three year follow-up (p=0.32). No additional procedure related myocardial infarctions were observed in the second and third year of follow-up. The Kaplan-Meier and landmark incidence estimates of the cumulative incidence of the combined endpoint target vessel related death/nonfatal MI demonstrates that the distribution of this combined endpoint over time was similar in both SES and BMS groups from beginning to end of follow-up (first year: log-rank test p=0.28; three years: log-rank test p=0.19) (Figure 3).

## Revascularization

An additional 13 patients underwent revascularization procedures after the first year of follow-up (Table 2). Most were target vessel related (10/13, 77%) and approximately half were target lesion related (7/13, 54%). Though a significant difference was observed between SES and BMS groups for the number of patients undergoing a revascularization procedure (target vessel or target lesion related) during the first year of follow-up, this difference was no longer statistically significant after three year follow-up. This was due to the fact that relatively more SES patients underwent a revascularization procedure during the next 2 years of follow-up reducing the magnitude of the benefit of SES over BMS: an additional 9 patients in the SES group and another 4 patients in the BMS group. The same trend was observed for target

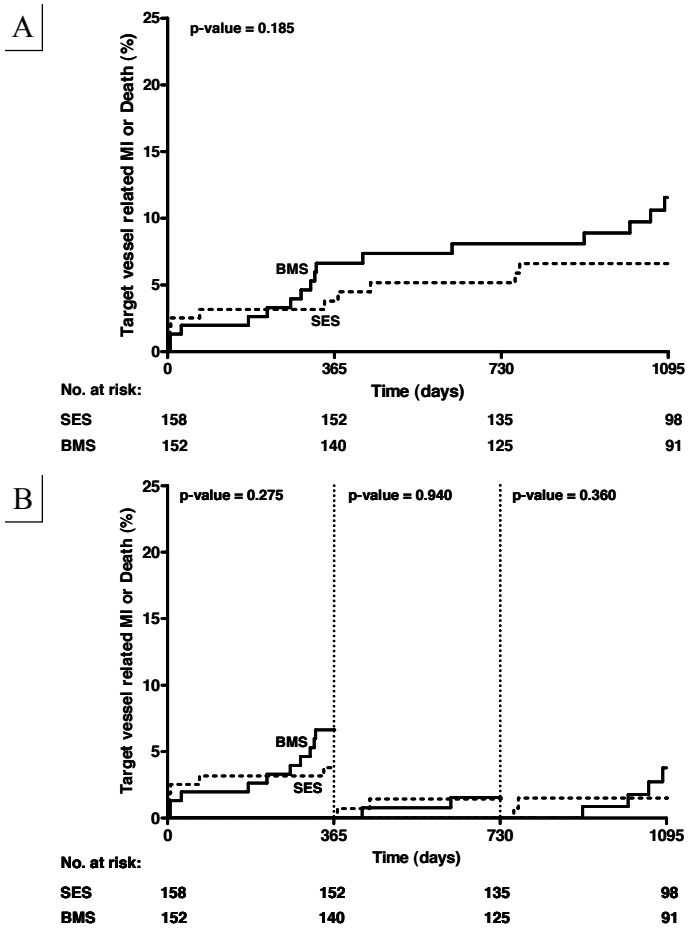


**Figure 3.** Kaplan-Meier (panel A) and landmark incidence (panel B) estimates for the combined endpoint target vessel related nonfatal MI or death.
MI = myocardial infarction. Other abbreviations as in figure 1.

vessel related revascularizations and for target lesion related procedures. Figure 4 shows the cumulative incidence of target lesion revascularization procedure over the complete follow-up period (panel A) and for each year separately (panel B). The cumulative incidence of patients undergoing target lesion revascularization was significantly lower in the SES group during the first year of follow-up compared to the BMS group (log-rank test p=0.006). A more similar cumulative incidence was observed during the next years of follow-up (3 years: log-rank test p=0.05).

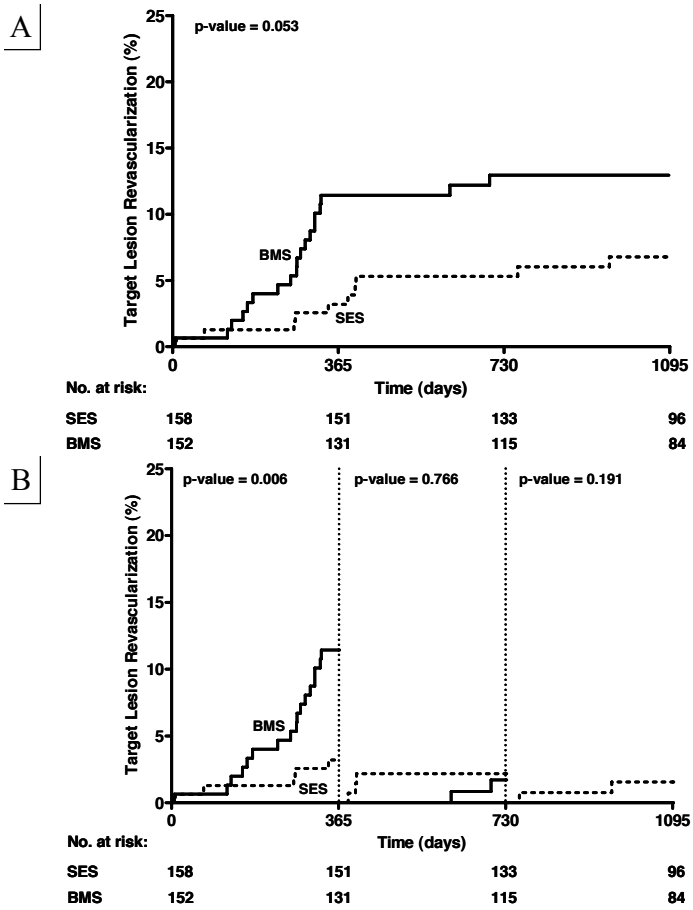


**Figure 4.** Kaplan-Meier (panel A) and landmark incidence estimates (panel B) for target lesion revascularization.
Abbreviations as in figure 1.

## Target vessel failure

Table 2 shows that the combined endpoint target vessel failure (death/MI-/revascularization related to target vessel) occurred overall less frequently in the SES group than in the BMS group, particularly due to the difference in events occurring during the first year (first year: 7.0% vs. 15.1% of patients respectively, p=0.02; three year total: 12.0% vs. 19.7%, p= 0.06). Correspondingly, figure 5 demonstrates that a statistically significant difference in the cumulative incidence of target vessel failure between SES and BMS patients was observed only in the first year after the index procedure (first year: log-rank test p=0.02; three years: log-rank test p=0.06).

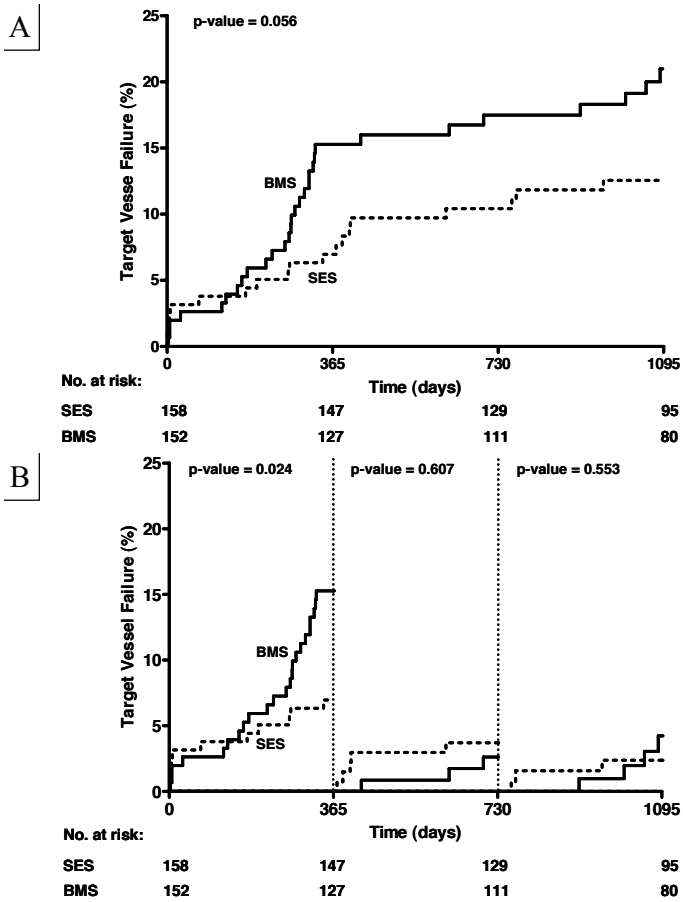


**Figure 5.** Kaplan-Meier (panel A) and landmark incidence (panel B) estimates for the combined endpoint target vessel failure.
Abbreviations as in figure 1.

## Stent thrombosis

In table 2 the number of patients experiencing definite, probable or possible stent thrombosis is reported for SES and BMS groups [5]. Three cases of very late (definite) stent thrombosis were seen in the SES group (1.9%) versus none in the BMS group (p=NS). Figure 6 demonstrates the cumulative incidence of total stent thromboses (total of definite, probable and possible) for both stent type groups during 3 years of follow-up. Comparison of the cumulative incidence of stent thrombosis for the entire follow-up period, showed that the event rate was similar in the SES and BMS groups (Figure 6, log-rank test p=0.56).

Despite the low incidence of stent thrombosis, results of the multivariate analysis suggest that a reference diameter of ≥3mm was related to an increased hazard of definite stent thrombosis in the overall patient population (adjusted: HR 10.2, 95%CI 1.1-92.5; p=0.039), independent of stent type.

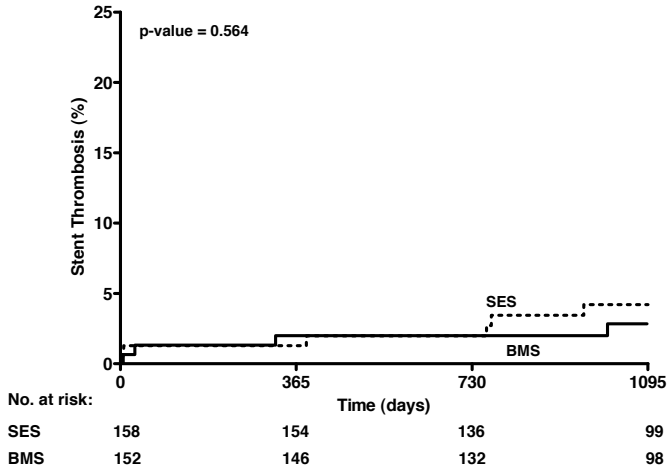


**Figure 6.** Kaplan-Meier estimates of the cumulative incidence of stent thrombosis. Abbreviations as in figure 1.

## DISCUSSION

Key findings of this randomized study were: (1) Clinical outcome at three year follow-up was comparable for STEMI patients treated with either SES or BMS, and (2) the overall benefit of SES offered over BMS reflected mostly the advantage achieved during one year of follow-up. Although the total number of events was relatively lower in the SES treated group compared to the BMS treated group, the statistical advantage in terms of target vessel revascularizations gradually declined during three year follow-up due to more similar event rates after one year.

## Drug-eluting vs. bare-metal stents in STEMI patients

Though primary PCI has been shown to be superior to medical therapy alone in patients presenting for acute myocardial infarction, particularly for STEMI patients[6-8], data regarding efficacy and safety of DES use in these patients is still relatively scarce. Randomized studies investigating DES use for off-label indications often excluded patients with acute myocardial infarction[9;10]. In addition, observational studies investigating DES use in patients with acute myocardial infarction had varying and sometimes conflicting results, or were unable to correct for dissimilar duration of dual antiplatelet therapy[11-14]. Most randomized studies thus far including this study reported DES (including SES) to be superior to BMS at 12 months follow-up when comparing DES with BMS treatment for primary PCI in STEMI patients[1;15-21]. In these studies DES mainly reduced the need for repeat revascularization procedures, but did not significantly reduce 12 month rates of death or myocardial infarction.

## Drug-eluting vs. bare-metal stents: Short vs. long-term

Recent results of the current randomized trial suggest that the maximum benefit of SES over BMS, in terms of repeat revascularizations, is reached within the first year after index-intervention. This is supported by data from investigators of large registry studies such as the study from Mauri et al [14] who reported that drug-eluting stents were associated with reduced rates of death and repeat revascularization at 2-years follow-up as compared to bare-metal stents. The significant difference of event rates consisted chiefly of the markedly reduced cumulative event rates of DES in the first year of follow-up, after which event rates were comparable between DES and BMS. Other studies reached the same conclusion[22-24].

Similarly, at an update of the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON) presented at EuroPCR 2009, investigators reported that at 4 years, SES were able to maintain their initial advantage in terms of revascularization rates over BMS. Though it is perhaps questionable whether the trial's follow-up was complete enough to draw definitive conclusions (only 70% of original cohort), again the same time-dependent trend was observed as demonstrated by equal increases in the rate of target vessel revascularizations in SES and BMS groups (4% each) after the first year of follow-up [18]. Moreover, the recently published short- and long-term data of the Paclitaxel- or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty (PASEO) Trial further confirms this pattern [21].

Results of the present study were also remarkably similar to the 3-year outcome of a large observational study by Applegate et al, who investigated DES versus BMS for "off-label" indications (not restricted to patients with myocardial infarction) in 1246 DES treated patients and 1147 BMS treated patients [22]. DES benefit seemed to occur entirely within the first year, with similar rates of target vessel revascularization, death and nonfatal MI in the second and third years. Abovementioned examples including results of the current study confirm a consistent pattern of time-dependent benefit of DES over BMS that decreases

in magnitude after the first year. Newer stents with better long term performance have not been tested in this study, but may potentially have a significantly better long-term performance.

### Limitations

The clinical results of this study cannot be seamlessly translated into general daily clinical practice, as this was a single-center study in a selected group of patients and patients were followed in a strict-guideline based out-patient protocol[2], which is not common practice yet. Event rates in daily clinical practice can be expected to be in general higher than in this study. Furthermore, the follow-up study was not designed to detect small differences in the incidence of stent thrombosis between the groups. It is possible that with a larger sample size, the borderline non-significant differences of target vessel related events between SES and BMS groups may still have been significant after 3 years. A trend toward a "catch up phenomenon" is visible, but the results should be interpreted with caution. It deserves mentioning that the power calculation for sample size of the main MISSION! intervention study[1] was based on angiographic late luminal loss which was not an endpoint in this 3-year follow-up study. In addition, complete clinical follow-up was not available for all patients. However, it is highly unlikely that patients lost to follow-up experienced a serious clinical event such as revascularization or MI, as this would probably have led to admission at the PCI center and therefore would not have gone unnoticed. Finally, the original study design dictated angiographic follow-up at 9-months which was discussed in a previous publication[1]. We cannot exclude that the routine angiographic follow-up did result in additional revascularization procedures, perhaps magnifying differences between BMS and SES in the first year of follow-up. It did however not influence the long-term event rates. Furthermore, the 1-year MISSION treatment program included regular visits and ischemia detection by stress/rest myocardial perfusion scanning at 3 months after STEMI, which facilitated in treatment decision-making.



## CONCLUSION

The significant SES benefit (compared to BMS) in STEMI patients at 1 year follow-up in terms of target vessel revascularizations declined to some extent due to more similar target vessel revascularization rates during the 2 subsequent years. Rates of death and nonfatal recurrent MI remained comparable.

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# Chapter 4

## Impact of sirolimus-eluting stent implantation compared to bare-metal stent implantation for acute myocardial infarction on coronary plaque composition at 9 months follow-up: A virtual histology intravascular ultrasound analysis. Results from the Leiden MISSION! intervention study.

Jael Z. Atary[1], Sandrin C. Bergheanu[1], Bas L. van der Hoeven[1], Douwe E. Atsma[1], Marianne Bootsma[1], Frank van der Kley[1], Katja Zeppenfeld[1], J. Wouter Jukema[1,2], Martin J. Schalij[1]

[1]Department of cardiology, Leiden University Medical Center, Leiden, the Netherlands.
[2]Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, the Netherlands.

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## ABBREVIATIONS

| | |
|---|---|
| AMI | Acute myocardial infarction |
| BMS | Bare-metal stent |
| CRP | C-reactive protein |
| CSA | Cross-sectional area |
| EEM | External elastic membrane |
| IVUS | Intravascular ultrasound |
| Mean LD | Mean lumen diameter |
| MLD | Minimum lumen diameter |
| PTCA | Percutaneous transluminal coronary angioplasty |
| QCA | Quantitative Coronary Angiography |
| SES | Sirolimus-eluting stent |
| STEMI | ST-segment elevation myocardial infarction |
| VH-IVUS | Virtual histology intravascular ultrasound |

## ABSTRACT



### Aims

To evaluate effects of sirolimus-eluting stents (SES) compared to bare-metal stents (BMS) at stent edges in patients with acute myocardial infarction (AMI).

### Methods and Results

Clinical, angiographic, intravascular ultrasound (IVUS) and virtual histology (VH)-IVUS results were obtained and analyzed in 20 SES and 20 BMS AMI patients at the index procedure and at 9 months follow-up. Quantitative angiography and IVUS showed a trend toward decreases in mean lumen diameter, vessel volume, minimum lumen area and mean lumen area at both stent edges of BMS, and at the proximal edge of SES. At the distal stent edge, a significant difference between BMS and SES treated patients in mean lumen area was found ($\Delta$-0.8 ± 1.6mm$^2$ versus $\Delta$0.2 ± 0.8mm$^2$ respectively, p =0.04). Furthermore, in-stent SES had a larger lumen volume (SES: 167.7 ± 59.2mm$^3$ versus BMS: 125.1± 43.8mm$^3$; p =0.02) and less neointima volume (7.3 ± 9.1mm$^3$ versus 53.2 ± 35.1mm$^3$; p <0.001). Neither SES nor BMS demonstrated a significant effect on plaque composition at follow-up VH-IVUS analysis.

### Conclusion

A significant difference between SES and BMS treated patients was observed with respect to mean lumen diameter distal to the stented segment which suggests a downstream effect of sirolimus elution.

## INTRODUCTION

The treatment of patients with acute myocardial infarction (AMI) changed significantly over the last decades. Early pharmacological and more recently mechanical reperfusion strategies improved the prognosis of AMI patients further supported by optimal medical treatment (including antiplatelet therapy, ACE inhibitors, betablockers and statins) and life style changes in the chronic phase after the acute event. Procedural outcome also improved due to improved operator experience, continuous refinement of catheter and balloon technology, and the introduction of intracoronary stents. More recently drug eluting stents (DES) have been introduced. Although the efficacy of DES is proven in patients with stable coronary artery disease the role of DES in AMI patients is still under debate.[1-4] Despite the positive effects of DES on restenosis, the increased risk of subacute thrombosis tempered the initial enthusiasm as subacute stent thrombosis is a devastating event associated with high mortality rates and myocardial infarction.[5-9] In AMI patients the initial event is caused by disruption or erosion of a vulnerable plaque[10-12] leading to acute thrombosis. The increased risk of stent thrombosis associated with DES is caused by incomplete/delayed neointimal coverage and may be prevented to some extent in most patients with stable coronary artery disease by prolonged dual antiplatelet therapy. Although after implantation of a stent the ruptured plaque will be covered it is unclear what happens proximal and distal to the stent segments. Some studies suggest that the eluted drug in case of a DES may not only have an effect on the stented segment but also on adjacent segments.[13-15] It is therefore of interest to study these segments during the initial procedure and during follow-up. In this study we evaluated the effects of DES compared to bare-metal stents (BMS) on the proximal and distal segments using Intravascular Ultrasound imaging (IVUS) in AMI patients at baseline and at 9 months follow-up. Although IVUS allows cross-sectional imaging of coronary arteries and provides a comprehensive assessment of the atherosclerotic plaque, it cannot provide detailed data about its tissue components. Detecting changes in tissue components may increase our comprehension of in vivo development of potentially vulnerable plaque. Therefore, additionally Virtual histology (VH-) IVUS using spectral analysis of the radiofrequency ultrasound backscatter signals to analyze plaque composition and morphology was used. VH-IVUS allows identification of four different components of atherosclerotic plaques: fibrous, fibro-fatty, dense calcium, and necrotic core.[16]

## METHODS

### Study design and population

Patients for this substudy were selected from the randomized MISSION! intervention study (Current Controlled Trials number, ISRCTN62825862,[4]). The original MISSION! study was

designed to compare the outcome of the sirolimus coated Cypher stent (Cypher Select™, Cordis Corp., Miami Lakes, Florida) with the bare-metal Vision stent (Multilink Vision™, Guidant Corp., Indianapolis, Indiana) in patients with AMI.[4] The study was approved by the institutional ethical committee. Written informed consent was obtained from all patients before enrollment and before the follow-up catheterization at 9 months. The study protocol, inclusion and exclusion criteria, endpoint definition and main outcomes of the study were published previously.[4]

For this substudy, a group of consecutive patients were included for whom not only clinical, angiographic and IVUS data were performed, but for which also Virtual Histology analysis was performed from both the index procedure and the 9 months follow-up study. Throughout the study period all patients were treated according to the institutional STEMI protocol which included standardized out-patient follow-up.[17] In brief, all patients had symptoms of STEMI that started <9 hours before arrival at the catheterization laboratory and an ECG that demonstrated a STEMI (ST segment elevation ≥0.2mV in ≥2 contiguous precordial leads [V1-V4], or ≥ 0.1mV ST elevation in other leads, or a new left bundle branch block).

Key exclusion criteria were age <18 years or >80 years; the presence of a left main lesion of ≥50% stenosis; triple vessel disease, defined as ≥50% stenosis in three major epicardial vessels; previous percutaneous coronary intervention or bypass grafting of the culprit vessel; failed thrombolytic therapy for the index infarction; reference diameter of the culprit lesion of less than 2.25mm or larger than 3.75mm; and lesion length ≥24mm.



## Procedure protocol

Before the index procedure all patients received 300mg of aspirin, 300-600mg of clopidogrel, and an intravenous bolus of abciximab (25µg /kg), followed by a continuous infusion of 100µg/kg for 12 hours. At the start of the procedure 5000IU of heparin was administered. Coronary lesions were treated according to current interventional practice. If more than one stent was required, the additional stent was of the same assigned study type.

After intervention IVUS imaging was performed to document angiographic result. Each angiogram and ultrasound sequence was preceded by 200-300µg of intracoronary nitroglycerin.

After the procedure aspirin (100mg/day) was prescribed indefinitely and clopidogrel (75mg/day) for 12 months. During follow-up, patients were treated with beta-blockers, statins and ACE-inhibitors or ATII-blockers, according to current guidelines.[17] Patients were seen at the out-patient clinic at 30 days, 3, 6, and 12 months. Follow-up angiography and (VH-) IVUS image acquisition was performed at 9 months follow-up.

## Quantitative coronary angiography (QCA)

Coronary angiograms obtained at baseline and at 9 months follow-up were digitally recorded and analyzed blinded to the assigned treatment.

The analysis was performed using automated edge-detection software (CMS version 6.0, Medis Medical Imaging Systems, Leiden, The Netherlands) at a single projection showing the most severe stenosis. The same projection was used at follow-up. The proximal and distal edges were evaluated up to 5mm from the stent.

## IVUS analysis

IVUS imaging was performed with motorized pull-back (0.5mm/s) starting at least 10mm distal to the stent, ending at the coronary ostium. A 2.9F 20MHz catheter and a dedicated IVUS console (Eagle Eye, Volcano Corp. Rancho Cordova, California, USA) were used.[18] Before imaging, 200-300µg of intracoronary nitroglycerin were administered. Analysis was performed by analysts that were blinded to the assigned treatment using customized software (QCU-CMS 4.14, Medis, Leiden, The Netherlands) for analysis of the quantitative grayscale data.

External elastic membrane (EEM) cross sectional area (CSA) and lumen CSA of segments 5mm proximal and distal to the stent were determined per frame and vessel volume, mean lumen area and minimal lumen area for these segments were compared to the same parameters at follow-up.

## Virtual histology analysis

VH images were generated simultaneously during motorized pull-back (figure 1). Images were acquired at every R-peak during continuous ECG registration. Data were stored digitally on CD for off-line analysis. Atherosclerotic coronary lesions were characterized by classification trees based on mathematical autoregressive spectral analysis of IVUS backscattered data (pcVH software version 2.2, Volcano Therapeutics). Fibrous areas were marked in green, fibro-fatty in yellow, dense calcium in white and necrotic core in red on the reconstructed color-coded tissue map. The area and volumes of each plaque component were calculated automatically by the pcVH software. PcVH analysis software is commercially available image analysis software developed by Vocano Therapeutics and the technique has been validated in past histopathological validation studies of VH-IVUS.[19;20]

Measurements were made for the region of interest, which was defined as the segment of minimal 5mm to maximal 10mm distal and proximal to the stented segment. This range was chosen instead of the conventional 5mm distance because: 1) it was unclear, assuming that there would be a downstream effect of the drug on plaque composition, how far the effect would reach and 2) as it was expected that these effects were likely to be small, it was considered preferable to include as much potentially affected longitudinal distance as

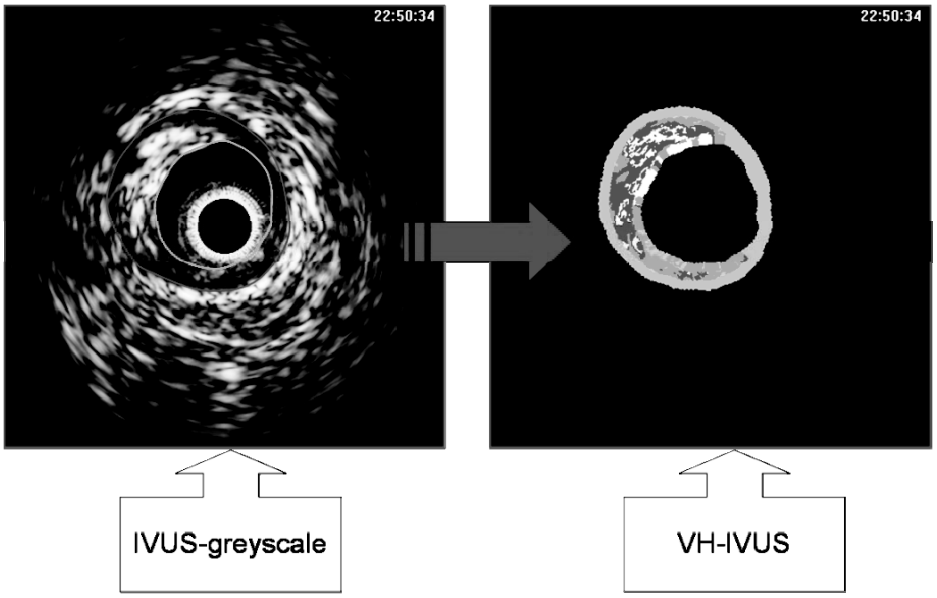


**Figure 1.** Illustration of creating an image with virtual histology intravascular ultrasound.
IVUS = intravascular ultrasound; VH-IVUS = virtual histology intravascular ultrasound.



possible. Catheterization images of the index procedure and of 9 months follow-up were analyzed side-by-side to ensure that the same segments were studied.

Although the volumetric analysis of the software could not be adjusted for repeated frames (implicating that the volume analysis of the same segment at different points of time could slightly differ) this problem was solved by using relative plaque volumes for final analysis (percentage of total plaque). Repeated frames were caused by the catheter getting stuck during pullback. In the 40 cases presented in this study only a small number of such frames were observed. Nevertheless, to minimize their influence on results for absolute plaque areas, repeated frames were ignored during this analysis.

## Statistical analysis

Continuous data are reported throughout this text and in the tables as mean ± standard deviation. Evenly distributed continuous data were analyzed by utilizing the independent sample t-test. Unevenly distributed continuous data were analyzed using an equivalent non-parametric test and the Mann-Whitney U test. For comparison to follow-up, analysis of continuous data at different points in time was performed by the paired Student's t-test. Categorical data are summarized as proportions and were compared with Pearson's $\chi^2$ -test or Fisher exact test in case of one or more cells in the contingency table with expectation less than 5, as appropriate. All tests weretwo-sided, a p-value of $<0.05$ was considered significant.

## RESULTS

Forty patients who received a SES (n=20) or BMS (n=20) during a primary PTCA were included in this substudy. There were no significant differences in baseline patient characteristics between the two patient groups (Table 1).

**Table 1.** Baseline characteristics.

| | BMS (n=20) | DES (n=20) | p-value |
|---|---|---|---|
| Male | 18 (90) | 13 (65) | 0.130 |
| Mean age | 62 (41-79) | 59 (29-75) | 0.418 |
| Cardiovascular risk factors: | | | |
| Hypertension | 5 (25) | 7 (35) | 0.731 |
| Hyperlipidemia | 5 (25) | 4 (20) | 1.000 |
| Smoking | 12 (60) | 15 (75) | 0.501 |
| Diabetes Mellitus | 1 (5) | 5 (25) | 0.184 |
| Prior MI | 3 (15) | 1 (5) | 0.598 |
| Family History of CAD | 8 (40) | 13 (65) | 0.205 |
| Medication at discharge: | | | |
| Aspirin | 20 (100) | 20 (100) | 1.000 |
| Statin | 20 (100) | 20 (100) | 1.000 |
| β-Blocker | 20 (100) | 20 (100) | 1.000 |
| Clopidogrel | 20 (100) | 20 (100) | 1.000 |
| ACE/AT2-inhibitor | 19 (95) | 20 (100) | 1.000 |
| Anticoagulant | 0 | 0 | |
| Medication at 12 months: | | | |
| Aspirin | 20 (100) | 17 (85) | 0.230 |
| Statin | 20 (100) | 20 (100) | 1.000 |
| β-Blocker | 19 (95) | 19 (95) | 1.000 |
| Clopidogrel | 20 (100) | 17 (85) | 0.230 |
| ACE/AT2-inhibitor | 19 (95) | 19 (95) | 1.000 |
| Anticoagulant | 0 | 3 (15) | 0.230 |
| Target vessel: | | | |
| LAD | 9 (45) | 11 (55) | 0.752 |
| RCA | 8 (40) | 2 (10) | 0.065 |
| LCX | 3 (15) | 7 (35) | 0.273 |
| No. of vessels diseased: | | | |
| 1 | 9 (45) | 8 (40) | 1.000 |
| 2 | 9 (45) | 10 (50) | 1.000 |
| 3 | 2 (10) | 2 (10) | 1.000 |

Values are expressed as number (%) or as age (min-max).
BMS = bare-metal stent; CAD = coronary artery disease; MI = myocardial infarction; LAD = left anterior descending artery; RCA = right coronary artery; LCX = left circumflex artery; SES = sirolimus-eluting stent.
Hyperlipidemia= Total cholesterol ≥190 mg/dl or previous pharmacological treatment.
Hypertension = Blood pressure ≥140/90 mm Hg or previous pharmacological treatment.

## Angiographic results

Index-procedure and follow-up QCA-results for minimum lumen area and mean lumen diameters are reported in table 2. In BMS patients both minimum and mean lumen diameter decreased at both sides of the stent at follow-up though this did not reach statistical significance at the distal stent edges (MLD proximal edge: from 2.76 ± 0.42mm to 2.62 ± 0.46mm; p =0.03 and Mean LD proximal edge: from 3.05 ± 0.48mm to 2.94 ± 0.46mm; p =0.03, MLD distal edge: from 2.43 ± 0.48mm to 2.21 ± 0.67mm; p =0.10 and Mean LD from 2.65 ± 0.55mm to 2.48 ± 0.69mm; p =0.19).

In SES patients a similar (although non-significant) decline in lumen area was observed at the proximal stent edge, the distal MLD and Mean LD however tended to increase (MLD) or remained unchanged (Mean LD) during follow-up (MLD proximal edge: from 2.74 ± 0.37mm to 2.68 ± 0.46mm; p =0.40 and Mean LD from 3.04 ± 0.57mm to 2.94 ± 0.57mm; p =0.09, MLD distal edge: from 2.38 ± 0.39mm to 2.44 ± 0.53mm; p =0.41 and Mean LD from 2.61 ± 0.37mm to 2.61 ± 0.5 mm; p =0.97).

**Table 2.** Results of Quantitative Coronary Angiography at baseline and at follow-up.

| | BMS | | | SES | | |
|---|---|---|---|---|---|---|
| | Baseline | Follow-up | p-value | Baseline | Follow-up | p- value |
| Proximal stent edge: | | | | | | |
| Minimal lumen diameter (mm) | 2.8 ± 0.4 | 2.6 ± 0.5 | 0.03* | 2.7 ± 0.4 | 2.7 ± 0.5 | 0.40 |
| Mean lumen diameter (mm) | 3.1 ± 0.5 | 2.9 ± 0.5 | 0.03* | 3.0 ± 0.6 | 2.9 ± 0.6 | 0.09 |
| Distal stent edge: | | | | | | |
| Minimal lumen diameter (mm) | 2.4 ± 0.5 | 2.2 ± 0.7 | 0.10 | 2.4 ± 0.4 | 2.4 ± 0.5 | 0.41 |
| Mean lumen diameter (mm) | 2.7 ± 0.6 | 2.5 ± 0.7 | 0.19 | 2.6 ± 0.4 | 2.6 ± 0.5 | 0.97 |

Data expressed as lumen diameters (mm) ± standard deviation. *p = <0.05
BMS = bare-metal stent; SES = sirolimus-eluting stent.

## IVUS grayscale results

Quantitative post procedural and follow-up IVUS data are summarized in tables 3 and 4. At the proximal stent edge, vessel volume and lumen areas decreased in both BMS and SES patients at 9 months follow-up (BMS: -3.6% and -0.5% and SES: -7.2% and -8.2%). The mean lumen area decreases significantly in the SES group at the proximal stent edges (p =0.03).

At follow-up, vessel volume and mean lumen area of the distal stent edge of the BMS group tended to decline (overall decrease of -5.0% and -6.3% respectively, p=ns), while they increased in the SES group (vessel volume increase of 1.5% and mean lumen area increase of 3.4%, p=ns). There were no significant differences between BMS and SES groups in vessel volume and mean lumen area changes except for mean lumen area at the distal stent edge (Δ-0.8 ± 1.6mm$^2$ versus Δ0.2 ± 0.8mm$^2$ respectively, p =0.04; table 4). Within the stented segment however, the SES group demonstrated a significantly larger

**Table 3.** Results of Coronary Ultrasound at stent edges at baseline and at follow-up

| | BMS | | | SES | | |
|---|---|---|---|---|---|---|
| | Baseline | Follow-up | p-value | Baseline | Follow-up | p- value |
| Proximal stent edge: | | | | | | |
| Vessel volume ($mm^3$) | 83.2 ± 27.6 | 80.7 ± 25.6 | 0.54 | 76.0 ± 34.5 | 66.7 ± 37.9 | 0.22 |
| Minimal lumen area ($mm^2$) | 6.9 ± 2.7 | 6.3 ± 2.5 | 0.14 | 6.5 ± 1.7 | 6.6 ± 1.6 | 0.82 |
| Mean lumen area ($mm^2$) | 8.5 ± 3.1 | 8.0 ± 3.6 | 0.24 | 8.6 ± 2.3 | 7.9 ± 2.3 | 0.03* |
| Distal stent edge: | | | | | | |
| Vessel volume ($mm^3$) | 72.6 ± 29.7 | 67.1 ± 26.0 | 0.09 | 54.3 ± 22.2 | 56.1 ± 20.3 | 0.21 |
| Minimal lumen area ($mm^2$) | 6.3 ± 2.7 | 5.7 ± 2.5 | 0.11 | 5.3 ± 1.7 | 5.5 ± 1.7 | 0.52 |
| Mean lumen area ($mm^2$) | 7.8 ± 3.5 | 7.0 ± 3.0 | 0.07 | 6.5 ± 1.6 | 6.7 ± 1.7 | 0.34 |

Data expressed as volumes ($mm^3$) or as areas ($mm^2$) ± standard deviation.
*p= <0.05.
Abbreviations as in table 2.

**Table 4.** Results of Coronary Ultrasound for the stented segment and stent edges at 9 months follow-up

| | BMS | SES | p-value |
|---|---|---|---|
| Stented length | 24.5 ± 7.0 | 23.4 ± 7.1 | 0.65 |
| Mean number of stents | 1.4 ± 0.5 | 1.3 ± 0.5 | 0.42 |
| Stented segment | | | |
| Area ($mm^2$) | | | |
| Minimal stent area | 6.1 ± 1.1 | 6.0 ± 1.5 | 0.72 |
| Mean stent area | 7.3 ± 1.0 | 7.5 ± 1.7 | 0.59 |
| Volume ($mm^3$) | | | |
| Stent volume | 178.4 ± 56.3 | 175.1 ± 59.0 | 0.87 |
| Lumen volume | 125.1± 43.8 | 167.7 ± 59.2 | 0.02* |
| Neointimal volume | 53.2 ± 35.1 | 7.3 ± 9.1 | <0.001* |
| Percentage neointimal volume | 30.0 ± 14.8 | 4.6 ± 5.6 | <0.001* |
| Proximal stent edge: | | | |
| Δ Vessel volume ($mm^3$) | -2.5 ± 14.7 | -9.4 ± 27.1 | 0.42 |
| Δ Minimal lumen area ($mm^2$) | -0.6 ± 1.4 | 0.1 ± 1.1 | 0.17 |
| Δ Mean lumen area ($mm^2$) | -0.5 ± 1.4 | -0.7 ± 1.1 | 0.66 |
| Distal stent edge | | | |
| Δ Vessel volume ($mm^3$) | -5.6 ± 12.5 | 0.5 ± 3.9 | 0.08 |
| Δ Minimal lumen area ($mm^2$) | -0.6 ± 1.5 | 0.2 ± 1.3 | 0.09 |
| Δ Mean lumen area ($mm^2$) | -0.8 ± 1.6 | 0.2 ± 0.8 | 0.04* |

Data expressed as volumes ($mm^3$) or as areas ($mm^2$) ± standard deviation.
*p= <0.05.
Δ = alteration in volume (mm3) or area (mm2) from baseline.
Abbreviations as in table 2.

lumen volume (SES: 167.7 ± 59.2mm$^3$ versus BMS: 125.1± 43.8mm$^3$; p =0.02) at follow-up. Also in SES, less neointima volume (7.3 ± 9.1mm$^3$ versus 53.2 ± 35.1mm$^3$; p <0.001) and lower percentage neointimal volume (4.6 ± 5.6% versus 30.0 ± 14.8%; p <0.001) were found at follow-up when compared to BMS.

**Table 5.** Results of Virtual Histology Analysis for relative plaque volume per component at baseline and at follow-up.

| | BMS | | | SES | | |
|---|---|---|---|---|---|---|
| | Baseline | Follow-up | p-value | Baseline | Follow-up | p-value |
| Proximal segment | | | | | | |
| Fibrous (%) | 56.3 ± 7.2 | 57.3 ± 7.3 | 0.56 | 57.0 ± 8.9 | 58.4 ± 7.7 | 0.49 |
| Fibro-fatty (%) | 31.1 ± 12.4 | 27.7 ± 8.0 | 0.18 | 31.0 ± 15.4 | 31.6 ± 14.9 | 0.87 |
| Necrotic core (%) | 9.0 ± 7.8 | 10.7 ± 5.2 | 0.36 | 8.4 ± 7.3 | 9.2 ± 7.9 | 0.46 |
| Dense Calcium (%) | 3.6 ± 3.4 | 4.2 ± 3.3 | 0.44 | 3.7 ± 4.5 | 4.3 ± 4.8 | 0.40 |
| Distal Segment | | | | | | |
| Fibrous (%) | 62.8 ± 9.7 | 57.2 ± 12.4 | 0.05* | 57.7 ± 20.7 | 52.8 ± 24.1 | 0.35 |
| Fibro-fatty (%) | 25.0 ± 14.3 | 27.2 ± 12.8 | 0.41 | 25.0 ± 12.9 | 22.7 ± 13.9 | 0.60 |
| Necrotic core (%) | 8.9 ± 6.2 | 10.2 ± 8.4 | 0.40 | 5.7 ± 5.3 | 6.7 ± 6.2 | 0.55 |
| Dense Calcium (%) | 3.3 ± 3.9 | 5.5 ± 10.5 | 0.25 | 1.6 ± 1.8 | 2.9 ± 3.6 | 0.09 |

Data expressed as relative proportions of plaque volume (%) ± standard deviation. *p = <0.05
Abbreviations as in table 2.



## Virtual Histology results

Post procedural and follow-up VH-IVUS results for relative volumes of the different plaque components are reported in table 5. The relative increase and decrease of each plaque component volume is illustrated in figure 2. Except for a significant decrease of the fibrous plaque component volume of the distal edge segment of BMS (p =0.05), plaque composition did not change significantly in either group. The data for mean areas at baseline and follow-up are summarized in table 6 and the relative increase/decrease of mean area of every plaque component at follow-up is depicted in figure 3. Again, no significant difference in mean area of the four plaque components is discernable between follow-up and baseline in either group.

As it was considered possible that by using the calculated means of data from the edge segments any differences between baseline and follow-up in both stent type groups may have been obscured, it was decided to perform an additional VH-IVUS analysis of the frame just distal from the stent edge at baseline and at follow-up for all 40 cases. However, this analysis too revealed no significant differences for plaque composition areas between post-intervention and follow-up and between the two stent types (not shown).

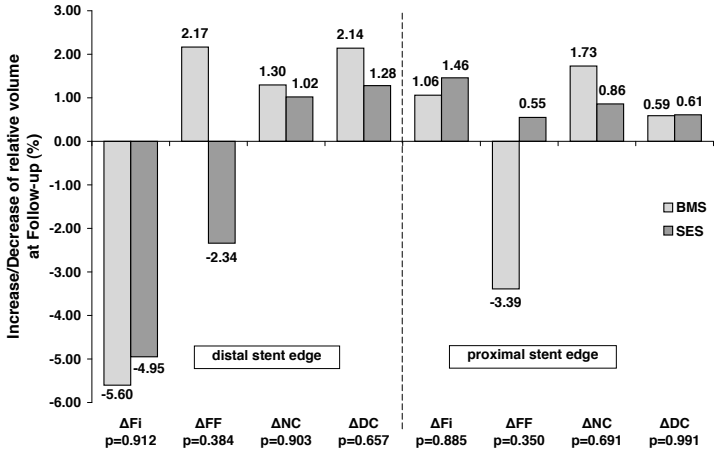


**Figure 2.** Relative volume changes over 9 months time (Δ%).
Measurements for BMS are set out next to SES. P-values are reported to indicate statistical significance of differences in plaque component changes between BMS and SES. None are significant.
BMS = Bare-metal stents; SES = Sirolimus-eluting stents; Δ = change in relative volume of mentioned plaque component; Fi = fibrous; FF = fibro-fatty; DC = dense calcium; NC = necrotic core.

**Table 6.** Results of Virtual Histology Analysis for relative plaque area per component at baseline and at follow-up

| | Bare-metal stent | | | SES | | |
|---|---|---|---|---|---|---|
| | Baseline | Follow-up | p-value | Baseline | Follow-up | p-value |
| Proximal segment | | | | | | |
| Fibrous ($mm^2$) | 3.2 ± 1.3 | 3.2 ± 1.3 | 0.76 | 3.6 ± 2.0 | 3.4 ± 1.8 | 0.15 |
| Fibro-fatty ($mm^2$) | 1.7 ± 1.1 | 1.5 ± 0.7 | 0.27 | 1.6 ± 0.9 | 1.5 ± 1.0 | 0.43 |
| Necrotic core ($mm^2$) | 0.6 ± 0.6 | 0.6 ± 0.4 | 0.64 | 0.6 ± 0.7 | 0.7 ± 0.8 | 0.94 |
| Dense Calcium ($mm^2$) | 0.3 ± 0.3 | 0.3 ± 0.3 | 0.93 | 0.3 ± 0.4 | 0.3 ± 0.4 | 0.81 |
| Distal Segment | | | | | | |
| Fibrous ($mm^2$) | 2.1 ± 1.1 | 1.9 ± 1.0 | 0.06 | 1.0 ± 1.5 | 0.9 ± 1.1 | 0.27 |
| Fibro-fatty ($mm^2$) | 0.9 ± 0.6 | 1.0 ± 0.7 | 0.56 | 0.4 ± 0.5 | 0.4 ± 0.7 | 0.89 |
| Necrotic core ($mm^2$) | 0.3 ± 0.2 | 0.3 ± 0.3 | 0.96 | 0.1 ± 0.2 | 0.1 ± 0.3 | 0.68 |
| Dense Calcium ($mm^2$) | 0.1 ± 0.2 | 0.1 ± 0.2 | 0.92 | 0.1 ± 0.1 | 0.1 ± 0.2 | 0.16 |

Data expressed as mean areas of the plaque components ($mm^2$) ± standard deviation.
Abbreviations as in table 2.

## Clinical outcome

One BMS patient and one SES patient underwent a target lesion revascularization due to restenosis. No patient died during the follow-up period of 12 months. Three BMS patients and two SES patients underwent revascularization of a vessel other than the culprit vessel at different points of time within a 12 months follow-up period. Adherence to medication was high (table 1), no sub-acute thrombosis was observed.

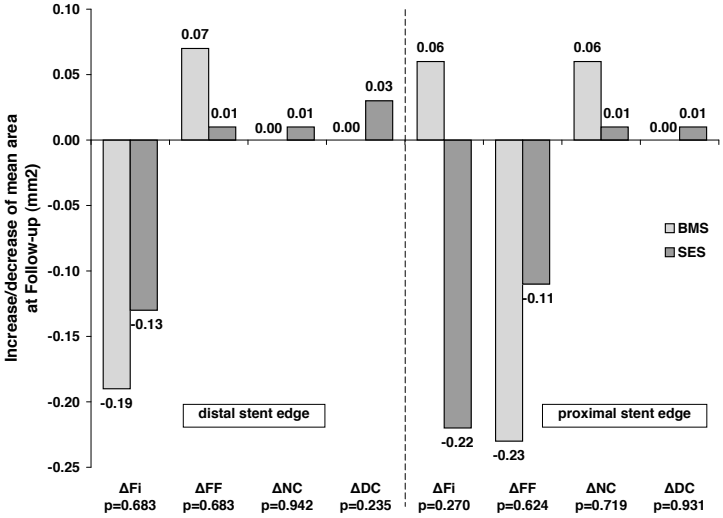


**Figure 3.** Mean area changes over 9 months time.
Measurements for BMS are set out next to SES. P-values are reported to indicate statistical significance of differences in plaque component changes between BMS and SES. None are significant.
$\Delta$ $mm^2$ = change in mean area of mentioned plaque component; Other abbreviations as in figure 2.



## DISCUSSION

To our knowledge, this is the first follow-up study that compares vascular plaque composition and remodeling at stent edges between BMS and SES treated patients. The main findings of this study are: (1) at distal and proximal stent edges in BMS patients there is a trend towards negative vascular remodeling while there is a trend towards positive remodeling at the distal stent edges in SES treated patients resulting in a significant difference between the two groups; (2) plaque composition at the stent edges did not change significantly during the 9 months follow-up in either SES or BMS patients.

Sirolimus-eluting stent implantation results in a significant reduction of restenosis compared to the results obtained with bare-metal stents in patients with stable and unstable angina.[14;21] However, inconsistent and limited data have been presented about their safety and efficacy in patients with acute myocardial infarction.[1-4] Sirolimus is a potent anti-inflammatory, immunosuppressive and antiproliferative drug effective in inhibiting in-stent neointimal hyperplasia.[22] These potent antiproliferative effects can also induce positive remodeling and stent malapposition and may cause deleterious local phenomena such as necrosis or apoptosis. [4;13;22] These effects may potentially affect plaque composition behind the stent, the vessel wall, and as a result of downstream effects of the eluted drug may also affect plaque composition at the distal stent edge.

Clinical data support the hypothesis of drug elution distal to the stent. In recent trials, SES implantation resulted in higher restenosis rates at the proximal edge of the stent compared to the distal edge.[14] One expects the concentration and therefore the effects of the drug to be strongest in the direction of the blood flow. This seems to be confirmed by a study by Degertekin et al. showing a trend towards positive remodeling only at the distal stent edge but not at the proximal edge.[13] Comparative results have been found in several other studies. Investigators of the RAVEL trial reported a trend toward larger lumen areas at distal edge which was thought to be due to higher downstream effect of the drug. A study from Jimenez-Quevedo et al further confirmed these findings by reporting a significant increase in lumen dimensions at stent edges of SES compared to lumen reduction at stent edges in BMS in patients with diabetes.[22;23] Our findings are in agreement with this, as we observed a trend towards positive remodeling at the distal stent edges in SES patients, though, similar to Degertekin et al, not statistically significant.

Several studies reported that stent edge burden is an important periprocedural predictor of stent edge restenosis after BMS and SES implantations.[24-26] In the present study population the stent edge plaque burden may have been too small to be affected significantly by the drug.

Thus far, effects of sirolimus on proximal and distal stent edges have not been fully evaluated. Serruys et al reported a vascular response at the proximal and distal stent edges after paclitaxel-eluting stent implantation.[15] The paclitaxel-eluting stent induced positive remodeling 1mm proximal and 3 to 4mm distal to the stent edges which resulted in less late luminal loss compared to BMS.

Little is known about the effects of sirolimus on the plaque composition at the proximal and distal stent edges. Our findings suggest that plaque composition at the stent edges was not affected by the drug since no significant differences could be detected between BMS and SES patients at follow-up. This is interesting given that an effect of sirolimus on vascular lumen dimensions was clearly present distal to the stent as well as a detectable effect on neointima volume inside the stent as demonstrated by the IVUS grayscale data. As expected, within the stented segment, SES was associated with significantly less neointimal hyperplasia when compared to BMS, a well known effect.[4;22] At the stent edges however, a decrease in local drug delivery may have occurred, which may have caused the drug to be ineffective in inducing changes in plaque composition at stent edges. However, changes in plaque composition caused by the drug may be subtle and missed by the VH-IVUS technique.

Similar data were observed in a study from Aoki et al who reported in a long-term follow-up study of 23 event-free patients treated with SES that no significant changes in plaque echogenicity at the distal stent edges (5mm) had taken place across multiple time points of follow up.[27] At the same time investigators did see a change of plaque echogenicity behind the stent struts between 2 years and 4 years of follow up. This is interesting as this suggests that alterations in plaque composition take place very late (>2 years) after stent

implantation and that they are very localized, therefore possibly not involving a measurable downstream edge effect.

It may be that the remodeling effect on the vessel at the distal stent edge is a general effect that is caused merely by a delayed healing response. Caramori et al. demonstrated persistent vasomotor dysfunction distal to coronary stents implanted 6 months earlier.[28] The anti-proliferative effect of sirolimus may merely cause a prolonged healing response with concomitant delayed recovery of endothelial function as suggested by Hofma et al.[29] It has been suggested before that delayed vascular healing may cause positive remodeling and incomplete stent apposition.[30;31]

In addition, past studies suggested that sirolimus or the polymer might induce apoptosis or necrosis.[32;33] It was suggested that the strong hydrophobic property of the compound partitions highly into arterial tissue resulting in drug concentrations that exceed the applied bulk concentration.[33;34] This highly concentrated local delivery of a potent drug may lead to increased vascular toxicity which in turn may lead to an inflammatory response. Pires et al, investigated histopathological effects of sirolimus- and paclitaxel-eluting cuffs in a murine model for restenosis on underlying diseased atherosclerotic arteries.[33] While paclitaxel significantly increased apoptosis, internal lamina elastic disruption, and decreased medial and intimal smooth muscle cells and collagen, vascular histopathological analysis revealed that sirolimus had no significant adverse effects on vascular pathology. This further supports our finding of unaffected plaque composition in SES.



## Limitations

This study is limited by the fact that it was a single-center study and that, due to the complex nature of the study design, the patient sample size for which all the above mentioned imaging modalities were available was relatively small.[4] Nonetheless, though it may not be possible to firmly conclude that no difference of effect on plaque composition exists between SES and BMS on stent edges after 9 months of follow up, the data indicates that these differences are possibly of smaller magnitude than anticipated. The relatively short follow-up of 9 months may have been a possible limitation, as changes in plaque composition may take much longer to develop than was presumed. Larger and longer follow-up studies of well-matched patient populations will be able to tell just how much of a difference there truly is.

Secondly, using VH-IVUS analysis at the index procedure made the border detection a more complex process.[35;36] Inaccurate detection of borders shared by thrombus, plaque and lumen might have caused measurement errors of plaque composition.

## CONCLUSION

This study demonstrates a trend towards positive remodeling at the distal stent edges in SES patients and a significant inhibition of neointimal hyperplasia within the stented segment at follow-up as compared to BMS treated patients. The effect on the distal stent edge suggests a downstream effect of sirolimus elution despite the fact that an effect on plaque composition was not observed.

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# Chapter 5

## Aspiration thrombectomy during primary percutaneous coronary intervention as adjunctive therapy to early (in-ambulance) abciximab administration in patients with acute ST elevation myocardial infarction: An analysis from Leiden MISSION! acute myocardial infarction treatment optimization program.

Tarek A. N. Ahmed[1,2], MD; Jael Z. Atary[1], MD; Ron Wolterbeek[3], MD; Hosam Hasan Ali, MD,PhD[2]; Samir S. Abdel-Kader[2], MD,PhD; Martin J. Schalij[1],MD,PhD; and J. Wouter Jukema[1*], MD,PhD

[1] Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands
[2] Department of Cardiology, Assiut University, Assiut, Egypt
[3] Department of Medical Statistics, Leiden University Medical Center, Leiden, The Netherlands

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## ABSTRACT

### Background

The benefits of early abciximab administration and thrombus aspiration in STEMI patients undergoing PPCI have been previously elaborated. However, whether there is adjunctive effect of thrombus aspiration among STEMI patients, with angiographic evidence of thrombus, receiving early abciximab prior to hospital arrival remains unclear. Methods

In the context of a fixed protocol for PPCI, 158 consecutive patients with STEMI were enrolled, in whom abciximab was started early before arrival at the hospital (in-ambulance); 79 patients who had PPCI with thrombus aspiration (thrombectomy-facilitated PCI group), were compared to 79 who had PPCI without thrombus aspiration (Conventional PCI group) in a prospective non-randomized study. The primary end point was complete ST-segment resolution within 90min. Secondary endpoints included enzymatic infarct size as well as LVEF assessed by Gated-SPECT. MACE were evaluated up to 12 months.

### Results

Both groups were comparable for baseline clinical and angiographic characteristics. The rate of ST-segment resolution was significantly higher in the thrombectomy-facilitated group (p=0.002), and multivariable logistic regression analysis identified only thrombectomy as an independent predictor of ST-segment resolution (odds ratio= 6.7, 95% CI = 2.4-18.4, p< 0.001). No difference was observed between both groups in enzymatic infarct size assessed by peak CK (p=0.8), and peak Tn-T levels (p=0.5). Also the LVEF at 3-months was similar (p=0.9). At 12 month clinical follow-up, thrombus aspiration was however associated with reduced all-cause mortality (log-rank p= 0.03). Conclusion

Among STEMI patients treated with PPCI and in-ambulance abciximab, it appears that a selective strategy of thrombus aspiration still has additive benefit.

## INTRODUCTION

It has been widely observed that primary percutaneous coronary intervention (PPCI) offers greater reperfusion benefits in the setting of acute myocardial infarction (MI) compared to intravenous thrombolytic therapy.[1] However, despite a good epicardial flow after PPCI, a considerable percentage of patients have impaired myocardial perfusion mainly due to embolization of the microcirculation.[2] Poor myocardial reperfusion is associated with adverse outcome including reduced left ventricular function and mortality.[3-5]

Recent studies demonstrated that GP IIb,IIIa platelet receptor antagonists have positive effects on reperfusion in the setting of primary percutaneous coronary interventions, with improved clinical outcome.[6] Many studies showed that these benefits are more apparent when GP IIb IIIa platelet receptor antagonists are introduced as early as achievable in the setting of acute myocardial infarction.[7-12]

Additionally, numerous adjunctive coronary devices have been developed in an attempt to decrease or prevent distal embolization during revascularization and thereby trying to improve clinical outcome as well.

Recent randomized trials demonstrated that patients treated with a thrombectomy catheter showed better angiographic and electrocardiographic signs of myocardial reperfusion, as well as improved 1 year clinical outcome.[13-16] These data have been confirmed by recent meta-analyses demonstrating that adjunctive manual thrombectomy in the setting of primary PCI is associated with improved epicardial and myocardial perfusion, less distal embolization [17], as well as improved clinical outcome.[18]

However, it is still unknown whether there is a possible benefit of using thrombus aspiration devices in the setting of PPCI among STEMI patients receiving early GP IIb IIIa platelet receptor antagonists. Therefore, in this study the results of adjunctive manual thrombus aspiration using aspiration thrombectomy catheter were compared to no thrombus aspiration in a consecutive group of STEMI patients treated with PPCI and early "in-ambulance" abciximab administration according to the adapted Mission protocol.[19,20]

## METHODS

### Study design

This is a single center non-randomized prospective study. All patients were treated according to the institutional STEMI protocol (MISSION!) implemented at Leiden University Medical Centre (LUMC) since February 2004, which includes a standardized prehospital, in-hospital and outpatient clinical framework for decision making and treatment.[19,20] The tertiary center provides a round-the-clock service of PPCI with highly experienced PCI physicians and dedicated nurses.

## Inclusion and exclusion criteria

The inclusion criterion was a diagnosis of acute MI defined by chest pain suggestive of myocardial ischemia for at least 30 minutes, with a time from onset of symptoms of <9 hours before hospital admission, and an ECG with ST-segment elevation of >0.1 mV in ≥2 leads. Exclusion criteria were recent surgery, recent stroke, hemorrhagic diatheses, and known contraindications for therapy with abciximab, aspirin, clopidogrel or heparin.

## Study groups

A total of 158 consecutive patients; who fulfilled the inclusion and exclusion criteria for this study, and who received early in-ambulance abciximab, were enrolled: 79 consecutive patients, in whom a thrombectomy catheter was used at the start of the procedure (the thrombectomy facilitated PCI group); were compared to 79 consecutive patients within the same period, in whom thrombectomy catheter was not used (the conventional PCI group). The study complies with the Declaration of Helsinki. The MISSION! protocol has been approved by the local ethics committee.

## Medication

All patients received abciximab (Centocor B.V., Leiden, The Netherlands) as a bolus injection of 0.25 mg/ kg bodyweight, followed by 0.125 mcg/kg/min with a maximum of 10 mcg/ min as a continuous infusion for 12 hr. Abciximab administration started early in the ambulance according to the adapted MISSION! Protocol.[19,20] Furthermore all patients received an equivalent of 300 mg of acetylsalicylic acid, 600 mg clopidogrel as a loading dose in the ambulance and heparin given as a bolus of 5000 IU at the start of the PCI procedure. After the procedure, all patients received aspirin (75 mg/day) indefinitely and clopidogrel (75 mg/day) for one year. Other medications, including b-blockers, ACE-inhibitors, nitrates, and statins, were prescribed according to MISSION! protocol.

## Invasive Procedure and Angiographic Evaluation

All PPCI was performed through a 6F femoral sheath. Patients underwent PPCI and stenting of the IRA according to standard techniques. The choice of stent (bare-metal stent or drug-eluting stent) was left to the operator's discretion. Direct stenting, which is stent placement without balloon pre-dilatation, was performed only in cases presenting clear views of the arterial lesion with adequate flow. We also considered stent placement which was only preceded by thrombectomy as direct stenting. Otherwise, the patient was subjected to balloon angioplasty and stenting was done subsequently. The choice of the balloon size was left to the operator's decision. Stent implantation was successfully completed in all patients, apart from only one patient in the thrombectomy facilitated PCI group where the procedure was complicated by a spiral dissection occurring after thrombectomy and had to undergo emergency coronary artery bypass graft (CABG), and this patient survived and completed the

follow-up period. The choice of performing thrombectomy was left to the operator's discretion. Thrombectomy was often, but not exclusively, performed when high thrombus burden was observed at the initial angiographic image of the target vessel. There was no change in the frequency of use of thrombectomy over the time period of the study. Thrombus was assessed according to the criteria summarized by Mabin et al.[21] These criteria include the presence of an intraluminal central filling defect or lucency surrounded by contrast material that is seen in multiple projections; the absence of calcium within the defect; and persistence of contrast material within the lumen. Thrombus score was graded as previously described by the TIMI Study Group.[22,23] We further categorized the thrombus score into 2 overall grades; a high thrombus grade (grades 4 and 5), and a low thrombus grade (grades 1-3). We decided to use this cut-off value in line with 2 recent studies[24,25] suggesting prognostic implications of this cutoff. Coronary flow was graded according to thrombolysis in myocardial infarction (TIMI) criteria.[26] TIMI flow grade was evaluated at baseline and after the PCI procedure. Procedural success was defined as residual stenosis <20% and TIMI flow grade 3. The coronary angiograms were reviewed off-line by two independent interventional cardiologists who were blinded to the clinical data.

## Thrombectomy catheter

The Export Aspiration Catheter (Medtronic Corporation, USA) is a 6F thrombus aspiration catheter.[13] Thrombosuction was started proximal to the occluded site, gently pushing the catheter through the occlusion and then pulling it in a proximal direction, keeping negative pressure once the occlusion was crossed or if there was no longer backflow in the syringe. This could be repeated several times. Withdrawal of the catheter from the artery and from the guiding catheter was performed with permanent negative pressure. After each pass the catheter was flushed and the syringe emptied over a filter, to show the retrieved debris.

## End-points and clinical follow-up

According to the MISSION! Protocol all patients were seen at the dedicated out-patient clinic after 1, 3, 6, and 12 months. The primary endpoint was ST-segment resolution within 90 min. after PPCI; secondary endpoints were enzymatic infarct size and LVEF as assessed by Gated-SPECT. Also major adverse cardiac events (MACE) occurring within one year of follow-up were recorded. These include all-cause death, cardiac death, reinfarction, target vessel and target lesion revascularization; death was regarded as cardiac unless an unequivocal non-cardiac cause of death was established. Reinfarction was defined as recurrent symptoms with new ST-segment elevation and elevation of cardiac markers to at least twice the upper limit of normal. Target vessel (TVR) and target lesion (TLR) revascularization were defined as any revascularization procedure of the target vessel or target lesion (from 5 mm distally to the stent up to 5 mm proximally to the stent), respectively. All major adverse cardiac events were assessed and classified by an interventional cardiologist unaware of the treatment allocation.

## Electrocardiographic data

The 12-lead ECG was recorded at presentation and within 90 min after PPCI. The magnitude of ST-segment elevation is measured 60 milliseconds from J point. ST-segment score is calculated as the sum of ST-segment elevation > 0.1 mV for leads V1 through V6 and I, II, and aVL in anterior infarction and I, II, aVF, V5, and V6 in non-anterior infarction (27). All ECGs were collected and analyzed by an investigator blinded to the assigned treatment. Total ST-segment elevation at inclusion was compared with that taken within 90 min after PPCI. A complete ST-segment resolution was calculated, defined as resolution of the initial ST-segment elevation of ≥70%.[28]

## Enzymatic Infarct Size

Creatine kinase (CK) activity and cardiac troponin-T (Tn-T) concentration in plasma were determined at admission and every 6 hr in the first 48 hr after PPCI. Subsequently these levels were determined every day up to discharge, unless clinical events suggested repeat measurements. Peak levels of CK and Tn-T in plasma were calculated as a measure of infarct size in each patient by an investigator blinded to the assigned treatment.



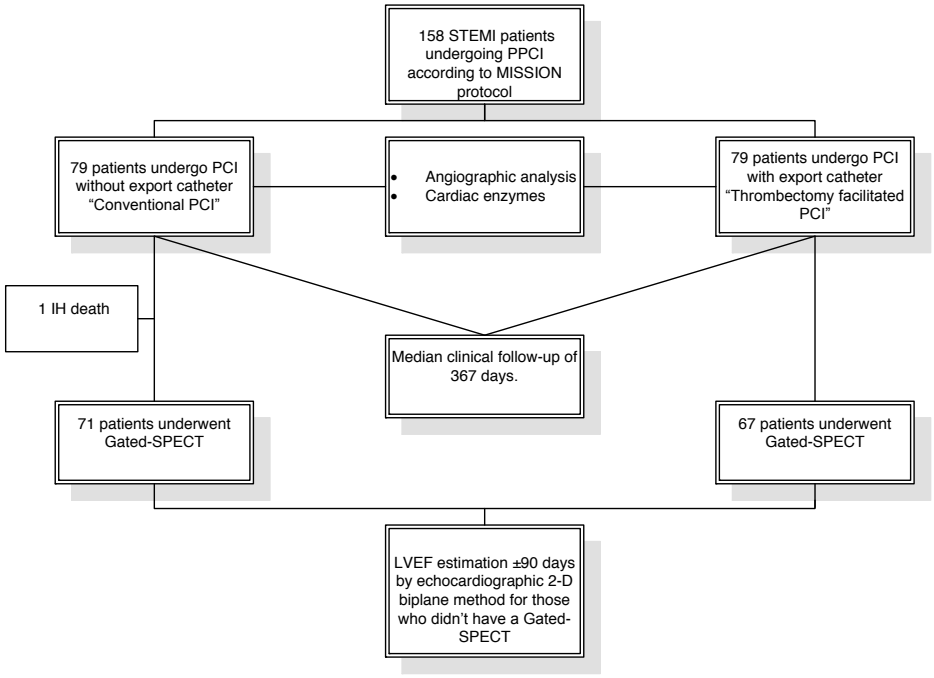


**Figure 1.** Flow diagram of the study patients.
LVEF: left ventricular ejection fraction; PPCI: primary percutaneous coronary intervention; SPECT: single photon emission computed tomography; STEMI: ST elevation myocardial infarction; IH: in hospital.

### Myocardial Perfusion Imaging

According to the MISSION! Protocol all included patients were enrolled for a myocardial perfusion study at 90 days post-PPCI. An ECG gated SPECT acquisition at rest using intravenous Technetium 99 m Tetrofosmin (MYOVIEW, Amersham, Buckinghamshire, UK) was used to measure the left ventricular ejection fraction (LVEF) 90 days after PPCI. LVEF was calculated using an automated and validated method (QGS software, version 2.0; Cedars-Sinai Medical Center, Los Angeles, CA, USA). Detailed methods are described elsewhere.[29] Patients in whom the gated SPECT could not be performed due to technical difficulties, LVEF estimated by echocardiographic biplane method was used instead. LVEF assessment was done by an investigator blinded to the assigned treatment.

### Statistical analysis

Categorical variables were compared using the $X^2$ test or Fisher's exact test. Continuous normally distributed data were tested by student t-test or in the case of a non-Gaussian distribution by a nonparametric test for independent samples (Mann Whitney *U* test). One year clinical outcomes were analyzed using Kaplan Meier methodology and were compared with log-rank test pooled over strata. Multivariable linear regression and logistic regression analyses were used to create models for both PCI groups (as the variable of interest) corrected for thrombus grade, infarct related artery, proximal location of the culprit lesion and symptoms to balloon time (as potential confounders), to identify whether thrombectomy is an independent predictor for the end points of ST-segment resolution, infarct size assessed by cardiac enzymes or LVEF. All tests were two-sided, and a p-value of $< 0.05$ was considered significant. All analyses were performed with PASW version 17.0 statistical software (SPSS Inc. - An IBM Company, Chicago, IL, USA).

## RESULTS

### Study population

One-hundred and fifty-eight patients were included in the study according to the eligibility criteria (Figure 1 Flow diagram). The baseline clinical characteristics were comparable between the two groups (Table 1).

### Angiographic and peri-procedural findings

Angiographic and procedural data are summarized in Table 2. There was a significantly higher rate of high grade thrombus in the thrombectomy facilitated group ($p<0.001$), also there was a significantly higher rate of balloon predilatation in the conventional PCI group ($p= 0.002$).

**Table 1.** Baseline characteristics.

| | Conventional PCI N=79 | Thrombus aspiration N=79 | p |
|---|---|---|---|
| Age in years | 59±10 | 56±12 | 0.1[a] |
| Male, n (%) | 59(75) | 62(78) | 0.6[b] |
| History, n (%) | | | |
| Hypertension | 28(35) | 24(30) | 0.5[b] |
| Hypercholesterolemia | 17(21) | 24(30) | 0.2[b] |
| Smoking | 53(67) | 49(62) | 0.7[b] |
| Family history | 31(39) | 36(45) | 0.4[b] |
| Diabetes mellitus | 7(9) | 6(8) | 0.7[b] |
| Previous MI | 8(10) | 8(10) | 1.0[b] |
| Previous PCI | 5(6) | 7(9) | 0.5[b] |
| Previous CABG | 1(1) | 4(5) | 0.2[b] |
| Symptoms to balloon (min) | 135(90-195) | 140(93-225) | 0.7[c] |
| Previous aspirin | 16(20) | 10(13) | 0.2[b] |
| Previous clopidogrel | 0(0) | 1(1) | 1.0[b] |
| Previous statins | 12(15) | 13(16) | 0.8[b] |

Data are presented as mean ± standard deviation, number (%) of patients or median (Interquartile range).

MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting. Hypercholesterolemia= Total cholesterol ≥190 mg/dl or previous pharmacological treatment. Hypertension = Blood pressure ≥140/90 mm Hg or previous pharmacological treatment.

[a] Compared using unpaired t test.

[b] Compared using Chi-square or Fisher exact test.

[c] Compared using Mann-Whitney U test.



## Electrocardiographic evaluation:

The rate of post-PCI complete ST-segment resolution of ≥ 70% was observed more frequently in the thrombectomy facilitated PCI group (87% vs. 65%, p=0.002) (Table 3).

Multivariable logistic regression analysis using the aforementioned potentially relevant factors identified only aspiration thrombectomy as an independent predictor of complete ST-segment resolution within 90 min. Post-PPCI (odds ratio= 6.7, 95% CI = 2.4-18.4, p< 0.001).

## Enzymatic infarct size assessment

Peak levels of CK and Troponin-T were comparable in both PCI groups (p = 0.8 and 0.5, respectively) (Table 3.). Multivariable linear regression analysis for Peak levels of CK and Tn-T including the aforementioned factors did not identify PCI groups as an independent predictor of higher peak CK (*B* = 186.3, 95% CI= -515.1 – 887.6, p=0.6) and Troponin T (*B* = 2.04, 95% CI= -0.51 – 4.58, p=0.1).

**Table 2.** Angiographic and procedural results.

| | Conventional PCI N=79 | Thrombus Aspiration N=79 | P |
|---|---|---|---|
| Infarct related artery, n (%) | | | 0.2[b] |
| Left main a. | 1(1) | 2(2) | |
| Left anterior descending a. | 31(39) | 28(35) | |
| Circumflex a. | 15(19) | 7(9) | |
| Right coronary a. | 32(40) | 42(53) | |
| Diseased vessels, n (%) | | | 0.2[b] |
| 1-vessel | 44(56) | 48(61) | |
| 2-vessel | 26(33) | 28(35) | |
| 3-vessel | 9(11) | 3(4) | |
| Proximal culprit lesion, n (%) | 35(44) | 40(50) | 0.4[b] |
| Abciximab | 78(98.7) | 79(100) | 0.9[b] |
| Initial TIMI flow grade, n (%) | | | 0.8[b] |
| 0 | 41(52) | 39(49) | |
| 1 | 14(18) | 15(19) | |
| 2 | 13(16) | 17(21) | |
| 3 | 11(14) | 8(10) | |
| Final TIMI flow grade, n (%) | | | 0.3[b] |
| 1 | 0(0) | 2(2) | |
| 2 | 11(14) | 13(16) | |
| 3 | 68(86) | 64(81) | |
| Drug eluting stents, n (%) | 45(57) | 52(70) | 0.1[b] |
| Stent number | 1.5±0.7 | 1.5±1.0 | 0.8[a] |
| Multiple stents, n (%) | 31(39) | 24(32) | 0.4[b] |
| Predilatation, n (%) | 66(83) | 49(62) | 0.002[b] |
| Thrombus detected, n (%) | 75(95) | 78 (98.5) | 0.8[b] |
| Thrombus grade, n (%) | | | <0.001[b] |
| High thrombus grade (Grades 4, 5) | 29(39) | 65(83) | |
| Low thrombus grade (Grades 1, 2, 3) | 46(61) | 13(17) | |

Data are presented as mean ± standard deviation, number (%) of patients.
TIMI, Thrombolysis In Myocardial Infarction.
[a] Compared using unpaired t test. [b] Compared using Chi-square or Fisher exact test.

## Three-month LV function evaluation

One-hundred and thirty-eight patients underwent LV function assessment by myocardial perfusion scintigraphy (MYOVIEW) (Figure 1). Patients who did not undergo scintigraphy had their LV function assessed using biplane 2-D echocardiographic evaluation at 3 months, and one patient had unavailable data regarding the LV function assessment post-PCI due to in-hospital death. LVEF was not significantly different between both groups (p=0.9) (Table 4).

Multivariable linear regression analysis including the aforementioned factors did not identify PCI groups as an independent predictor of improved LVEF (*B* = -1.8, 95% CI= -6.5 – 2.9, p=0.5).

**Table 3.** Postprocedural electrocardiographic and laboratory results.

| | Conventional PCI N=79 | Thrombus aspiration N=79 | p |
|---|---|---|---|
| 90-min. complete ST-segment resolution, (%) | 45/69(65) | 66/76(87) | 0.002[b] |
| Peak CK (U/l) | 2095±1873 | 2286±2168 | 0.8[a] |
| Peak Tn-T(µg/l) | 6.2±8.5 | 5.8±6.1 | 0.5[a] |

Data are presented as mean ± standard deviation, number (%) of patients
CK, creatine kinase; Tn-T, Troponin T.
[a] Compared using Mann-Whitney U test.
[b] Compared using Chi-square or Fisher exact test.

**Table 4.** Three months scintigraphic and 1-year clinical outcomes.

| | Conventional PCI N=79 | Thrombus aspiration N=79 | p |
|---|---|---|---|
| LVEF by Gated-SPECT | 53.35±13.8 | 53.46±11.8 | 0.9[a] |
| Clinical follow up period | 368(362-397) | 367(188-391) | 0.1[c] |
| Clinical end-points, n (%): | | | |
| Cardiac death | 3(4) | 0(0) | 0.08[b] |
| All-cause death | 5(6) | 0(0) | 0.02[b] |
| Reinfarction | 2(0) | 0(0) | 0.1[b] |
| TVR | 3(4) | 5(6) | 0.7[b] |
| TLR | 4(5) | 2(2) | 0.6[b] |
| MACEs | 10(13) | 7(9) | 0.4[b] |

Data are presented as mean ± standard deviation, number (%) of patients or median (Interquartile range).
LVEF, left ventricular ejection fraction; SPECT; Single Photon Emission Computed Tomography; TVR, target vessel revascularization; TLR, target lesion revascularization; MACE, Major adverse cardiac events.
[a] Compared using unpaired t test.
[b] Compared using Chi-square or Fisher exact test.
[c] Compared using Mann-Whitney U test.



## Clinical outcomes

All patients were followed for a median of 367 days, 5 patients died in the conventional PCI group (including one in-hospital death) vs. 0 patients in the thrombectomy facilitated PCI group (p= 0.02), three (4%) of those deaths were cardiac (p=0.08). The 2 non-cardiac deaths were due to hepatic failure and terminal renal failure. Three (4%) patients underwent a target vessel revascularization in the conventional PCI group vs. 5(6%) patients in the

thrombectomy facilitated group (p= 0.7). Target lesion revascularization occurred in 4(5%) patients in the conventional PCI group vs. 2(2%) patients in the thrombectomy facilitated group (p= 0.6). Recurrent myocardial infarction occurred in 2 patients in the conventional PCI group vs. 0 patients in the thrombectomy facilitated group (p= 0.1). Overall MACE occurred in 10(13%) patients in the conventional PCI group vs. 7(9%) in the thrombectomy facilitated group (p= 0.4) (Table 4).The Kaplan-Meier curves showed that allocation to thrombectomy was associated with a significant reduction in 1-year all-cause mortality (log-rank p= 0.03); ( Figure 2), and a trend towards a reduction of the combined endpoint of cardiac death or reinfarction (log-rank p= 0.056); (Figure 3)

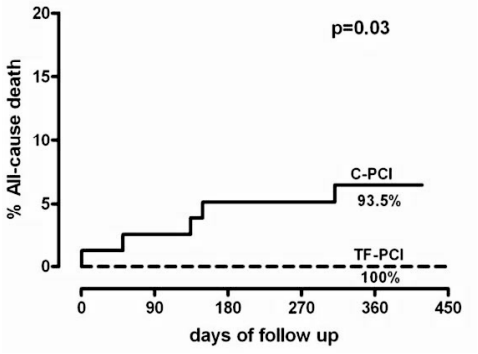


**Figure 2.** Kaplan-Meier 12 month cumulative event free survival from the endpoint of all-cause death.
TF-PCI: Thrombectomy facilitated PCI group; C-PCI: conventional PCI group.

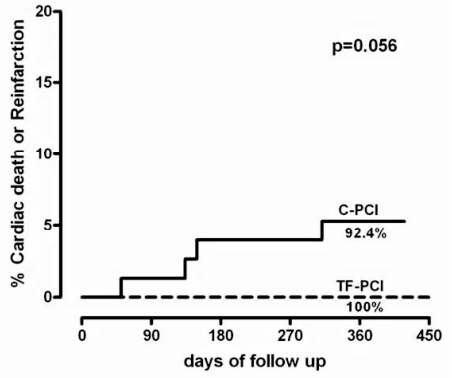


**Figure 3.** Kaplan-Meier 12 month cumulative event free survival from the combined endpoint of cardiac death or reinfarction. TF-PCI: Thrombectomy facilitated PCI group, C-PCI: conventional PCI group.

## DISCUSSION

The main findings of this study are: 1) A strategy of thrombus aspiration before stenting during primary PCI among patients treated with early abciximab was associated with a higher rate of complete ST-segment resolution (≥ 70%) within 90 min post-PCI. 2) Thrombus aspiration was associated with a lower incidence of all-cause mortality, and a trend towards a lower incidence of combined end-point of cardiac death or reinfarction through a 1-year median clinical follow up. TVR, TLR and overall MACE were similar in both groups.

Unlike the TAPAS trial [16], where abciximab was administered during the procedure of PPCI, our study provides a unique experience of the adjunctive influence of thrombus aspiration to early abciximab administration before PPCI. In the ATTEMPT study [18], Burzotta and colleagues have interestingly shown that the benefit of thrombectomy was

more evident in patients who received IIb,IIIa-inhibitors thus suggesting a possible additive benefit of thrombectomy in patients treated with IIb,IIIa-inhibitors. It might be speculated that pharmacological and mechanical thrombus remodeling are synergic to obtain the best myocardial reperfusion and, consequently, the best clinical outcome. Indeed, in the ATTEMPT study, patients treated by both thrombectomy and IIb,IIIa-inhibitors had the lowest mortality rate, those who had none of these treatments had the highest mortality rate, while patients receiving only one of these therapies exhibiting intermediate outcome. On the other hand, in the VAMPIRE trial[40], where GP IIb,IIIa receptor antagonists were not used at all, patients presenting late after STEMI (>6 hours after symptoms) appeared to benefit the most from thrombectomy, suggesting that the use of GP IIb,IIIa receptor antagonists would have influenced the results. In our study, patients received abciximab prior to PCI, where abciximab was started before the arrival to the hospital. The benefits of this has been investigated in previous RCTs[7,8,10-12], and in the study conducted by Hassan et al [9] in the context of the MISSION protocol, where it has been found that very early administration of abciximab (in-ambulance) significantly improves early reperfusion in STEMI patients treated with PPCI, this was also reflected clinically with smaller infarct size, improved LV function and a lower risk of heart failure on follow up. This may explain why some of our study outcomes including enzymatic infarct size, LVEF, and some of the clinical end-points did not differ between the 2 groups, as it is likely that the early abciximab administration supersedes the influence of thrombectomy catheter.



## Procedural characteristics

In the current study there was a significantly higher rate of direct stenting among the thrombectomy facilitated group, a finding which is consistent with other randomized controlled trials.[13,14,16,30-34] This can be explained by the fact that thrombus aspiration establishes a better antegrade coronary flow which allows selection and placement of a stent of appropriate length and diameter without the need for further balloon predilatation.

## ST-segment resolution

The effect of manual thrombus aspiration on the surrogate markers of myocardial reperfusion has been widely discussed in many studies. ST-segment resolution post-PCI is one of the most widely used and assessed markers. In our study there was a significantly higher rate of complete ST-segment resolution within 90 min in the thrombectomy facilitated PCI group. This outcome is in accordance with some previous randomized controlled trials (RCTs)[14,16,31,34-37], and two recent large meta-analyses[38,39] On the other hand, some other RCTs revealed no significant difference in the rate of ST-segment resolution among both randomized groups.[13,30,33,40,41]

### Enzymatic infarct size:

In our study there was no significant difference between both study groups regarding the enzymatic infarct size as estimated by peak levels of CK and Tn-T. Several trials assessing thrombus aspiration devices measured infarct size using biochemical markers with variable results. The largest study published to date, using the Export catheter system, the TAPAS trial, also showed no difference in peak CK and CKMB levels between groups with and without thrombus aspiration.[16]. The same was also noted in the EXPIRIA trial.[14] On the contrary, it has been noted by Kaltoft and colleagues in their randomized trial that peak Tn-T was significantly higher in the thrombus aspiration group [41], a result that has also been reported in the randomized trial by Anderson and colleagues.[42]

### Left ventricular ejection fraction (LVEF)

There is a variety of conflicting data about the effect of thrombus aspiration on the infarct size which is the best surrogate end point for the assessment of new therapeutic tools in the setting of acute myocardial infarction[43,44], and which is reflected by improved LV systolic function. In our study there was no benefit in terms of LVEF after thrombus aspiration, which is consistent with some previous trials.[14,30,31,33,40-42,45] Other trials showed different results from our study.[36,46]

### Clinical follow-up

In our study clinical data of the patients were available for a relatively long follow-up period (around 1 year), revealing that allocation to export aspiration thrombectomy was associated with lower incidence of all-cause mortality, in accordance with the findings of the 2 large RCTs using the export catheter; TAPAS[16] and EXPIRIA[14], the meta-analysis conducted by Bavry and colleagues[38], and the large patient-data pooled analysis; ATTEMPT study.[18] In our study also there was a trend towards lower incidence of the combined end-points of cardiac death or re-infarction, in agreement with TAPAS trial[16] and ATTEMPT study.[18] On the other hand, the incidence of cardiac death in our study was not different between both groups, unlike the findings in the TAPAS[16] and EXPIRIA[14] trials; however the large meta-analysis presented by Bavry et al[38], as well as the ATTEMPT study [18] only showed benefits in terms of all-cause mortality and not in cardiac mortality, moreover in the TAPAS trial[16] analysis of cardiac death after 30 days showed no significant difference between export aspiration group and conventional PCI group. Our study, in consistence with the TAPAS trial[16], showed no difference between both groups regarding TVR/TLR, suggesting that thrombus aspiration has no influence on neointima hyperplasia.

### Limitations

Our study is a single-center, non-randomized, prospective study. However, we tried to overcome this limitation by taking two groups of consecutive patients within the same time

period, who were comparable regarding the baseline clinical and procedural characteristics. All patients were submitted to the fixed MISSION protocol throughout the study period. This is a rigorously standardized protocol concerning pre-, peri-, and post-PPCI treatment up to 1 year[19,20], so it is unlikely that procedural changes over time would have influenced the outcome.

In our study, there was a higher tendency to use the thrombus aspiration catheter in patients with higher thrombus grades. In Kishi et al[47], the size of the thrombus was not a predictor of no-reflow phenomenon or distal embolization. Moreover, in our study there was comparable base-line TIMI flow rate between both groups (TIMI flow 0 was 52% in the conventional PCI group vs. 49% in the export facilitated PCI group).

Better techniques are required to analyze the thrombus burden, especially with the fact that most of the patients are presented with totally occluded infarct related artery on the initial angiography which limits the analysis of the thrombus burden; most of those patients subtend large thrombus burden but still some do not.

## CONCLUSION

Among STEMI patients treated with PPCI and receiving early (in-ambulance) abciximab, it appears that the adjunctive use of manual thrombectomy significantly improves post-procedural ST-segment resolution, and may be associated with a lower clinical event rate. Therefore, although no benefit was observed regarding the enzymatic infarct size or LV function as assessed by Gated-SPECT, it appears that a selective strategy of thrombus aspiration still has an additive benefit, even with early abciximab administration. This needs further confirmation in appropriately powered randomized trials.

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# Chapter 6

## Distribution of culprit lesions in patients with ST-segment elevation acute myocardial infarction treated with primary percutaneous coronary intervention.

M. Louisa Antoni, MD, Jael Z. Atary, MD, Kai-Hang Yiu, MD, Victoria Delgado, MD, PhD, Eduard R. Holman, MD, PhD, Ernst E. van der Wall, MD, PhD, Joanne D. Schuijf, PhD, Martin J. Schalij, MD, PhD, Jeroen J. Bax, MD, PhD

From the Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands.

## ABSTRACT

### Aims

Data regarding the distribution of vulnerable lesions in the coronary arteries are scarce. The aim was to evaluate the frequency and distribution of culprit lesions in patients with ST-segment elevation acute myocardial infarction (AMI). In addition, the location of culprit lesions was related to infarct size.

### Methods and results

Consecutive patients (N=1533, mean age 61±12 years) were evaluated. All patients were treated with primary percutaneous coronary intervention and underwent 2-dimensional echocardiography <48 hours of admission. The majority of the culprit lesions were located in the left anterior descending coronary artery (LAD,45%), followed by the right coronary artery (RCA,38%) and left circumflex coronary artery (LCX,14%). Subanalysis demonstrated that patients with a culprit lesion in the LAD and LCX had significantly higher peak cardiac enzymes compared to patients with culprit lesions in the RCA. In addition, patients with proximal LAD and LCX lesions had significantly worse left ventricular function compared to patients with mid or distal lesions.

### Conclusion

Plaque rupture resulting in AMI is more likely to occur in the proximal parts of the LAD and RCA. In addition, the location of culprit lesions was related to infarct size. Therefore, knowledge of the distribution of vulnerable lesions is important for identifying patients at risk for acute coronary events.

## INTRODUCTION

Acute coronary syndromes are primarily due to rupture of an atheromatous plaque with superimposed thrombosis. Therefore, identification of vulnerable lesions which are prone to rupture is important and has been studied extensively. Previous studies have particularly focused on characteristic histomorphologic features of vulnerable lesions.[1,2] Besides in the setting of randomized trials, no data have been reported regarding the distribution of culprit lesions among the different coronary arteries in patients presenting with a ST-segment elevation acute myocardial infarction (AMI).[3-5] Furthermore, data about the distribution of culprit lesions within the different segments of the coronary arteries in patients presenting with AMI are scarce.

Accordingly, the aim of the current study was to evaluate the frequency and distribution of culprit lesions within the 3 coronary arteries and within the different segments of the coronary arteries in a large population of patients presenting with ST-segment elevation AMI. In addition, the location of the culprit lesions was related to infarct size as assessed with peak cardiac enzymes and residual left ventricular (LV) systolic function.

## METHODS

Since February 2004, all patients admitted with ST-segment elevation AMI were identified and included in an ongoing registry (MISSION!).[6] The diagnosis ST-segment elevation AMI was defined based on criteria of typical chest pain, elevated cardiac enzyme levels, and typical changes on the electrocardiogram.[7] All patients underwent immediate coronary angiography to identify the location of the culprit lesion followed by primary percutaneous coronary intervention (PCI). Patient data were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands) and analyzed retrospectively.[8,9] Standardized angiographic projections were chosen for the visual classification of the coronary artery map into segments according to the guidelines of the American College of Cardiology/American Heart Association.[10,11] The infarct-related vessel was determined on the coronary artery territory subtended by the regions of acute electrocardiographic changes. If the culprit vessel had more than 2 lesions, the most severe proximal stenosis or a stenosis identified with thrombus was considered as the culprit lesion. Patients were not included if no clear culprit lesion could be identified on coronary angiography. Patients were treated according to the institutional AMI protocol, which includes 2-dimensional echocardiography performed within 48 hours of admission to assess residual LV function using LV ejection fraction calculated by the biplane Simpson's technique from the apical 2- and 4-chamber views.[6,12]

Continuous data are presented as mean ± standard deviation and categorical data are presented as frequencies and percentages. Differences in baseline characteristics between the 3 coronary arteries or the different segments of the coronary arteries were evaluated with 1-way analysis of variance or chi-square test, as appropriate. Of note, patients with a bypass graft identified as culprit vessel were not included in these analyses. Post-hoc comparisons were performed using the Bonferroni adjustments for multiple comparisons. For all tests, a p value <0.05 was considered statistically significant.

## RESULTS

A total of 1533 consecutive patients were evaluated. Mean age of the patient population was 61.3 ± 12.2 years and mean LV ejection fraction was 45.8 ± 8.6% (Table 1). Before primary PCI, mean TIMI flow of all patients was 0.6 ± 1.0. Among the 1533 culprit lesions studied, the majority of the patients showed a 100% stenosis (1013 patients, 66%) or 99% stenosis (279 patients, 18%). Only 6 (0.4%) patients showed a culprit lesion with 50% stenosis, 78 (5%) patients with 75% stenosis and 157 (10%) patients with 90% stenosis as determined by semiquantitative grading.

Table 2 shows the distribution of the culprit lesions. The majority of the culprit lesions were located in the left anterior descending coronary artery (LAD, 668 patients, 45%) and



**Table 1.** Baseline characteristics of the patient population

| | All patients (N = 1533) |
|---|---|
| Clinical characteristics | |
| Age (years) | 61.3 ± 12.2 |
| Male gender | 1158 (76%) |
| Medical History | |
| Current smoking | 715 (47%) |
| Diabetes | 182 (12%) |
| Family history of coronary artery disease | 618 (40%) |
| Hyperlipidemia | 299 (20%) |
| Hypertension | 533 (35%) |
| Prior myocardial infarction | 140 (9%) |
| Infarct size | |
| Peak creatine phosphokinase level (U/l) | 2229 ± 2890 |
| Peak cardiac troponin T level (µg/l) | 5.9 ± 6.5 |
| TIMI flow | 2.9 ± 0.4 |
| Multivessel disease | 718 (54%) |
| Left ventricular ejection fraction (%) | 45.8 ± 8.6 |

Hyperlipidemia= Total cholesterol ≥190 mg/dl or previous pharmacological treatment.
Hypertension = Blood pressure ≥140/90 mm Hg or previous pharmacological treatment.

**Table 2.** Distribution of coronary occlusions

| Vessel segment | Number of occlusions | LV ejection fraction (%) |
|---|---|---|
| Left main (segment 11) | 16 (1%) | 37.1 ± 8.1 |
| Ramus intermedius (segment 28) | 15 (1%) | 47.9 ± 7.5 |
| RCA | 588 (38%) | 46.8 ± 8.2 |
| Proximal (segment 1) | 249 (42%) | 46.2 ± 8.4 |
| Mid (segment 2) | 218 (37%) | 47.2 ± 7.7 |
| Distal (segment 3) | 96 (16%) | 47.2 ± 8.0 |
| Posterior descending (segment 4) | 14 (2%) | 48.7 ± 11.2 |
| Posterior lateral (segment 6) | 11 (2%) | 43.8 ± 9.3 |
| LAD | 688 (45%) | 44.6 ± 8.9 |
| Proximal (segment 12) | 401 (58%) | 43.7 ± 8.8 |
| Mid (segment 13) | 243 (35%) | 45.5 ± 8.9 |
| Distal (segment 14) | 20 (3%) | 45.6 ± 11.2 |
| Diagonal 1 branch (segment 15) | 23 (3%) | 50.5 ± 7.3 |
| Diagonal 2 branches (segment 16) | 1 (0.1%) | 48.0 ± 0 |
| LCX | 214 (14%) | 47.4 ± 7.8 |
| Proximal (segment 18) | 82 (38%) | 45.1 ± 8.7 |
| Mid (segment 19) | 81 (38%) | 48.8 ± 6.9 |
| Distal segment 19a) | 3 (1%) | 47.7 ± 2.9 |
| Obtuse marginal 1 (segment 20) | 41 (19%) | 48.9 ± 7.0 |
| Obtuse marginal 2 (segment 21) | 7 (3%) | 49.4 ± 7.3 |
| Bypass graft | 12 (0.8%) | 44.3 ± 8.6 |

LAD: left anterior descending coronary artery; LCX: left circumflex artery; RCA: right coronary artery and LV: left ventricular.

the right coronary artery (RCA, 588 patients, 38%) and only a small number of culprit lesions were located in the left circumflex coronary artery (LCX, 214 patients, 14%). Culprit lesions were not uniformly distributed, but tended to be clustered in the proximal or mid vessel segments. In addition, a relatively high percentage was located in the first obtuse marginal branch (41 patients, 19% of all LCX lesions). No differences in baseline characteristics were observed between lesion localization within the coronary arteries except for prior myocardial infarction. Patients with prior myocardial infarction more often had the culprit lesion located in the distal part of the coronary artery compared to the mid and proximal parts (17% vs. 7% and 8%, respectively, $p = 0.002$).

Infarct size was assessed with peak cardiac enzymes (peak creatine phosphokinase (CPK) level and peak cardiac troponin T (cTnT) level) and residual LV function. Both peak CPK level and peak cTnT level were significantly lower in patients with a RCA culprit lesion compared to patients with a LAD culprit lesion (1634 ± 3424 U/l vs. 2674 ± 2565 U/l, $p < 0.001$ and 4.0 ± 4.2 µg/l vs. 7.2 ± 7.4 µg/l, $p < 0.001$, respectively) or a LCX culprit lesion (1634 ± 3424 U/l vs. 2282 ± 1830 U/l, $p = 0.02$ and 4.0 ± 4.2 µg/l vs. 6.0 ± 5.3 µg/l, $p < 0.001$, respectively).

No significant differences in peak cardiac enzymes were observed between patients with a LAD and LCX infarction.

In addition, the level of peak cardiac enzymes was evaluated for the proximal, mid and distal segments of the coronary arteries. The RCA and LCX demonstrated no significant differences for the proximal, mid or distal culprit lesions (RCA: p = 0.71 and p = 0.37 and LCX: p = 0.11 and p = 0.07 for peak CPK level and peak cTnT level, respectively). However, LAD proximal culprit lesions resulted in significant higher peak cardiac enzymes compared to lesions in the mid part (3192 ± 2886 U/l vs. 2092 ± 1885 U/l, p <0.001 and 8.4 ± 8.0 µg/l vs. 5.8 ± 6.5 µg /l, p <0.001) or the distal part of the LAD (3192 ± 2886 U/l vs. 1261 ± 1219 U/l, p = 0.005 and 8.4 ± 8.0 µg/l vs. 4.0 ± 4.2 µg/l, p = 0.04).

Residual LV function assessed with LV ejection fraction differed significantly between patients with different culprit vessels (ANOVA p <0.001) (Table 1). Post-hoc analysis demonstrated that patients with the LAD as culprit vessel had significantly lower LV ejection fraction as compared to patients with the RCA or LCX as culprit vessel (44.6 ± 8.9% vs. 46.8 ± 8.2%, p <0.001 and 44.6 ± 8.9% vs. 47.4 ± 7.8%, p = 0.001, respectively). Further subanalysis of the different segments per culprit vessel revealed that patients with proximal culprit lesions in the LAD and LCX had significantly worse LV function compared to patients with mid and distal lesions (43.7 ± 8.8% vs. 45.5 ± 8.9% and 45.6 ± 11.2%, p = 0.04 for proximal, mid and distal LAD lesions and 45.1 ± 8.7% vs. 48.8 ± 6.9% and 47.7 ± 2.9%, p = 0.02 for proximal, mid and distal LCX lesions). However, no differences in LV function were observed for the different locations of culprit lesions in the RCA (p = 0.37).



## DISCUSSION

Patients with ST-segment elevation AMI treated with primary PCI were more likely to have a LAD or RCA culprit lesion than a LCX culprit lesion. However, infarct size assessed with peak cardiac enzymes demonstrated no significant differences between LAD and LCX infarctions, whereas RCA infarctions were significantly smaller. In addition, patients with proximal lesions in the LAD or LCX demonstrated worse LV function as compared to patients with lesions in the mid and distal parts, whereas no significant difference was observed between patients with proximal, mid or distal occlusions of the RCA.

The results of the present study provide further evidence for what has been described in smaller populations.[11] Wang et al. determined the location of coronary lesions in 208 consecutive patients with ST-segment elevation AMI.[11,13] The authors showed that culprit lesions tended to cluster within the proximal third of the coronary vessels. However, the distance from the ostium to the lesion depended upon which coronary artery was involved. Gibson et al. described that median distances from the ostium to the culprit lesion differed according to the coronary artery and the distance was the smallest in the LAD, followed by

the LCX and the RCA.[13] Interestingly, the same phenomenon has been observed in a large population of 30,386 patients with non-ST elevation AMI undergoing PCI described by Dixon et al, and thus, the current findings may be generalized for all culprit lesions including those of patients with unstable angina.[14]

Although information about the distribution of culprit lesions is important, understanding why plaque ruptures are less likely to occur in the LCX and why proximal occlusions are more prone to rupture remains challenging. To some extent, these observations may be explained by the fact that ischemic events of the LCX artery are underdiagnosed due to limited sensitivity of the 12-lead ECG for detection of ischemia on the lateral and posterior walls.[15,16] Previous studies have reported that only 33% of patients with a LCX occlusion present with ST-segment elevation on the ECG.[17] Recently, From et al. confirmed this hypothesis by demonstrating that in a group of 1500 patients with ST-segment elevation and non-ST-segment elevation AMI, patients with a LCX occlusion were less likely to present with ST-segment elevation on ECG and were referred less frequently for primary PCI.[15] However, among the group of patients presenting with non-ST-segment elevation AMI, patients with a LCX occlusion had the highest peak enzymes. Another explanation for the lower frequency of culprit lesions observed in the LCX may be the greater variation in anatomy as compared to the LAD and RCA. In a large proportion of the population, the LCX is relatively small with few pronounced side-branches, which may also explain why patients with an occlusion of the LCX may be more likely to present with a non-ST-segment elevation AMI or without any changes on the ECG.[15,17] Moreover, since vessel diameter plays an important role in the development of atherosclerosis, it is conceivable that as a consequence also plaque rupture may differ among the coronary arteries. The anatomy of the LCX may result in lower wall shear stress, whereas proximal segments of the coronary arteries conversely may be areas of high shear stress which determine the risk of plaque rupture.

In conclusion, the present study demonstrates that plaque rupture resulting in ST-segment elevation AMI is more likely to occur in the proximal parts of the LAD and RCA. In addition, the location of the culprit lesions in the different coronary arteries was related to infarct size. Therefore, knowledge of the distribution of vulnerable lesions is important for the identification of patients at risk for acute coronary events.

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# Chapter 7

## Acute Myocardial Infarction Treatment of Young versus Elderly patients: Insights from the Leiden MISSION! program.

Jael Z. Atary,[a] M. Louisa Antoni,[a] Su San Liem,[a] Bas L. van der Hoeven,[a] J. Wouter Jukema,[a] Douwe E. Atsma,[a] Marianne Bootsma,[a] Katja Zeppenfeld,[a] Ernst E. van der Wall,[a] Martin J. Schalij,[a]

[a]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands.

## ABSTRACT

### Background

Lack of data about outcome of aggressive acute myocardial infarction (AMI) treatment in older patients may potentially contribute to significant underutilization of optimal treatment in this cohort. The authors evaluated clinical success of AMI treatment in the elderly population and analyzed several contributing factors.

### Methods

A total of 1002 consecutive and unselected AMI patients were admitted between 2006 and 2009. Patients were divided into 2 groups according to age: 841(84%) patients <75years and 161(16%) patients ≥75years. All were treated according to the MISSION! AMI protocol. Baseline characteristics, time delay from onset of symptoms to arrival at the catheterization room, 1year mortality, medication at discharge and compliance at 12months were documented.

### Results

Age group ≥75years had 20% less male patients, as well as lower prevalence of risk factors for coronary artery disease. More than 90% of AMI patients in both age groups were treated with primary PCI, with similar initial procedural success. Patients ≥75years had significantly longer time delays than patients <75years (median 193minutes vs. 150minutes respectively, p=0.033). In-hospital mortality was significantly higher in older AMI patients. However, age was only a significant independent predictor of 90day mortality. After 3months, low ejection fraction and diabetes were more important predictors. Patients ≥75years attending the outpatient clinic 1year post MI were as persistent with their medication as younger patients.

### Conclusions

Despite a significantly higher mortality <3months post-MI in older patients, surviving patients have the potential to gain significant advantage from aggressive reperfusion, optimal medication and regular follow-up in the first year post-MI.

## INTRODUCTION

Despite the greater incidence and risk of acute myocardial infarction (AMI) among older patients[1-3], there is still a considerable lack of data regarding success of aggressive AMI treatment in this group and factors contributing to clinical outcome. Several factors thought to contribute to the higher AMI mortality associated with older age are a higher prevalence of atypical clinical presentation delaying diagnosis[3], less persistent use of medication[4], as well as cardiovascular structural and physiological changes that predispose patients to more adverse outcomes with and without reperfusion therapy[5-8]. Nevertheless, patients 75 years of age and older with AMI, constitute a heterogeneous group and lack of data about outcome of aggressive AMI treatment may potentially contribute to significant underutilization of optimal AMI treatment in this cohort[3;9]. Moreover, the need for data regarding clinical characteristics and outcome of elderly AMI patients is ever increasing, as they constitute a rapidly growing group in the Western world[10]. The present study 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).

## METHODS

### Patient population and protocol

Consecutive and unselected patients presenting from January 2006 to January 2009 with AMI at the Leiden University Medical Center were included in the present study. Patients were all treated according to the MISSION! AMI protocol, as previously described in detail[11]. The protocol is based on ACC/AHA/ESC guidelines[2] for the treatment of AMI and focuses on the reduction of onset of symptoms-to-balloon time, optimization of pharmacological treatment, and structured secondary prevention during follow-up. In brief, all patients considered eligible for primary percutaneous coronary intervention (PCI) had electrocardiographic ST segment changes and additional evidence supporting the clinical diagnosis of an acute MI, including prolonged ischemic signs and symptoms (≥20 minutes), biomarker evidence of myocardial necrosis, or both[12]. Eligible patients were transferred directly to the PCI center's Cardiac Care Unit. The catheterization room was operational within 20 minutes, 24 hours a day, 7 days a week. Before the procedure all patients received 300 mg of aspirin, 300 to 600 mg of clopidogrel, and an intravenous bolus of abciximab (25 μg/kg), followed by a continuous infusion of 10 μg/kg/min for 12 h. At start of the procedure, 5,000 IU of heparin was given. Lesions were treated according to current interventional practice. MI was confirmed by detection of rise and/or fall of cardiac biomarkers with at least one of the following: (1) symptoms of ischemia: (2) ECG changes indicative of new ischemia development of the pathological Q wave, (3) imaging of new loss of viable myocardium or new regional wall motion abnormality.

## Follow-up

After hospital discharge, patients were offered a cardiac rehabilitation program and benefited from intensive out-patient follow up for the period of 1 year[11]. Outpatient clinic visits were scheduled for 30 days, 3 months, 6 months and 12 months after the index event.

## Data collection

Data of all patients (including baseline characteristics, time delay, cardiac history, and medication up to one year) was recorded by medical staff at the department of cardiology. All data was documented in the departmental electronic patient system (EPD-Vision®, LUMC, Leiden, The Netherlands). Survival status at 12 months was ascertained by medical records and data from the community population registry.

## Endpoints

Baseline clinical characteristics, time delay (minutes) from onset of symptoms to arrival at the catheterization room, 1-year mortality, medication at hospital discharge, and medication compliance at 12 months were all points of interest.

## Statistical analysis

Continuous data are expressed as mean (±standard deviation) or as median ($25^{th}$-$75^{th}$ percentile); dichotomous data are presented as numbers and percentages. Differences between categorical data were tested for statistical significance using a Pearson chi-square test using continuity correction where appropriate. Continuous normally distributed data were tested by student t-tests or in the case of a non-Gaussian distribution by a nonparametric test for independent samples. Survival was analyzed by method of Kaplan-Meier with corresponding log-rank test for differences in distribution between the curves. Univariate and multivariate Cox regression analysis was performed to determine a relation between potential risk factors at baseline and the incidence of all cause death. All variables with an unadjusted p value of $<0.10$ entered the multivariate regression model. A wide range of variables were considered including age, gender, clinical characteristics such as risk factors for CAD, cardiac history, treatment delay, and procedure and infarction related characteristics (see table 1). Only adjusted Hazard Ratio (HR) is reported in the text with the corresponding 95% confidence interval (CI). Also, univariate and multivariate logistic regression analysis was performed using the same methodology as described above to determine a relation between potential risk factors at baseline and time delay $\geq$150 minutes. Variables considered included age, gender, risk factors for CAD and cardiac history. Only adjusted Odds Ratio (OR) is reported in the text with the corresponding 95% CI. All tests were two-sided, a p-value of $< 0.05$ was considered significant.

## RESULTS

### Patient population

A total of 1002 consecutive AMI patients were admitted at the PCI center between 2006 and 2009. For study purposes, patients were divided into two groups according to age at presentation: 841 (84%) patients younger than 75 years and 161(16%) patients ≥75 years.

### Clinical characteristics

Clinical characteristics according to age group are shown in Table 1 and figure 1. The statistically most significant differences between patients ≥75 years and patients <75 years were a 20% lower proportion of male patients in the older patient group (Figure 1, panel A), as well as a lower prevalence of risk factors such as smoking, hyperlipidemia, BMI ≥30 kg/m$^2$ and family history of coronary artery disease (CAD). In addition, Figure 1, Panel B demonstrates that older patients were less likely to have ≥3 risk factors for CAD. Table 1 furthermore shows that more patients aged ≥75 years were using cardiovascular and antiplatelet agents prior to the index event compared to younger patients.

More than 90% of AMI patients in both age groups were treated with percutaneous coronary intervention (Table 1). Significantly more patients in the age group ≥75 years were observed with multi-vessel disease, however LAD related infarctions were equally distributed between the two age groups. A similar percentage of patients failed to attain a postprocedural Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in both age groups (Table 1).

### Time delay and infarct size

Figure 1, Panel C, shows that older patients had significantly longer time delays from onset of symptoms to arrival at the catheterization room than patients younger than 75 years (median 193 minutes versus 150 minutes respectively, p=0.033). Due to the larger proportion of female patients in the older group, an additional analysis was conducted to evaluate how gender influenced the difference in time delay between the age groups. When split up by gender, male patients ≥75 years had a median 20 minute longer time delay than younger male patients. Older female patients had a median 45 minute longer time delay when compared to female patients <75 years. When considering age and gender in a multivariate logistic regression analysis, age ≥75 years remained a significant predictor of time delay ≥150 minutes from symptom onset to arrival at the catheterization room (OR 1.51, 95% CI 1.05-2.16, p=0.026), while gender did not (OR 1.31, 95% CI 0.95-1.80, p=0.098). However, interaction between age ≥75 years and female gender was observed, increasing the OR to 2.15 (95% CI 1.25-3.70, p=0.006) for a time delay ≥150 minutes.

In line with these findings, peak troponin T values were significantly higher in older patients compared to the younger patients (median 4.31 µg/L versus 3.22 µg/L respectively,

**Table 1.** Baseline characteristics

| Age group (years) | <75y (n=841) | ≥75y (n=161) | p-value |
|---|---|---|---|
| Male gender | 669 (79%) | 93 (58%) | <0.001* |
| Mean age (years±SD) | 57±10 | 80±4 | <0.001* |
| Range (min-max) | 22-74 | 75-91 | |
| Risk factors | | | |
| Smoking | 494 (59%) | 47 (29%) | <0.001* |
| Family History | 380 (45%) | 30 (19%) | <0.001* |
| Hyperlipidemia † | 181 (22%) | 18 (11%) | 0.003* |
| Hypertension ‡ | 287 (34%) | 75 (47%) | 0.002* |
| Diabetes Mellitus | 104 (12%) | 28 (18%) | 0.08 |
| BMI ≥30 kg/m$^2$ | 156 (19%) | 21 (13%) | 0.19 |
| Cardiac History | | | |
| Prior Myocardial Infarction | 90 (11%) | 21 (13%) | 0.36 |
| Prior percutaneous coronary intervention | 72 (9%) | 8 (5%) | 0.14 |
| Prior coronary artery bypass grafting | 17 (2%) | 9 (6%) | 0.018* |
| Medication before MI | | | |
| Beta-blocker | 163 (19%) | 44 (27%) | 0.020* |
| Aspirin | 137 (16%) | 48 (30%) | <0.001* |
| Statin | 165 (20%) | 30 (19%) | 0.81 |
| ACE-inhibitor | 97 (12%) | 31 (19%) | 0.007* |
| Angiotensine II-antagonist | 61 (7%) | 17 (11%) | 0.14 |
| Diuretic | 85 (10%) | 31 (19%) | 0.001* |
| Ca-antagonist | 76 (9%) | 28 (17%) | 0.001* |
| Time delay: | | | |
| Onset symptoms-cath. room (median min [interquartile range]) | 150 (101-281) | 193 (120-288) | 0.033* |
| Procedure related: | | | |
| Percutaneous coronary intervention | 788 (94%) | 149 (93%) | 0.59 |
| Coronary artery bypass grafting | 5 (1%) | 2 (1%) | 0.70 |
| Conservative treatment | 48 (6%) | 10 (6%) | 0.80 |
| Multivessel disease | 427 (51%) | 106 (66%) | 0.001* |
| Related to left anterior descending artery | 340 (40%) | 65 (40%) | 0.99 |
| Postprocedural TIMI flow grade <3 | 66 (8%) | 16 (10%) | 0.34 |
| Infarction size related: | | | |
| Peak troponin T (median µg/L [interquartile range]) | 3.22 (1.20-6.75) | 4.31 (1.71-8.08) | 0.008* |
| Peak CPK (median U/L [interquartile range]) | 1322 (586-2635) | 1366 (634-2442) | 0.96 |
| LVEF 3 months post-MI (%) | 56 (46-63) | 57 (47-66) | 0.44 |
| In-hospital deaths | 6 (1%) | 17 (11%) | <0.001* |

* p<0.05; † Total cholesterol ≥190 mg/dl or previous pharmacological treatment.
‡ Blood pressure ≥140/90 mm Hg or previous pharmacological treatment.

p=0.008) (Table 1). Of note, when patients who died in-hospital were excluded from this

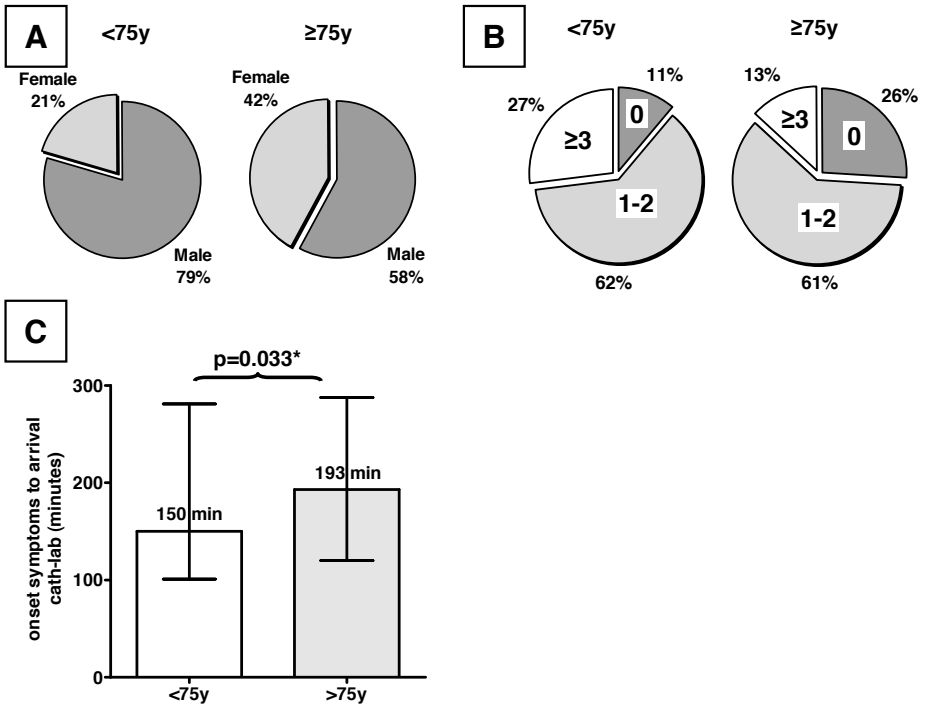


**Figure 1.** Baseline characteristics according to age group.
Panel A: Gender distribution (%).
Panel B: Prevalence of 0, 1-2 and ≥3 risk factors for coronary artery disease per age group (%).
Panel C: Bar graph showing time interval from onset of symptoms to arrival at the catheterization room (minutes) per age group. Top of bar represents median time (minutes). Error bars indicate 25$^{th}$ and 75$^{th}$ percentiles.

analysis, peak troponin T values were not significantly different between the old and young age groups (median 3.83 µg/L versus 3.19 µg/L respectively, p=0.083). Correspondingly, at 3 months post-MI the mean left ventricular ejection fraction (LVEF, derived $^{99m}$ tetrofosmin gated myocardial perfusion SPECT) of surviving patients was similar between the age groups (Table 1).

## Survival

One year survival data was complete for all patients (n=1002). In-hospital mortality was significantly higher in patients aged 75 years and older when compared to younger patients (17/161, 11% versus 6/841, 0.7%, respectively; p<0.001). All of these early deaths were caused by complications related to the index event.

Figure 2 demonstrates 1-year cumulative all-cause mortality stratified by age group. Panel A demonstrates that the trend of higher mortality in the age group ≥75 years compared to the age group <75 years was continued throughout the first year (p<0.001). Eighteen

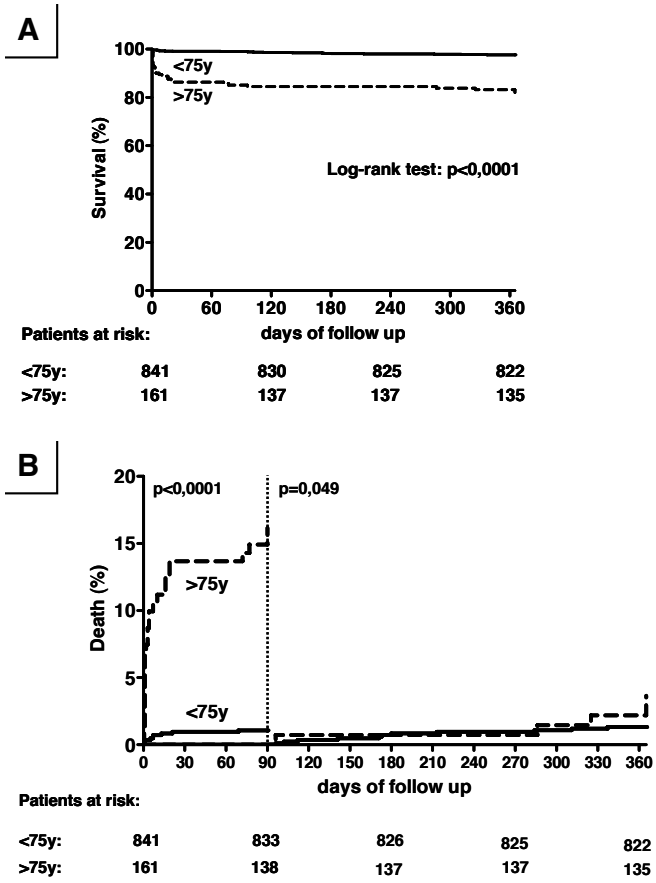


**Figure 2.** Mortality
Panel A: Kaplan-Meier plot of the cumulative incidence of all-cause death.
Panel B: Landmark incidence analysis plot of the cumulative incidence of all-cause death.

percent of patients (n=29) died within the first year post-MI in the age group ≥75 years, compared to 2% of patients (n=20) in the age group <75 years. Panel B emphasizes the more pronounced difference in the cumulative rate of relatively early deaths post-MI (landmark set at 90 days) and shows that both early and late (from 90 days to 1 year) mortality was significantly higher in the group aged ≥75 years. Multivariable Cox regression analysis of 0 to 90 day mortality revealed that age (adjusted HR 1.14, 95%CI 1.08-1.19, p<0.001), post-procedural TIMI flow grade <3 (adjusted HR 8.74, 95%CI 3.72-20.52, p<0.001), and time from onset of symptoms to arrival at the catheterization room (adjusted HR 1.001, 95%CI 1.00-1.001, p=0.009) were strong independent predictors of early mortality with TIMI flow grade <3 being the strongest predictor (Table 2). Multivariable Cox regression analysis of 90 day -1 year mortality revealed only diabetes (adjusted HR 4.39, 95% CI 1.24-15.6, p=0.022)

**Table 2.** Association with mortality 0-90 days post-MI and 90 days - 1 year post-MI.

| | Mortality 0 - 90 days | | | |
|---|---|---|---|---|
| | Unadjusted HR (95% CI) | p-value | Adjusted HR (95% CI) | p-value |
| Age | 1.12 (1.10-1.16) | <0.001 | 1.14 (1.08-1.19) | <0.001* |
| Male gender | 0.55 (0,27-1.11) | 0.093 | 1.01 (0.40-2.50) | 0.99 |
| Treatment delay | 1.000 (1.00-1.001) | 0.014 | 1.001 (1.00-1.001) | 0.009* |
| Multivessel disease | 1.97 (0.90-4.32) | 0.091 | 1.37 (0.52-3.60) | 0.53 |
| TIMI flow grade <3 | 6.29 (3.03-13.0) | <0.001 | 8.74 (3.72-20.52) | <0.001* |
| | Mortality 90 days – 1 year | | | |
| | Unadjusted HR (95% CI) | p-value | Adjusted HR (95% CI) | p-value |
| Age | 1,05 (1.01-1.10) | 0.020 | 1.05 (0.98-1.12) | 0.19 |
| Diabetes Mellitus | 4.06 (1.48-11.18) | 0.007 | 4.39 (1.24-15.6) | 0.022* |
| Prior MI | 2.73 (0.88-8.46) | 0.082 | 1.81 (0.43-7.63) | 0.42 |
| LVEF | 0.94 (0.90-0.98) | 0.001 | 0.94 (0.89-0.98) | 0.005* |

Only significant variables shown. These were the variables that were incorporated into the multivariate model (variables with an unadjusted p-value of <0.10). Unadjusted and adjusted Hazard Ratio (HR) is reported with the corresponding 95% confidence interval (CI). * p<0.05

and left ventricular ejection fraction (adjusted HR 0.94, 95% CI 0.89-0.98, p=0.005) as significant independent predictors of death (Table 2).

## Medication prescription and compliance

Table 3 shows medication prescription at hospital discharge, the number of (alive) patients that failed to attend the 12 month appointment at the outpatient clinic and the percentage of patients (as proportion of the patient group that did attend) that were still on optimal medication at 12 months.

Medication prescription at discharge was more or less optimal in both age groups. When aspirin was not prescribed at discharge, it was often due to anticoagulant treatment (alongside clopidogrel). In such cases aspirin was withheld in order to avoid increased risk of bleeding complications. Anticoagulants were prescribed in case of atrial fibrillation, severely impaired LV function or LV aneurysm.

A significantly larger percentage of patients in the age group ≥75 years failed to return to the outpatient clinic at 12 months when compared to the younger age group (37% of 132 alive patients versus 16% of 820 alive patients, respectively; p<0.001). However, medication compliance in the patients that did attend at 12 months was high and similar between the age groups.

**Table 3.** Medication prescription, follow-up and compliance.

| Age group (years) | <75y | ≥75y | p-value |
|---|---|---|---|
| Hospital discharge: | (n=841) | (n=161) | |
| Alive at discharge | 835/841 (99%) | 144/161 (89%) | <0.001* |
| Aspirin | 793/835 (95%) | 135/144 (93%) | 0.49 |
| Statin | 818/835 (98%) | 140/144 (97%) | 0.60 |
| Beta blocker | 793/835 (95%) | 132/144 (92%) | 0.28 |
| Clopidogrel | 810/835 (97%) | 140/144 (97%) | 1.00 |
| ACE inhibitor | 810/835 (97%) | 135/144 (94%) | 0.08 |
| Alive 1 year post-MI | 820/841 (98%) | 132/161 (82%) | <0.001* |
| Failed to attend 12 month visit | 131/820 (16%) | 49/132 (37%) | <0.001* |
| 12 Month Visit: | (n=689) | (n=83) | |
| Aspirin | 623/689 (90%) | 72/83 (87%) | 0.29 |
| Statin | 664/689 (96%) | 78/83 (94%) | 0.44 |
| Beta blocker | 636/689 (92%) | 75/83 (90%) | 0.54 |
| Clopidogrel | 656/689 (95%) | 78/83 (94%) | 0.82 |
| ACE inhibitor | 666/689 (97%) | 78/83 (94%) | 0.36 |

* $p<0.05$



## DISCUSSION

Key findings of this study were (1) AMI patients in the age group of ≥75 years presented with significantly less modifiable risk factors of CAD than younger AMI patients; (2) In-hospital mortality was significantly higher in older AMI patients than in younger AMI patients despite similar postprocedural TIMI flow grades, and: (3) Despite a significantly higher cumulative incidence of mortality 1 year post-MI in older AMI patients, age was only a significant independent predictor of 90 day mortality. In the period of 90 days to 1 year post-MI other contributing risk factors such as LV ejection fraction and diabetes were more important predictors of mortality.

Elderly patients included in this study had less modifiable risk factors of CAD than younger patients, a so-called "survivor effect" that was also seen in other studies [3;13]. It is not unreasonable that older patients, who experience MI at a later stage in life, are likely to have less risk factors for CAD than those who experience MI at a younger age. Furthermore, as patients were unselected and consecutively enrolled in the study, they truly reflect the patient population in the region of the PCI center, which may be a more healthy population than the patients enrolled in other studies [14;15]. The significantly longer treatment delays in the older patient group were in part caused by the larger proportion of female patients as demonstrated by multivariate logistic regression analysis, but other contributing factors that were not considered may include atypical symptoms, electrocardiographic presentations that

were difficult to interpret, a greater likelihood that patients were first transported to a center without PCI facility as seen in previous studies, and perhaps a greater inclination of elderly patients to wait longer before alerting emergency services [3;16;17].

It is well known that elderly patients are more likely to experience an AMI and to die after a MI than younger patients [18]. However, though it is well known that age is a significant risk factor for post-MI death, not all older patients are equally vulnerable to poor functional outcomes [14;19].

Older patients surviving the index event had similar cardiac function compared to the younger patients at three months post-MI. After 3 months the difference in mortality between the two age groups was less pronounced than in the first three months post-MI (borderline significant: p=0.049) and results of the multivariate analysis confirmed that age was no longer a significant predictor of 1-year mortality in patients surviving the first three months post-MI. This outcome is consistent with findings from a recent large registry study, which found that two out of three patients experienced a favorable functional outcome (neither death nor functional decline) at 1 year post-MI regardless of age [14]. Other studies often included a patient population in which older patients were treated less aggressively and with less patients undergoing primary PCI than the younger patients [3] or included patients from a time period when AMI treatment was not up to current standards [13]. Also, most of these studies divided mortality into 30 day mortality and 1 year mortality, not looking at other time windows.

Although older post-MI patients have consistently been shown to receive fewer evidence-based treatments, even when eligible[20-23], patients surviving the acute phase post-MI have similar potential for favorable outcomes to those of younger patients as evidenced by results of the present study and other studies [14] where patients of both age groups were treated equally aggressive. Prescription of beneficial cardiovascular medication at discharge was optimal in post-MI patients of all ages in the population studied, an encouraging finding as medication underuse at discharge is not uncommon in older patients [15]. Of the surviving patients at 1 year post-MI 20% more patients of the older age group failed to return to the outpatient clinic compared to younger patients, possibly related to more comorbidities or the perception that follow-up was not needed. It has been reported before that older patients are less likely to be persistent with evidence-based cardiovascular medicine after discharge from an acute coronary syndrome event [4]. However, surviving patients of the older age group that returned to the outpatient clinic were as persistent with their medication regimen as the younger patients, possibly a positive effect of the intensive follow-up of the MISSION! outpatient protocol [11].

## Limitations

There are potential limitations to the present study that should be considered when interpreting the results. As this was a single center, single region study, conclusions may not pertain to patients of other centers or regions. Furthermore, as data on prevalence of baseline risk

factors and baseline medication use was derived largely from patient self-report, it should be considered with the necessary caution.

Finally, as this is an observational study, there is a possibility of unmeasured confounding. However, due to the large amount of data that was available for the study population, it was possible to adjust for a wide range of potential confounders in the multivariable analysis, and these did not alter the findings.

## CONCLUSION

Given that old age is associated with greater morbidity and mortality after a MI, most clinicians would have considered age to remain the most important risk factor of mortality throughout the first year post-MI. However, results demonstrated that older patients surviving the first 3 months post-MI have similar outcomes to younger patients in terms of cardiac function and that age was a not a significant risk factor of 1-year mortality in survivors three months after MI. Therefore, though conservative treatment may be the adequate choice for some patients, results of this study suggest that older patients have the potential to gain significant advantage from aggressive and invasive AMI treatment and that age alone should not preclude intensive treatment after an MI.

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# Chapter 8

## Prognostic value of heart rate in patients after acute myocardial infarction treated with Primary percutaneous coronary intervention.

M. Louisa Antoni, MD*, Jael Z. Atary, MD*,
Victoria Delgado, MD*, Matteo Bertini, MD*, Eduard R. Holman, MD, PhD*,
Don Poldermans, MD, PhD†, Ernst E. van der Wall, MD, PhD*,
Martin J. Schalij, MD, PhD*, Jeroen J. Bax, MD, PhD*

*Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; †Erasmus Medical Center University, Rotterdam, the Netherlands.

## ABSTRACT

### Objectives

The aim was to evaluate the prognostic value of heart rate in patients with acute myocardial infarction (AMI) treated with primary percutaneous coronary intervention (PCI).

### Background

Recently, heart rate has been described as an important risk factor for reinfarction, revascularization and heart failure in patients with left ventricular dysfunction. Currently, most patients with AMI are treated with primary PCI and left ventricular function is relatively preserved. The clinical relevance of heart rate in this patient population is unknown.

### Methods

A total of 1102 consecutive AMI patients treated with primary PCI were evaluated. Heart rate was measured by 12-lead electrocardiography at time of admission. The endpoint was a composite of all-cause mortality, nonfatal reinfarction, coronary revascularization and hospitalization for heart failure.

### Results

During a mean follow-up of 20 months, 89 patients died (8%), 38 patients (3%) had a nonfatal reinfarction, 169 patients (15%) underwent revascularization and 45 patients (4%) were hospitalized for heart failure. After adjustment for known risk factors, a heart rate of 72bpm or higher was associated with a significant increased risk for the composite endpoint and all separate events. In addition, every increase of 5bpm resulted in an increased adjusted relative risk of 8% for the composite endpoint, 9% for mortality, 17% for reinfarction, 7% for revascularization and 11% for hospitalization for heart failure.

### Conclusions

Baseline resting heart rate is a strong risk factor for adverse outcome in AMI patients and preserved left ventricular function. The present study provided further evidence for targeting low heart rate in patients after AMI.

## INTRODUCTION

Resting heart rate is a simple cardiovascular parameter and has been well established as a strong predictor of mortality in patients with coronary artery disease.[1,2] Recently, heart rate has also been described as a risk factor for cardiovascular morbidity including reinfarction, revascularization and hospitalization for heart failure in patients with left ventricular dysfunction. The BEAUTIFUL study demonstrated that an elevated heart rate of 70 bpm or greater identified patients at increased risk of cardiovascular outcomes in patients with coronary heart disease and left ventricular dysfunction.[3] Acute myocardial infarction (AMI) is a major health problem in the western world despite the improved treatment strategies including reperfusion therapy.[4] Currently, most patients with AMI are treated with primary percutaneous coronary intervention (PCI), and therefore, left ventricular function is relatively preserved. The clinical relevance of resting heart rate in that currently growing population of post-AMI patients with preserved left ventricular function is unknown. Accordingly, the aim of the current study was to evaluate the relation between resting heart rate and long-term mortality and cardiovascular morbidity in patients with AMI treated with primary PCI. Importantly, all patients in the present patient population were treated with structurized evidence-based medical therapy including a high level of beta-blockers, initiated early after admission.[5,6]

## METHODS

### Patient population and study design

Since February 2004 consecutive patients admitted with an AMI with ST-segment elevation to our university hospital were included in an ongoing registry. All patients were treated with primary PCI according to the institutional AMI protocol, which is based upon the most recent American College of Cardiology/American Heart Association guidelines.[7] This protocol, designed to improve care around AMI, includes structurized evidence-based medical therapy, two-dimensional echocardiography and standardized follow-up at the outpatient clinic during 1 year after the index infarction, as described previously.[5] Echocardiography was performed within 48 hours of admission to quantify left ventricular ejection fraction according to the recommended biplane Simpson's method.[8] In addition, resting heart rate was measured by 12-lead electrocardiography at time of admission.

### Follow-up and endpoint definitions

All patients were followed prospectively according to the institutional protocol and the occurrence of adverse cardiac and non-cardiac events after the index infarction was noted.[5] Patients of whom more than 6 months follow-up data were lacking, were considered as lost to follow-up, and were excluded from further analysis. The primary endpoint was a composite

of all-cause mortality, nonfatal reinfarction, coronary revascularization and admission to hospital for new-onset of worsening heart failure. In addition, all clinical outcomes included in the composite endpoint were evaluated as individual endpoints. Nonfatal reinfarction was defined based on criteria of typical chest pain, elevated cardiac enzyme levels, and typical changes on the electrocardiogram.[9] All coronary revascularizations after discharge of the index infarction were included for the secondary endpoint.

### Statistical analysis

Continuous data are presented as mean ± standard deviation and categorical data are presented as frequencies and percentages. Differences between groups were evaluated using the unpaired Student's *t* test and chi-square test, where appropriate.

Elevated baseline heart rate was analyzed as a continuous variable, dichotomized according to a cutoff value of 72 bpm and categorized into intervals of 5 bpm. The cutoff of 72 bpm was derived from the patient population as the median heart rate of the total population and is in line with previous studies assessing the risk associated with an elevated heart rate.[1-3,10] Cox proportional hazards regression analyses were performed to relate elevated baseline heart rate to the different endpoints, adjusting for all variables with significant baseline differences between the patients with a heart rate less than 72 bpm and 72 bpm or greater. Peak creatine phosphokinase level and diastolic blood pressure were excluded from multivariate analysis to avoid co-linearity with peak cardiac troponin T level and systolic blood pressure.



Event rates were plotted in Kaplan-Meier curves for the composite endpoint and all separate clinical outcomes and the study population divided by the cutoff of 72bpm, and groups were compared using the log-rank test.

Finally, the incremental value of baseline resting heart rate as a continuous variable in addition to clinical risk factors for adverse outcome was assessed by comparison of model chi-square values. For this purpose, those characteristics were entered in the Cox proportional hazard model in a stepwise fashion. Subsequently, heart rate was entered individually. All statistical tests were two-sided, and a *P* value <0.05 was considered to be statistically significant.

## RESULTS

### Patient characteristics and follow-up

A total of 1193 patients were included. Four (0.3%) patients died before an electrocardiogram could be performed and 87 (7.3%) patients were lost to follow-up and were excluded from further analysis. The final patient population therefore comprised 1102 patients. The baseline characteristics of the patients are shown in Table 1. Patients with a heart rate of 72 bpm or greater were more likely to have diabetes, the left anterior descending coronary

**Table 1.** Baseline characteristics of patients

| | All Patients (n =1102) | Heart rate <72 bpm (n=537) | Heart rate ≥72 bpm (n=565) | *P** |
|---|---|---|---|---|
| Age (years) | 61 ± 12 | 61 ± 12 | 60 ± 12 | 0.32 |
| Male gender | 852 (77%) | 422 (79%) | 430 (76%) | 0.33 |
| Killip class ≥2 | 76 (7%) | 30 (6%) | 48 (9%) | 0.06 |
| Current smoking | 536 (49%) | 270 (49%) | 284 (53%) | 0.19 |
| Diabetes | 127 (12%) | 47 (9%) | 80 (14%) | 0.004 |
| Family history of CAD | 454 (43%) | 226 (43%) | 228 (42%) | 0.89 |
| Hyperlipidemia | 214 (20%) | 95 (18%) | 119 (22%) | 0.12 |
| Hypertension | 351 (32%) | 169 (32%) | 182 (33%) | 0.63 |
| Prior myocardial infarction | 91 (8%) | 40 (7%) | 51 (9%) | 0.34 |
| LAD culprit vessel | 513 (47%) | 214 (40%) | 299 (53%) | <0.001 |
| Multivessel disease | 551 (50%) | 256 (48%) | 295 (52%) | 0.13 |
| Peak CPK level (U/l) | 2406 ± 3132 | 2154 ± 3659 | 2685 ± 2471 | 0.01 |
| Peak cTnT level (µg/l) | 6.4 ± 6.9 | 5.6 ± 5.5 | 7.1 ± 7.9 | <.001 |
| Heart rate at admission (bpm) | 74 ± 18 | 60 ± 9 | 88 ± 14 | |
| TIMI flow | 2.9 ± 0.4 | 2.9 ± 0.4 | 2.9 ± 0.4 | 0.15 |
| Systolic blood pressure (mm Hg) | 135 ± 25 | 133 ± 25 | 137 ± 24 | 0.001 |
| Diastolic blood pressure (mm Hg) | 81 ± 16 | 78 ± 15 | 83 ± 16 | <0.001 |
| Left ventricular ejection fraction (%) | 45 ± 9 | 46 ± 8 | 44 ± 9 | <0.001 |
| ACE inhibitor / ARB at admission | 173 (16%) | 81 (15%) | 92 (16%) | 0.57 |
| Antiplatelets at admission | 171 (16%) | 81 (15%) | 90 (16%) | 0.68 |
| Beta-blocker at admission | 203 (19%) | 111 (21%) | 92 (16%) | 0.07 |
| Statins at admission | 181 (17%) | 82 (15%) | 99 (18%) | 0.28 |
| ACE inhibitor / ARB at discharge | 1037 (97%) | 513 (97%) | 524 (98%) | 0.24 |
| Antiplatelets at discharge | 1065 (100%) | 530 (100%) | 535 (100%) | 1.00 |
| Beta-blocker at discharge | 1003 (94%) | 490 (93%) | 513 (96%) | 0.02 |
| Statins at discharge | 1056 (99%) | 528 (100%) | 528 (99%) | 0.10 |

*P values are given for the comparison of patients who died of all-cause mortality versus patients who survived.
Hyperlipidemia= Total cholesterol ≥190 mg/dl or previous pharmacological treatment.
Hypertension = Blood pressure ≥140/90 mm Hg or previous pharmacological treatment.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CPK = creatine phosphokinase; cTnT = cardiac troponin T; LAD = left anterior descending coronary artery.

artery as the culprit vessel, higher peak cardiac enzymes, higher blood pressures, lower left ventricular ejection fraction and were less likely to be treated with beta-blockers at discharge.

During a mean follow-up duration of 20 ± 14 months, 277 patients (25%) reached the composite endpoint: 89 patients died (8%), 38 patients (3%) had a nonfatal reinfarction, 169 patients (15%) underwent revascularization and 45 patients (4%) were hospitalized for heart failure.

## Increased risk of adverse outcome associated with elevated heart rate

Table 2 shows the increased risk of adverse events associated with an elevated heart rate adjusted for all variables with significant differences between the groups with a heart rate less than 72 bpm and 72 bpm or greater. A resting heart rate of 72 bpm or higher was associated with a significant increased risk of all endpoints (Table 2). In addition, analyses with heart rate as a continuous variable showed that every increase of 5 bpm resulted in a significant higher risk for every endpoint. An increased adjusted relative risk of 8% was observed for the composite endpoint, 9% for mortality, 17% for reinfarction, 7% for revascularization and 11% for hospitalization of heart failure for every increase of 5 bpm.

**Table 2.** Adjusted hazard ratios for elevated heart rate at admission

| | Events, n (%) | Heart rate ≥72 versus <72 bpm | | Heart rate higher by 5 bpm | |
|---|---|---|---|---|---|
| | | Hazard Ratio (95% CI) | *P* | Hazard Ratio (95% CI) | *P* |
| Composite endpoint | 277 (25%) | 1.57 (1.20 – 2.05) | 0.001 | 1.08 (1.04 – 1.12) | <.001 |
| Mortality | 89 (8%) | 1.94 (1.04 – 3.63) | 0.04 | 1.09 (1.02 – 1.16) | 0.01 |
| Reinfarction | 38 (3%) | 2.41 (1.16 – 5.00) | 0.02 | 1.17 (1.09 – 1.25) | <0.001 |
| Revascularization | 169 (15%) | 1.40 (1.02 – 1.91) | 0.04 | 1.07 (1.03 – 1.11) | 0.001 |
| Heart Failure | 45 (4%) | 2.50 (1.21 – 5.16) | 0.01 | 1.11 (1.03 – 1.19) | 0.006 |



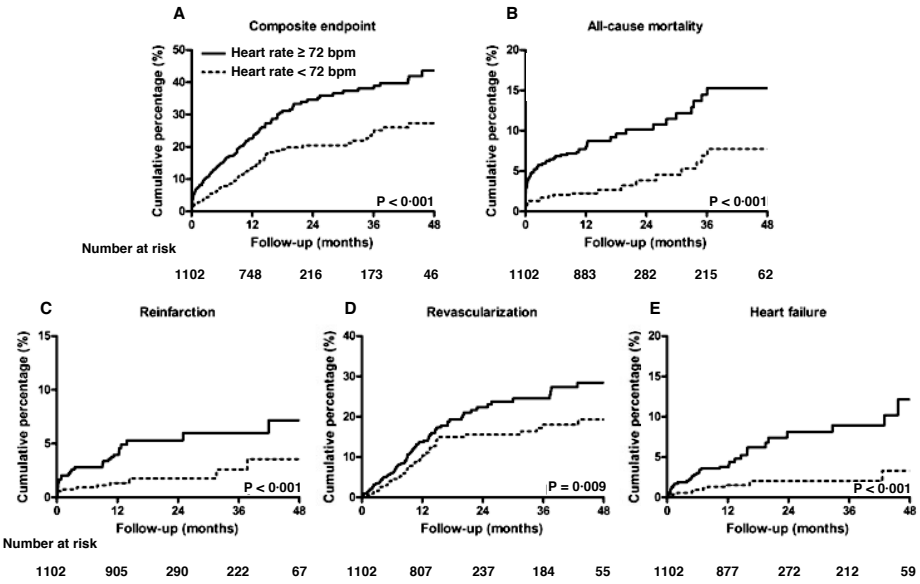


**Figure 1.** Cumulative risk of adverse events after acute myocardial infarction.
Kaplan-Meier time-to-event plots for baseline resting heart rate with a cutoff of 72 bpm and the composite endpoint, all-cause mortality, reinfarction, revascularization and hospitalization for heart failure.

Kaplan-Meier curves for the cutoff of 72 bpm and all endpoints are shown in Figure 1. The 4 year event rate in patients with a heart rate lower than 72 bpm compared to patients with a heart rate of 72 bpm or higher was 28% vs. 45% ($P$ <.001) for the composite endpoint, 8% vs. 17% ($P$ <0.001) for all-cause mortality, 4% vs. 7% ($P$ <0.001) for reinfarction, 19% vs. 28% ($P$ = 0.009) for revascularization and 3% vs. 12% ($P$ <.001) for hospitalization of heart failure.

Analyses of more comprehensive classification of baseline resting heart rates relative to a heart rate lower than 67 bpm are shown in Table 3. Interestingly, for all endpoints only a heart rate of 77 bpm or higher showed a significant increase in relative risk and the intermediate heart rate groups of 67 – 72 bpm and 72 – 77 bpm showed no increased risk.

The incremental prognostic value of baseline resting heart rate was assessed by calculating global chi-square values. Figure 2 shows that heart rate demonstrated to provide incremental value to baseline clinical information (diabetes, left anterior descending coronary artery as the culprit vessel, peak cardiac troponin T level, systolic blood pressure, left ventricular ejection fraction and treatment with beta-blockers at discharge) for the prediction of all clinical endpoints.

**Table 3.** Hazard ratios according to heart rate group

| | | Hazard Ratio (95% CI) | *P* |
|---|---|---|---|
| Composite endpoint | Heart rate <67 bpm | 1.00 | |
| | Heart rate 67 – 72 bpm | 0.92 (0.58 – 1.44) | 0.70 |
| | Heart rate 72 – 77 bpm | 1.18 (0.73 – 1.90) | 0.50 |
| | Heart rate ≥77 bpm | 1.96 (1.49 – 2.59) | <0.001 |
| Mortality | Heart rate <67 bpm | 1.00 | |
| | Heart rate 67 – 72 bpm | 0.57 (0.19 – 1.66) | 0.30 |
| | Heart rate 72 – 77 bpm | 0.79 (0.27 – 2.31) | 0.67 |
| | Heart rate ≥77 bpm | 2.72 (1.64 – 4.51 | <0.001 |
| Reinfarction | Heart rate <67 bpm | 1.00 | |
| | Heart rate 67 – 72 bpm | 0.28 (0.04 – 2.18) | 0.22 |
| | Heart rate 72 – 77 bpm | 1.19 (0.33 – 4.34) | 0.79 |
| | Heart rate ≥77 bpm | 2.20 (1.05 – 4.59) | 0.04 |
| Revascularization | Heart rate <67 bpm | 1.00 | |
| | Heart rate 67 – 72 bpm | 0.92 (0.54 – 1.57) | 0.76 |
| | Heart rate 72 – 77 bpm | 1.18 (0.67 – 2.06) | 0.57 |
| | Heart rate ≥77 bpm | 1.41 (1.00 – 1.99) | 0.05 |
| Heart failure | Heart rate <67 bpm | 1.00 | |
| | Heart rate 67 – 72 bpm | 1.88 (0.53 – 6.66) | 0.33 |
| | Heart rate 72 – 77 bpm | 2.01 (0.50 – 8.05) | 0.32 |
| | Heart rate ≥77 bpm | 5.13 (2.14 – 12.28) | <0.001 |

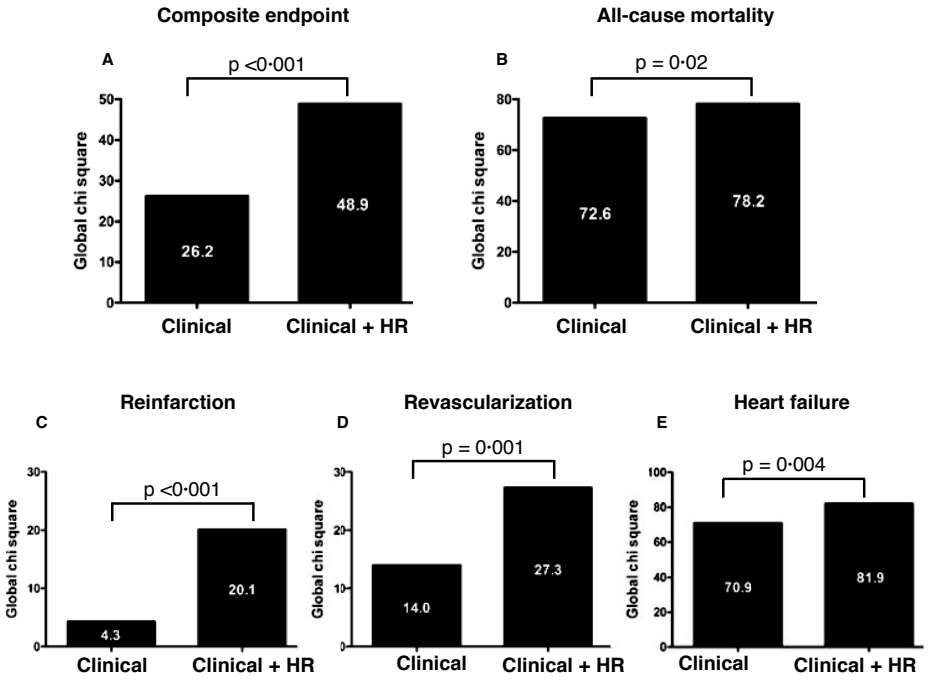




**Figure 2.** Incremental value of heart rate for the prediction of adverse events.
Incremental value of heart rate to baseline clinical information (diabetes, left anterior descending coronary artery as the culprit vessel, peak cardiac troponin T level, systolic blood pressure, left ventricular ejection fraction and treatment with beta-blockers at discharge) for the prediction of the composite endpoint, all-cause mortality, reinfarction, revascularization and hospitalization for heart failure.
HR = heart rate.

## DISCUSSION

The major finding of the current study was that baseline resting heart was a strong predictor of all-cause mortality, reinfarction, revascularization and heart failure in patients with AMI and relatively preserved left ventricular function. Moreover, for the prediction of all endpoints, resting heart rate provided incremental value to the traditional risk factors including the presence of diabetes, the left anterior descending coronary artery as culprit vessel, peak cardiac enzymes, blood pressure, left ventricular ejection fraction and treatment with beta-blockers.

The current results indicate for the first time the importance of heart rate control in patients with AMI and preserved left ventricular function. In patients with left ventricular dysfunction, an elevated heart rate has been described as an important risk factor for mortality and adverse events.[3] However, data about the relation between heart rate and patients with preserved left ventricular function after AMI are scarce. Several large trials have demonstrated the

relation between beta-blocker treatment and decreased mortality after AMI.[11,12] Of note, in the current population, all patients were treated according to the institutional protocol with evidence-based medical therapy including a high level of beta-blocker usage, and resting heart rate at admission remained an independent predictor of all endpoints after adjusting for treatment with beta-blockers at discharge. Every increase of 5 bpm in resting heart rate resulted in a significant higher adjusted risk ranging from 7% to 17% for each individual endpoint. These findings suggest that more aggressive lowering of heart rate in patients after AMI may have a beneficial effect on adverse events.

Although the association of heart rate and outcome has been investigated extensively, understanding the relation between heart rate and adverse events remains challenging. It is likely that heart rate is both a causative factor and an indicator of pathophysiologic processes. Heart rate influences myocardial oxygen demand and supply and consequently, also myocardial perfusion which may explain the strong relationship observed in the current study with outcome in patients after AMI.[13,14] In addition, an elevated heart rate has been associated with an increased risk of plaque rupture. Heidland et al. analyzed 106 patients who underwent 2 coronary angiography procedures within 6 months and reported a positive association between plaque rupture and a mean heart rate higher than 80 bpm, whereas medication with beta-blockers was associated with a reduced incidence of disruption of vulnerable plaques.[15]

Recently, the BEAUTIFUL investigators reported that ivabradine reduced the incidence of myocardial infarction and revascularization in patients with stable coronary artery disease, left ventricular dysfunction and a heart of 70 bpm or higher.[3,16] Conversely, ivabradine did not affect mortality and hospitalization for heart failure, suggesting that ivabradine protects patients more from ischaemia than from heart failure. A high resting heart is a modifiable risk factor, but existing medications including beta-blockers and calcium-channel blockers have other cardiovascular effects besides decreasing the heart rate. Ivabradine has been reported not to affect blood pressure, myocardial contractility, intracardiac conduction or ventricular repolarisation and therefore may provide pure lowering of the heart rate.[17-19] Thus far, only 1 study has been performed in patients after AMI with ivabradine demonstrating that the treatment was safe, feasible and well tolerated by the patients. Fasullo et al. investigated 155 patients with first anterior AMI randomized to metoprolol or ivabradine and reported a significant improvement in left ventricular volumes and ejection fraction in patients randomized to ivabradine compared to patients treated with metoprolol, but no difference in achieved heart rate.[20] In addition, several experimental studies in pigs and rats have demonstrated promising results including preservation of coronary reserve, attenuation of the decline in ejection fraction after AMI and significant reduction in infarct size.[21-23] Evidently, large prospective studies are needed to further determine whether a reduction in heart rate by ivabradine, beta-blockers or another strategy is the best approach to reduce the occurrence of adverse events in patients after AMI.

### Limitations

Finally, although baseline resting heart rate was a strong predictor of outcome in patients after AMI, the predictive value of heart rate at different periods after AMI could not be addressed. The assessment of the time course and changes in resting heart rate in relation to adverse events during follow-up would be interesting and will provide more insight in the mechanism between heart rate and adverse events. Another potential limitation of the study is that all-cause mortality rather than cardiac mortality was examined, because the classification of cardiac death is often problematic. However, because the mean age of the current population was 61 ± 12 years, it is likely that most deaths were cardiac in origin.

## CONCLUSION

In patients after AMI treated with primary PCI and preserved left ventricular function, resting heart rate at admission was a strong independent risk factor for all-cause mortality, reinfarction, revascularization and hospitalization for heart failure. The present study provides further evidence for targeting low heart rate in the currently growing population of post-AMI patients with preserved left ventricular function.

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# Chapter 9

# Structured care for patients after acute myocardial infarction: Sudden cardiac death prevention. Data from the Leiden MISSION! AMI study.

Jael Z. Atary, C. Jan Willem Borleffs, Su San Liem, Jeroen J. Bax, Bas L. van der Hoeven, Marianne Bootsma, Ernst E. van der Wall, Lieselot van Erven, Martin J. Schalij

Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands.

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## ABSTRACT

### Aim

To assess the number of patients in daily clinical practice that meets criteria for implantation of an implantable cardioverter defibrillator (ICD) following acute myocardial infarction (AMI) when treated according to an aggressive treatment protocol.

### Methods

Patients were treated according to the MISSION! protocol. The protocol encompasses pre-hospital, in-hospital and out-patient clinical framework for the acute and chronic treatment of AMI patients and the decision making regarding primary prevention of Sudden Cardiac Death (SCD).

### Results

A total of 676 consecutive AMI patients (78% male, mean age 59±12 years) treated according to the MISSION! protocol were included in this analysis. LVEF at 3 months was 54±10%. Only 39 (6%) patients met criteria for implantation of an ICD <1 year post-MI. These patients suffered more extensive infarctions as indicated by higher peak troponin T values (mean 14.5±8.3µg/l vs. 6.5±14.7µg/l; p<0.001) and had more LAD related infarctions (79% vs. 46%; p<0.001). Cumulative first appropriate therapy rate was 15% at 3 years follow-up. No sudden cardiac death was observed in the study population.

### Conclusions

Aggressive treatment of AMI patients and close monitoring after the index event according to a standardized protocol, results in only a small number of patients becoming candidate for prophylactic ICD implantation. An easy-to-use protocol combining aggressive reperfusion, optimal medication and a risk stratification algorithm tailored to fit within routine practice may help to maintain ICD implantation rates within manageable proportions.

## INTRODUCTION

Patients after acute myocardial infarction (AMI) are at risk of sudden death due to life threatening ventricular arrhythmias.[1] Large randomized trials demonstrated that both arrhythmic death and total mortality can be lowered by implantation of an Implantable Cardioverter Defibrillator (ICD) in post-MI patients with a low left ventricular ejection fraction (LVEF) with or without ventricular arrhythmias.[2-4] These findings resulted in a Class I indication for all patients with an ischemic cardiomyopathy and a low LVEF, even in the absence of ventricular arrhythmias.[5;6] Most of these trials however included patients years after the index event (more than 75% of patients in the two Multicenter Automated Defibrillator Trials [MADIT] were enrolled >6 months after MI and 89% in the Multicenter Unsustained Tachycardia Trial [MUSTT] were enrolled >1 year post MI). Furthermore with the current practice of aggressive reperfusion strategies to limit the extent of damage caused by the infarction it is not known how many patients will become candidate for ICD implantation in the year following the index event.

A regional AMI guideline implementation program (MISSION!) was developed to optimize the use of evidence-based medicine in practice.[7] MISSION! contains a pre-hospital, in-hospital and out-patient clinical framework for decision making and treatment of AMI patients. This prospective and well-defined cohort offers a unique opportunity to evaluate and follow patients after AMI and to assess the need for ICD treatment.

## METHODS

### Patients and protocol

Since 2004, all patients presenting with AMI at Leiden University Medical Center were treated according to the MISSION! protocol, as previously described in detail.[7] The protocol is based on the ACC/AHA/ESC guidelines for AMI and focuses on the reduction of onset of symptoms-to-balloon time, optimization of pharmacological treatment, and the structured prevention of SCD during follow-up.[8-10] The global in-hospital and out-patient clinical framework for the decision-making process and treatment up to one year following the index event is outlined in Figure 1.

AMI diagnosis was confirmed by the presence of an unstable coronary lesion on angiography and/or the elevation of cardiac biomarker(s) above normal levels. Patients without typical ST-elevation in-hospital, but with ischemic symptoms and elevated cardiac enzymes (CKMB and troponin T) were also diagnosed and included as AMI patients in the program.[11] In the absence of complications, the hospital admission was limited to three days. Patients on mechanical ventilation at the time of the index event were excluded from the pre-hospital and in-hospital MISSION! protocol. These patients did, however, receive the same

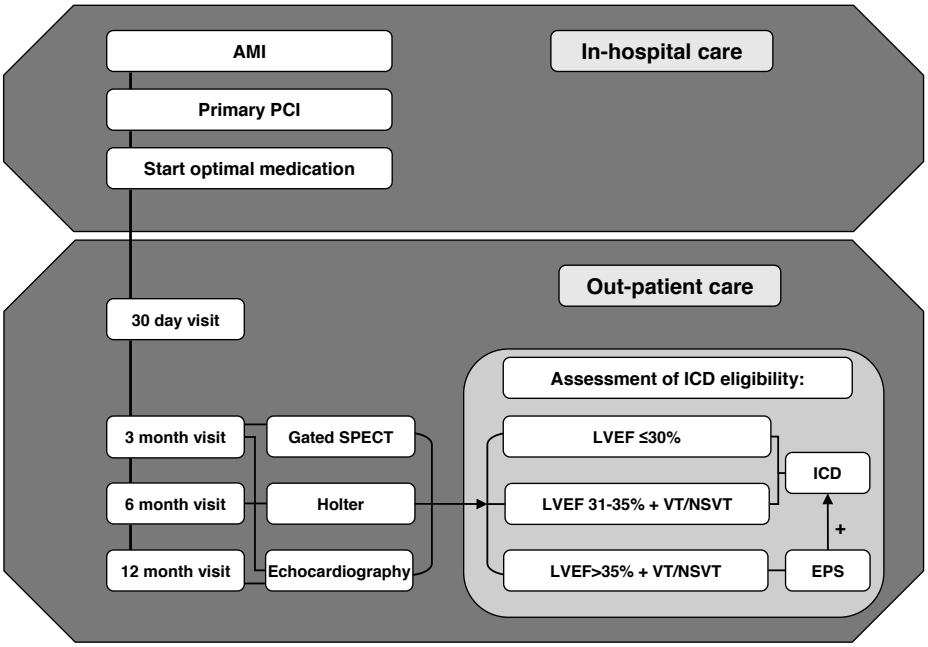


**Figure 1.** MISSION! protocol flowchart.



out-patient treatment after discharge. Patients were excluded from the study population in case of death prior to the acquisition of the gated single photon emission computed tomography (SPECT) three months after the index event, or if the assessment of LV function on gated SPECT was not possible due to poor image quality.

Data of each MISSION! patient was collected prospectively in an electronic patient file and data management system (EPD-VISION 6.01, Leiden University Medical Center).

## Follow-up

In the outpatient phase all patients were scheduled for regular clinical visits 30 days after the index event and after that every 3 months in the course of a year. Gated SPECT ($^{99m}$ tetrofosmin gated myocardial perfusion SPECT) was used as the preferred method for the assessment of LVEF and was conducted at 3 months follow-up.[12;13]

## ICD eligibility

The ICD screening part of the protocol was designed at a time when the guidelines for primary prevention of SCD were still evolving and was therefore based primarily on the large primary prevention ICD trials at the time.[2-4;6]

Patients were subsequently divided into the following groups, according to the LVEF: (1) LVEF ≤30%; (2) LVEF 31-35%; and (3) LVEF >35%. Patients with LVEF ≤30% as determined from gated SPECT were directly assigned to ICD therapy as in MADIT II.[4] Patients with LVEF

30-35% were considered eligible for ICD therapy when non sustained ventricular tachycardias (nsVT) were observed on 24-hour Holter monitoring similar to protocols of trials like MADIT I or MUSTT.[2;3] Patients with a LVEF ≥35% and abnormal 24-hour Holter monitoring revealing nsVT were also referred for an electrophysiological test to evaluate indication for antiarrhythmic therapy. It should be noted that this protocol differs from the most current guidelines that elevated ICD therapy for patients with LVEF <35% to a Class I indication regardless of the presence of nsVT.

### Endpoints

The primary endpoint was ICD eligibility, as determined by the described protocol. Secondary endpoints were all-cause death, further subdivided into death from cardiac causes, sudden death (unwitnessed), or non-cardiac death.

Furthermore, in patients receiving an ICD, a secondary endpoint was appropriate defibrillator therapy (antitachycardia pacing [ATP] or shock).

### ICD evaluation

Device interrogation was scheduled every 3 months. All printouts were checked for appropriate and inappropriate ICD therapy (ATP or shocks). Therapies were classified as appropriate when they occurred in response to VT or ventricular fibrillation (VF) and as inappropriate when triggered by sinus or supraventricular tachycardia, T-wave oversensing, or electrode dysfunction. Cutoff rate of the monitor or first therapy zone was noted.

### Statistical Analysis

Continuous data are expressed as mean ± SD; dichotomous data are presented as numbers and percentages. Differences at baseline were assessed using a Chi-square test using Yate's correction or student t-test for independent samples where appropriate. Event rates over time were analyzed by method of Kaplan-Meier. Univariable and multivariable cox regression analyses were performed as appropriate to determine a relation between potential risk factors at baseline and the incidence of all cause death. All variables with a p value of <0.25 entered the multivariable regression analysis. Only adjusted Hazard Ratio (HR) is reported with the corresponding 95% confidence interval (CI). All tests were two-sided, a p-value of < 0.05 was considered significant.

## RESULTS

### Patient population

From February 2004 until December 2006 799 patients were admitted with AMI at the Leiden University Medical Center and were treated according to the MISSION! protocol.

**Table 1.** Patient characteristics.

| | Total n=676 | No ICD indication n=637 | ICD indication n=39 | p-value |
|---|---|---|---|---|
| Demographics | | | | |
| Male | 529 (78) | 499 (78) | 30 (77) | 0.8 |
| Age (years) | 59 ± 12 | 59 ± 12 | 57 ± 13 | 0.2 |
| Medical History | | | | |
| Diabetes | 69 (10) | 66 (10) | 3 (7) | 0.8 |
| Hyperlipidemia | 149 (22) | 144 (23) | 5 (13) | 0.2 |
| Hypertension | 212 (31) | 199 (31) | 13 (33) | 0.7 |
| Current smokers | 336 (50) | 314 (49) | 22 (56) | 0.4 |
| Family History | 291 (43) | 273 (43) | 18 (46) | 0.7 |
| Previous myocardial infarction | 42 (6) | 39 (6) | 3 (7) | 1.0 |
| Previous PCI | 29 (4) | 26 (4) | 3 (7) | 0.5 |
| Previous CABG | 7 (1) | 7 (1) | 0 (0) | 1.0 |
| Clinical characteristics | | | | |
| Culprit vessel LAD | 325 (48) | 294 (46) | 31 (79) | <0.001 |
| Killip class at admission | | | | |
| I | 632 (93) | 595 (93) | 37 (95) | 1.0 |
| II | 23 (3) | 22 (3) | 1 (3) | 1.0 |
| III/IV | 21 (3) | 20 (3) | 1 (3) | 1.0 |
| Troponine T max (µg/l) | 6.9 ± 14.5 | 6.5 ± 14.7 | 14.5 ± 8.3 | <0.001 |
| CK (µg/l) | 2309 ± 1947 | 2185 ± 1820 | 4403 ± 2730 | <0.001 |
| Body mass index (kg/m²) | 26.4 ± 4.0 | 26.4 ± 4.0 | 25.3 ± 3.9 | 0.1 |
| Symptom-onset-balloon (minutes) | 288 ± 1282 | 287 ± 1317 | 303 ± 321 | 0.1 |
| Primary PCI | 655 (97) | 620 (97) | 35 (90) | 0.2 |
| Duration of hospitalization (days) | 3 ± 2 | 3 ± 2 | 6 ± 5 | <0.001 |
| LVEF | 54 ± 12 | 55 ± 11 | 31 ± 9 | <0.001 |
| Medication at discharge | | | | |
| Aspirin | 642 (95) | 604 (95) | 38 (97) | 0.7 |
| Statin | 670 (99) | 631 (99) | 39 (100) | 1.0 |
| ACE-inhibitor | 651 (96) | 612 (96) | 39 (100) | 0.7 |
| Beta-blocker | 627 (93) | 589 (93) | 38 (97) | 0.4 |
| Clopidogrel | 671 (99) | 632 (99) | 39 (100) | 1.0 |
| Anticoagulant | 33 (5) | 32 (5) | 1 (3) | 0.7 |

Values are expressed as n (%) or mean ± standard deviation.
Hyperlipidemia= Total cholesterol ≥190 mg/dl or previous pharmacological treatment.
Hypertension = Blood pressure ≥140/90 mm Hg or previous pharmacological treatment.

Forty-seven (6%) patients died < 3 months after the index event (before the gated SPECT test). Causes of death included progressive heart failure (41/47, 87%), sudden cardiac death (4/47, 9%), and non cardiac death (2/47, 4%). Additional patients were excluded from the analysis due to incomplete gated SPECT data (n=76, 10%).

Accordingly, a total of 123 (15%) patients were excluded from the analysis. The remaining 676 were included and were followed for a median of 32 months with an interquartile range (IQR) of 25 months (25$^{th}$ percentile) and 40 months (75$^{th}$ percentile).

## Study population

Baseline characteristics of the study population are reported in Table 1. Patients were mostly male (78%) and had a mean age of 59 ± 12 years (range 22-88). Frequent risk factors for cardiovascular disease included current smoking (50%), a family history of cardiovascular disease (43%), and hypertension (31%). Nearly all patients underwent a primary PCI procedure (97%); the remaining patients received thrombolytic therapy. Medication at discharge was optimal. When aspirin was not prescribed at discharge anticoagulant treatment was prescribed instead (alongside clopidogrel treatment) in order to avoid increased risk of bleeding complications. Anticoagulants were prescribed in case of atrial fibrillation, severely impaired LV function or LV aneurysm.

## Evaluating ICD eligibility

The mean LVEF, 3 months after the index event, was 54 ± 10%, as derived from gated SPECT. Twenty-five (4%) patients had a LVEF ≤30%, warranting ICD treatment. LVEF between 30% and 35% was observed in 27 (4%) patients, of whom 7 demonstrated nsVT on 24-hour Holter monitoring, indicating them for defibrillator implantation. Of the remaining 624 (92%) patients with LVEF ≥35%, another 7 patients were candidates for ICD based on inducible VT/VF during electrophysiological (EP) testing. Additionally, one patient received an ICD due to late (>48 hr) sustained VTs following the AMI and another 3 patients were treated with an ICD as a result of deterioration of LV function during the year following the index event.

Accordingly, 39 (6%) patients underwent ICD implantation, which was successful in all, without major complications.

## ICD group characteristics

As is shown in Table 1, the statistically most significant differences between patients with an indication for ICD therapy and patients without an indication for ICD therapy were more extensive infarctions in the implanted group, evidenced by a higher maximum troponin T and creatine kinase, longer duration of hospitalization, and more anterior infarctions. By definition, LV function was less in the ICD indicated group.

## Device therapy

During a median follow-up of the ICD treated population of 31 months (IQR 19 months and 42 months), 6 patients (15%) received appropriate device therapy for ventricular arrhythmias. Cumulative event rate was 8% (95% CI 0-16%) after 6 months, 15% (95% CI 4-27%) after one year, and 15% (95% CI 4-27%) after 3 years (Figure 2). No appropriate ICD discharge

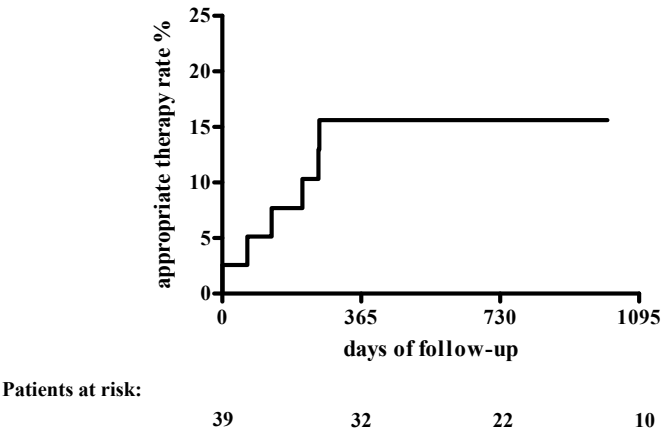


**Figure 2.** Kaplan-Meier curve for the cumulative rate of first appropriate ICD-therapy.

was observed in the implanted group with LVEF ≥35%. The group with LVEF ≤30% and those with LVEF between 30 and 35% did not demonstrate differences in the occurrence of appropriate ICD therapy (appropriate therapy in LVEF ≤30%: 19% vs. LVEF 30-35%: 29%, p=0.8). Inappropriate therapy occurred in 3 of 39 (8%) ICD recipients.



## Mortality

In the population, 12 patients (2%) died during follow-up. The 2 deaths occurring in the ICD treated group were related to progressive heart failure. Causes of death in the group without a defibrillator were progressive heart failure in 5 (50%), and non-cardiac in the other 5 (50%) patients. Of note, no cases of sudden death were observed. The 4 sudden deaths that occurred <3 months after the acute MI happened due to uncertain, but likely cardiac etiology and took place after hospital discharge. They are best described as sudden unexplained death and took place at day 13, 16, 25 and 51 post-MI respectively. All four patients had a left ventricular ejection fraction calculated with biplane echocardiography of >35%.

As is shown in Figure 3, the cumulative event-free follow-up after 3 years is 98% (95% CI 96-99%) for all-cause mortality, 99% (95% CI 98-100%) for cardiac mortality, and 100% for sudden death.

Multivariate cox regression analysis for mortality > 3 months after the index event revealed hyperlidemia (HR 5.9, 95%CI 1.3-26.1), no aspirin use at hospital discharge (HR 8.4, 95%CI 1.5-46.0) and no ACE-inhibitor use at discharge (HR 7.9, 95%CI 1.2-50.4) as independent predictors of death. Age, gender, peak troponine T, ICD treatment, culprit target vessel, other risk factors for CAD (including hypertension, smoking, diabetes, history of MI, family history of coronary artery disease) and LVEF could not be identified as independent predictors of death.

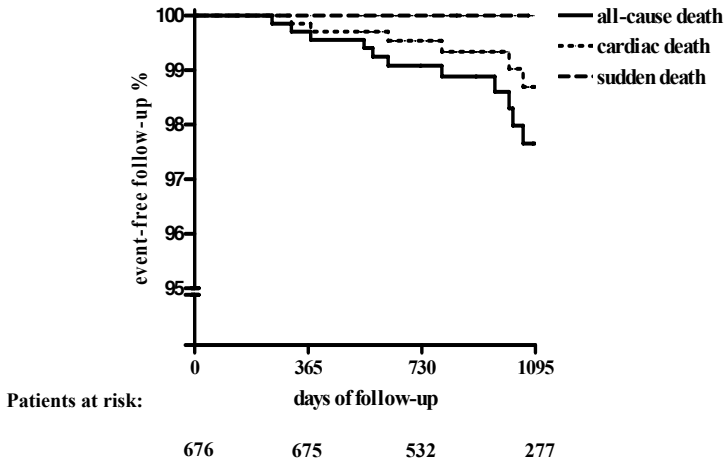


**Figure 3.** Kaplan-Meier curve for the event-free follow-up for mortality.

## DISCUSSION

In the assessment of an easy-to-use, structured protocol for the treatment of AMI patients and prevention of SCD, the findings can be summarized as follows: (1) Defibrillator implantation was warranted in only 6% of AMI patients; (2) No SCD occurred in the study population; (3) Compliance to evidence based medicine was excellent; (4) In ICD recipients, the cumulative event rate for appropriate ICD therapy was 15% at 3 years follow-up.

### Structured care for AMI patients

In past decades important insights have been gained into the management of patients with AMI. Measures such as rapid triage and quick access to reperfusion therapy can reduce treatment delay, prevent unnecessary infarct extension, and save lives.[14;15] Furthermore, the efficacy of early optimal pharmacological therapy has been recognized.[16] International guidelines on the optimal treatment of patients with AMI advocate early and aggressive reperfusion strategies and recommend use of a combination of evidence-based medicine and support programs to stimulate a healthier lifestyle.[8;10] The degree of compliance to these guidelines has proven to be independently correlated to 1-year mortality after AMI.[17] The pre-hospital, in-hospital and out-patient AMI treatment protocol called MISSION! was therefore designed to increase use of evidence-based medicine in daily clinical practice.[7]

### Prevention of SCD

AMI survivors are at increased risk for sudden death from cardiac causes, in most patients due to a ventricular arrhythmia.[1;18] Thus far, LV function has proven to be a strong indicator for an increased risk of SCD.[19-21] Prevention of severe LV dysfunction post-MI was addressed

by focusing on minimal treatment delays, aggressive reperfusion therapy and the use of early and consistent optimal pharmacological therapy.

Nuclear imaging (gated SPECT) functioned as gatekeeper for risk stratification at 3 months post-MI. It facilitated the first step toward the detection of patients at increased risk for SCD. A previous study highlighted the importance of scintigraphic evaluation of patients with coronary artery disease.[13]

## ICD indication

Large randomized trials have proven the beneficial effect of primary prevention ICD treatment in post-MI patients with a severely depressed LVEF.[3;4;22] Implementation of these findings in the current international guidelines significantly and rapidly expanded the indications for ICD implantation.[5] Correspondingly, while patients with LVEF 30-35% included in the present study were only considered eligible for ICD implantation when nsVT was observed on 24-hour Holter, the most current guidelines elevated ICD therapy for patients with LVEF <35% to a Class I indication regardless of the presence of nsVT.[5] Due to these rapid changes, clinicians have expressed concern 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.[23] Despite the in some ways more lenient ICD eligibility criteria as compared to current guidelines, the present study showed successfully that the proportion of post-MI patients potentially eligible for an ICD, when treated optimally and aggressively for AMI, is smaller than anticipated.[24-26] By using the pre-specified protocol merely 6% of AMI patients were identified as candidates for ICD implantation and no sudden deaths occurred in the study population.



## Device therapy

In the ICD treated population, the cumulative event rate for first appropriate ICD therapy at 3 years follow-up was 15% (95% CI 4-27%), which is lower than the event rates reported from trials like MADIT II (35%).[27] A possible explanation for this difference is the smaller ICD patient group in the current study and the more preserved LV function in the current study's ICD treated population (LVEF 31 ± 9%), when compared to the MADIT II population (LVEF 23 ± 5%). Furthermore, in MADIT II 42% of patients who underwent coronary revascularization, had the procedure >60 months before enrollment in the study (median 107 months) whereas patients in the current study were risk stratified for ICD implantation <1 year post-MI. The low arrhythmic event rate in the population selected with the MISSION! protocol suggests a low rate of potential SCD in these patients. As expected, appropriate ICD therapy was more frequent in patients with lowest LVEF. In the group with a more preserved LVEF (≥35%) none of the patients had appropriate ICD therapy.

Interestingly, all incidents of first appropriate therapy took place within the first year after ICD implantation, although the small number of ICD patients warrants caution in the

interpretation of the data. An increased tendency for arrhythmic events in the first year after implant is consistent with prior reported data on ICD patients.[28;29] The low percentage of patients benefiting from appropriate ICD therapy demonstrates that despite use of a structured protocol, accurate SCD risk stratification is difficult. Nevertheless, results from the eight year follow-up of the MADIT II trial [30] provides substantial evidence for long term mortality benefit of ICD therapy.

## Clinical implications

Using a standardized clinical protocol like the MISSION! algorithm can not replace personal judgment and individualized risk assessment, but can aid in applying evidence-based medicine in clinical practice and can help in achieving optimal results at the lowest possible cost, in terms of health, quality of life and finance.

Interestingly, results of the multivariable analysis suggested that ICD implantation in all patients with low LVEF, reduced the value of low LVEF as independent predictor of death. When ICD treatment was removed from the multivariable cox regression analysis low LVEF did regain its significant association with increased death rate. This seems to confirm that ICD treatment is probably the reason why low LVEF was not associated with (all-cause) death in the study population after the 3-month screening period. It remains possible that relatively short follow-up and small patient numbers in the low LVEF group were not sufficient to see a significantly different distribution of (particularly heart failure related) deaths between the low LVEF and the high LVEF group.

## Limitations

This is a single-center study based on the data of real clinical practice without the strict controlled conditions of a trial. Only patients with conclusive gated SPECT LVEF results were included in the study population in order to avoid confusion about the protocol. Excluded patients (n = 76, 10%) had either poor quality gated SPECT result due to irregular heartbeat or attenuation artifacts, or did not undergo gated SPECT because they either refused protocol or were involved in other treatment protocols. They did however undergo echocardiography at 3 months follow-up and had estimated biplane ejection fractions above 35% which excluded them as likely candidates for ICD implantation. Their inclusion would therefore not have changed the main outcome of the study.

Of note, screening for SCD prevention commenced 3 months after the acute event in contrast to current guidelines recommending a period of 40 days post MI. However, of all deaths occurring in the first 3 months after MI, the vast majority (46/47, 98%) occurred <40 days after AMI and therefore could not have been prevented by commencing screening after 40 days. Finally, three-year event rates should be interpreted with caution due to relatively short follow-up and the small number of patients that received an ICD.

## CONCLUSION

Aggressive treatment of AMI patients and close monitoring after the index event according to a standardized protocol, results in only a small number of patients becoming candidate for prophylactic ICD implantation. An easy-to-use protocol combining aggressive reperfusion, optimal medication and a risk stratification algorithm tailored to fit within routine practice may help to maintain ICD implantation rates within manageable proportions.

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# Chapter 10

# Right ventricular stimulation threshold at ICD implant predicts device therapy in primary prevention patients with ischemic heart disease.

Jael Z. Atary[1], C. Jan Willem Borleffs[1], Johanna G. van der Bom[2], Serge A.I.P. Trines[1], Marianne Bootsma[1], Katja Zeppenfeld[1], Lieselot van Erven[1], Martin J. Schalij[1]

[1]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands.
[2]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.

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## ABSTRACT

### Background

Myocardial excitability is known (amongst other reasons) to be related to the degree of ischemia, contractile dysfunction and heart failure. It was hypothesized that the right ventricular (RV) stimulation threshold has prognostic value with respect to the occurrence of ventricular arrhythmias (VAs) and patient survival in recipients of an implantable cardioverter defibrillator (ICD).

### Methods

Ischemic heart disease patients receiving an ICD at Leiden University Medical Center as primary prevention for sudden cardiac death were included in this study. RV-thresholds were determined at ICD implant. Data was collected on VAs triggering ICD therapy and on all-cause mortality.

### Results

A total of 689 consecutive patients were included (87% male, age 63±11 years, left ventricular ejection fraction [LVEF] 29±11%) and followed for a median 28 months. Post-implant RV-threshold was 0.7±0.5volt (V) at 0.5ms pulse duration. Best dichotomous separation was reached at a cut-off of 1V. During follow-up, 167 (24%) patients received appropriate ICD therapy, 88 (13%) had appropriate shocks and 134 (19%) died. Cumulative appropriate shock incidence for patients with RV-threshold ≥1V (n=166) was 16% at 1 year, 24% at 3 years and 34% at 5 years compared to 4%, 11% and 17% for patients with a RV-threshold <1V (n=523). Adjusted Hazard Ratio (HR) of RV-threshold ≥1V was 2.0 (95% CI 1.4-2.9) for appropriate therapy, 3.3 (95%CI 2.0-5.4) for appropriate shocks and 1.6 (95%CI 1.1-2.5) for mortality.

### Conclusion

The RV stimulation threshold at ICD implant has a strong independent prognostic value for the occurrence of ventricular arrhythmias triggering appropriate ICD therapy, appropriate shocks and mortality.

## INTRODUCTION

Following the results of several large randomized trials, current guidelines for prevention of sudden cardiac death (SCD) advocate implantation of an implantable cardioverter defibrillator (ICD) in patients with a low left ventricular ejection fraction (LVEF) without a prior life-threatening ventricular arrhythmia.[1-5] This strategy has led to an increasing number of ICD implantations in recent years and currently, a low LVEF is still the most effective and consistent parameter used to select patients at risk of SCD.[6-9] However, the rate of ventricular arrhythmias, triggering appropriate device therapy is relatively low (35-40%)[10] in this group of patients, warranting better risk-stratification for ICD implantation.

As the structure of cardiac tissue is affected by the pathological processes of infarction and subsequent fibrosis, the electrophysiological properties of the myocardium are altered significantly.[11-13] The changes in cardiac tissue structure caused by myocardial infarction may increase the risk of ventricular arrhythmias to occur. Furthermore these changes may increase the myocardial excitability threshold.[11-13] Consequently an increased excitability threshold may reflect an increased risk of ventricular arrhythmias.

In the current study, it was hypothesized that alterations of myocardial excitability caused by ischemic heart disease and reflected in part by changes in the stimulation threshold, may be of clinical use as a risk parameter for ventricular arrhythmias in primary prevention ICD patients.

## METHODS

### Patients and protocol

Since 1996, all patients who received an ICD system in the Leiden University Medical Center were prospectively documented in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center). Patients included in this study received an ICD between 1999 and 2007. Characteristics at baseline, data of the implant procedure, and data of all follow-up visits were recorded. For the current study, only patients with ischemic heart disease and a primary indication for defibrillator implantation were evaluated. We excluded patients with congenital structural, monogenetic heart disease, or non-ischemic heart disease for the present analysis. Furthermore, patients without a documented RV-threshold at implant were excluded for the present analysis.

Eligibility for ICD implantation in this population was based on international guidelines for the prevention of sudden cardiac death which, due to evolving guidelines may have changed over time. In the majority of patients, indication for an ICD was based on a depressed LVEF with or without non sustained ventricular tachycardia. Ischemic heart disease was defined as a history of myocardial infarction (presence of an unstable coronary

lesion on angiography and/or the elevation of cardiac biomarker(s) above normal levels), or a history of significant coronary artery disease (an angiographically estimated diameter stenosis of at least 50% in at least one coronary artery and exercise induced myocardial ischemia/perfusion defect) that resulted in coronary revascularization.

## ICD implantation

All defibrillator systems used were implanted transvenously without thoracotomy. The right ventricular lead was positioned in the right ventricular apex near the septum and adjustments, if necessary, were made to achieve an optimal pacing threshold. During the implant procedure standard testing of sensing and pacing thresholds and defibrillation threshold testing was performed. Used systems were manufactured by Biotronik (Berlin, Germany), Medtronic (Minneapolis, MN, United States), Boston Scientific (Natick, MA, United States, formerly CPI, Guidant [St. Paul, MN, United States]) and St. Jude Medical/Ventritex (St. Paul, MN, United States).

In this primary prevention patient cohort, defibrillators were programmed as follows: a monitor zone was programmed in all patients to detect ventricular arrhythmias faster than 150 bpm. No therapy was programmed in this zone. Ventricular arrhythmias faster than 188 bpm were initially attempted to be terminated with two bursts of antitachycardiapacing (ATP) and, after continuation of the arrhythmia, with defibrillator shocks. In the case of a ventricular arrhythmia faster than 210 bpm, device shocks were the initial therapy. Furthermore, atrial arrhythmia detection was set to >170 bpm with supraventricular tachycardia (SVT) discriminators enabled. Settings were adapted, only when clinically indicated (i.e. hemodynamic well tolerated ventricular tachycardia at high rate; ventricular tachycardia in the monitor zone). The stimulation threshold was determined by automatic decrementation of the stimulus voltage at constant pulse duration of 0,5ms after implant.



## Follow-up and endpoints

All patients visited the clinic for follow-up assessments every 3 to 6 months. Patients were followed up to February 2009. At each patient visit, a trained device specialist or cardiologist performed device interrogation and determined sensing, pacing thresholds, and lead impedance.

The primary endpoint was ventricular arrhythmia triggering appropriate defibrillator therapy (antitachycardia pacing [ATP] or shock) or appropriate shock only. Secondary endpoint was all-cause death.

## ICD evaluation

All printouts were checked for appropriate and inappropriate ICD therapy (ATP or shocks). Therapies were classified as appropriate when they occurred in response to ventricular tachycardia (VT) or ventricular fibrillation (VF) and as inappropriate when triggered by sinus or SVT,

T-wave oversensing, or electrode dysfunction. Cutoff rate of the monitor or first therapy zone was noted.

### Statistical Analyses

Continuous data are expressed as mean (±standard deviation) or as median ($25^{th}$/$75^{th}$ percentile); dichotomous data are presented as numbers and percentages. Differences at baseline were tested for statistical significance using a Chi-square test using Yate's correction or student t-test for independent samples where appropriate. Event rates over time were analyzed by method of Kaplan-Meier with corresponding log-rank test for differences in distribution between the curves. Since follow-up was performed every three to six months, patients without data in the past six months were censored at the date of their last visit.

We used multivariable Cox regression analyses to assess the association between stimulation threshold and ventricular arrhythmias independent of an increasing number of other risk factors including age, gender, cardiac resynchronization therapy, LVEF, history of atrial fibrillation/atrial flutter, use of amiodarone, use of beta-blocker, use of sotalol, and anterior-, lateral-, inferior- and posterior MI as potential confounders. Hazard Ratio (HR) is reported with the corresponding 95% confidence interval (CI). All tests were two-sided, a p-value of $< 0.05$ was considered statistically significant. Missing values of all the variables were seen only for the variable atrial fibrillation/atrial flutter, in less than 0.3% (n=2/689) of all patients. The regression models were done on the patients without missing values.

A receiver operating characteristic (ROC) curve analysis was used to measure the ability of the RV-threshold to discriminate between patients that received appropriate therapy and patients that did not.

## RESULTS

### Patient population

A total of 1086 consecutive ICD recipients with a primary prevention indication were registered in the electronic database system. Fifty patients (5%) were excluded due to incomplete follow-up data, 332 patients (31%) due to non-ischemic heart disease and 15 patients (1%) due to non-documented baseline RV-threshold measurements. The remaining 689 patients were included in the present analysis and followed for a median 28 months (interquartile range (IQR) 16 to 46 months).

The majority of patients (87% male, 63 ± 11 years, LVEF 29 ± 11%) had a history of myocardial infarction (84%) or coronary revascularization procedure (PCI 28%, CABG 43%) (Table 1). Median RV-threshold was 0.5V (IQR 0.5 to 0.8V) at 0.5ms pulse duration. ROC curve analysis of the RV-threshold suggested that a cutoff of 1V provided the best clinically useful dichotomous separation for assessment of the primary endpoint. A

**Table 1.** Baseline characteristics.

| | All patients n = 689 | RV threshold <1V n = 523 | RV threshold ≥1V n = 166 | p-value |
|---|---|---|---|---|
| Male sex | 600 (87) | 459 (88) | 141 (85) | 0.35 |
| Age (years) | 63 ± 11 | 63 ± 11 | 63 ± 11 | 0.81 |
| Hypertension | 318 (46) | 239 (46) | 79 (48) | 0.72 |
| Diabetes | 176 (26) | 130 (25) | 46 (28) | 0.40 |
| Smoking | 151 (22) | 118 (23) | 33 (20) | 0.50 |
| Prior myocardial infarction | 578 (84) | 436 (83) | 142 (86) | 0.55 |
| Anterior† | 304 (53) | 237 (54) | 67 (47) | 0.13 |
| Inferior† | 161 (28) | 112 (26) | 49 (35) | 0.043* |
| Lateral† | 76 (13) | 54 (12) | 22 (16) | 0.32 |
| Posterior† | 49 (9) | 36 (8) | 13 (9) | 0.76 |
| Prior PCI | 192 (28) | 145 (28) | 47 (28) | 0.92 |
| Prior CABG | 296 (43) | 226 (43) | 70 (42) | 0.86 |
| Hypercholesterolemia | 463 (67) | 364 (70) | 99 (60) | 0.051 |
| Family History of CAD | 300 (44) | 220 (42) | 80 (48) | 0.21 |
| AF/AFL flutter documented | 170 (25) | 123 (24) | 47 (28) | 0.26 |
| QRS width | 126 ± 34 | 125 ± 34 | 130 ± 34 | 0.10 |
| Creatinine clearance (ml/min) | 78 ± 35 | 78 ± 32 | 77 ± 43 | 0.70 |
| Ejection Fraction | 29 ± 11 | 29 ± 10 | 29 ± 13 | 0.90 |
| Cardiac resynchronization therapy | 335 (49) | 263 (50) | 72 (43) | 0.13 |
| Medication | | | | |
| Beta-blocker | 425 (62) | 345 (66) | 80 (48) | <0.001* |
| Sotalol | 75 (11) | 47 (9) | 28 (17) | 0.006* |
| ACE-inhibitor/ATII-antagonist | 580 (84) | 443 (85) | 137 (83) | 0.54 |
| Diuretics | 502 (73) | 375 (72) | 127 (77) | 0.27 |
| Statin | 560 (81) | 426 (82) | 134 (81) | 0.82 |
| Aspirin | 332 (48) | 255 (49) | 77 (46) | 0.76 |
| Oral anticoagulation | 400 (58) | 304 (58) | 96 (58) | 1.00 |
| Amiodarone | 110 (16) | 70 (13) | 40 (24) | 0.002* |

Values are expressed as n (%) or as mean ± standard deviation. * p <0.05
Hypercholesterolemia= Total cholesterol ≥190 mg/dl or previous pharmacological treatment.
Hypertension = Blood pressure ≥140/90 mm Hg or previous pharmacological treatment.
†Patients could fall into more than one infarction location category (i.e. anterolateral, inferoposterior infarction). AF: Atrial fibrillation; AFL: Atrial flutter.

RV stimulation-threshold ≥1V was observed in 166 (24%) patients. An equal distribution of lead types were used in both the RV threshold >1V group and the RV threshold <1V group (p=NS). There was not a significant difference between the groups in the use of any particular lead type (not shown).

Baseline characteristics distributed according to RV-threshold are reported in table 1. With the exception of infarct localization (higher number of inferior wall infarctions in the >1 RV threshold group (p=0.04)) baseline characteristics were similar.

Cardiac resynchronization therapy was combined with the defibrillator device in approximately 50% of cases of either group (RV-threshold <1V: 50%, RV-threshold ≥1V: 43%; p = 0.13). Concerning the use of drugs: Patients with a higher threshold more often used sotalol and amiodarone than patients with a threshold < 1V. Patients with lower threshold more often used beta-blockers. The use of other drugs was similar in both groups.

## Device therapy

During follow up, a total of 1615 episodes of ventricular arrhythmia were appropriately terminated by the ICD in 24% (n=167) of patients either by ATP or by shock delivery. A total number of 278 shocks were delivered appropriately by the ICD in 13% (n=88) of patients. Furthermore, 68 patients (10%) experienced inappropriate shocks. Figure 1 shows the distribution over time of first appropriate therapy and -shocks for the total patient cohort.

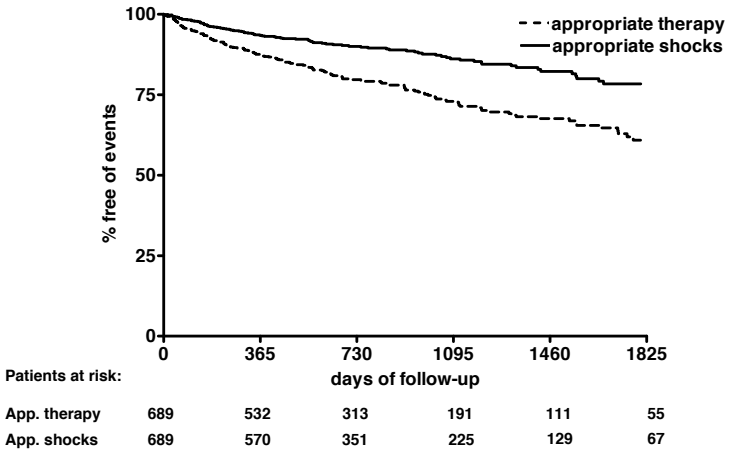


**Figure 1.** Kaplan-Meier Plot of Cumulative Incidence of first appropriate ICD therapy and appropriate shocks in the total study population.
App = appropriate; ICD = Implantable Cardioverter Defibrillator

Appropriate therapy during follow-up occurred more often in patients with a RV-threshold ≥1V (37%, 62 of 166 patients) when compared to patients with a RV-threshold <1V (20%, 105 of 523 patients). Furthermore, the number of patients that experienced appropriate ICD shocks was more than three times higher in the group with a RV-threshold ≥1V (26%, 43 of 166 patients) than in the group with a RV-threshold <1V (9%, 45 of 523 patients).

Figure 2 illustrates the time course of first appropriate therapy (panel A) and for first appropriate shocks (panel B) for patients with a RV-threshold <1V and a RV-threshold ≥1V. A significantly higher cumulative incidence of first ICD therapy and shocks was observed in the group with a RV-threshold ≥1V. Cumulative appropriate shock rate for patients with a RV-threshold ≥1V was 16% (95%CI 10-22%) at 1 year, 24% (95%CI 17-31%) at 3 years and 34% (95%CI 24-43%) at 5 years compared to 4% (95%CI 2-5%) at 1 year, 11% (95%CI 7-14%) at 3 years and 17% (95%CI 12-23%) at 5 years for patients with a RV-threshold <1V (log-rank p<0.001).

Post-implant RV-threshold ≥1V was found to be an independent and significant predictor of first appropriate ICD therapy (adjusted HR model 3: 2.0, 95%CI 1.4-2.9) and appropri-

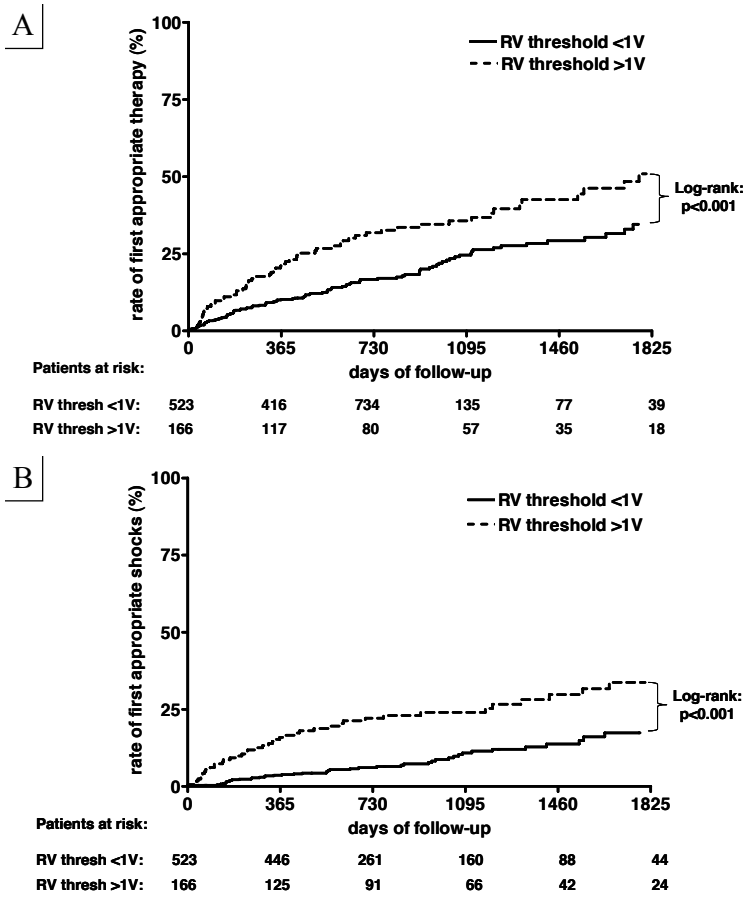


**Figure 2.**

A. Kaplan-Meier Plot of Cumulative Incidence of first appropriate ICD therapy.
B. Kaplan-Meier Plot of Cumulative Incidence of first appropriate ICD shocks.
RV = Right Ventricular; Thresh = threshold; other abbreviations as in Figure 1.

ate shocks (adjusted HR model 3: 3.3, 95%CI 2.0-5.4) after correcting for other potential confounders as listed.

With higher measurements of the RV-threshold, the percentage of patients experiencing appropriate shocks increased. The area under the ROC curve for RV-threshold was significantly greater than 0.5 (area under ROC curve 0.7; 95%CI 0.6-0.7; p<0.001). A high specificity was observed at a cut-off value around ≥1V (specificity 80% [95%CI 76-83%]) at the expense of sensitivity (49% [95%CI 38-60%]). The negative predictive value of the RV-threshold cut-off value of 1V was 91%.

## Mortality

One-hundred and thirty-four (19%) patients died during the follow-up period. Total mortality in patients with a RV-threshold ≥1V (28%, 47 of 166 patients) was higher compared to the group of patients with a RV-threshold <1V (17%, 87 of 523).

Cumulative survival (%) for the two study groups is displayed in Figure 3. A trend exists toward decreased patient survival in the patient group with a RV-threshold ≥1V. Cumulative survival in this group is 90% (95%CI 86-95%) at 1 year, 78% (95%CI 72-85%) at 3 years and 70% (95%CI 61-78%) at 5 years, compared to 94% (95%CI 92-96%) at 1 year, 81% (95%CI 77-85%) at 3 years and 73% (95%CI 67-79%) at 5 years in the group with a RV-threshold <1V. The log-rank test for this difference was not statistically significant (p=0.12).

However, post-implant RV-threshold ≥1V was found to be an independent and significant predictor of mortality after correcting for potential confounders as listed in table 2. After adjustment the mortality rate was 60 percent higher among those with RV-threshold ≥1V as compared to patients with RV-threshold <1V (adjusted HR model 3: 1.6, 95%CI 1.1-2.5) (Table 2).

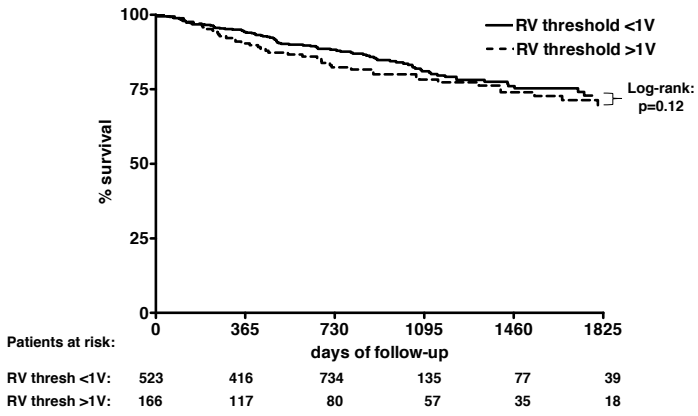


**Figure 3.** Kaplan-Meier Plot of Cumulative Incidence of Death.
Abbreviations as in Figure 2.

**Table 2.** Multivariable Cox regression analyses.

| | RV threshold <1V (n=523) | RV threshold ≥1V (n=166) | Unadjusted HR (95% CI) | Adjusted HR (95% CI) | | |
|---|---|---|---|---|---|---|
| | | | | Model 1 | Model 2 | Model 3 |
| Appropriate therapy | 105 (20) | 62 (37) | 1.8 (1.3-2.5) | 2.0 (1.4-2.9) p<0.001 | 2.0 (1.4-2.8) p<0.001 | 2.0 (1.4-2.9) p<0.001 |
| Appropriate shocks | 45 (9) | 43 (26) | 2.9 (1.9-4.4) | 3.3 (2.0-5.3) p<0.001 | 3.1(1.9-5.2) p<0.001 | 3.3 (2.0-5.4) p<0.001 |
| All-cause mortality | 87 (17) | 47 (28) | 1.3 (0.9-1.9) | 1.7 (1.2-2.6) p= 0.007 | 1.6 (1.1-2.4) p= 0.028 | 1.6 (1.1-2.5) p= 0.021 |

Values are expressed as n (%), or as HR = hazard ratio (95% CI = confidence interval).
Model 1 = adjusted for age, gender, cardiac resynchronization therapy, LVEF and inferior infarction;
Model 2 = additionally adjusted for beta-blocker-, sotalol- and amiodarone treatment.
Model 3 = additionally adjusted for anterior MI, lateral MI and posterior MI and history of AF/AFL.

## DISCUSSION

In this cohort of ICD treated patients with ischemic heart disease and a primary prevention indication for ICD treatment, a post-implant right ventricular stimulation threshold ≥1V was independently associated with (1) a higher occurrence of ventricular arrhythmias triggering appropriate therapy, (2) a 3-fold higher occurrence of ventricular arrhythmia triggering appropriate shocks and (3) a 60% higher risk of mortality compared to patients with a threshold <1V.



### Risk stratification for SCD

LV function is an established indicator for an increased risk of SCD.[6-8] Results of a series of randomized trials have resulted in a rise in the number of ICD implantations due to a great expansion in the indications for primary prevention ICD use.[1;3-5] However, the relatively low percentage of ICD patients who receive appropriate therapy (35-40% of patients in MADIT II and SCD-Heft)[1;10] suggested a considerable risk heterogeneity in the low LVEF-population. This has prompted a series of studies and secondary analyses from the major ICD trials in an attempt to identify factors that can be used to stratify patients with reduced LVEF into high- and low risk subgroups.[14-22] Given the complexity and limitations of some of these proposed stratification strategies, the RV stimulation threshold is a relatively easy to use, straightforward prognostic and, more importantly, electric measure of arrhythmic risk. It may assist clinicians in identifying ICD treated patients at high risk of receiving appropriate ICD therapy and a higher risk of death, therefore facilitating better evaluation of the prognosis post-implant. The present study can not provide an answer as to the value of the stimulation threshold as a pre-implant risk stratifier, it suggests only that the baseline stimulation threshold may enable some prognosis prediction post-implant, and may assist in guiding perhaps the medication regime or the frequency of outpatient visits especially for the group below the cutoff of 1V as the negative predictive value was 91%. Obviously such a cutoff

value should be treated just like any other "superficial" cutoff measure (like, for example a LVEF of 35% calculated by biplane echo). Common sense and personal and professional judgment is indispensable in solving such dilemmas.

In order to get to the stage of clinical usefulness, the pacing thresholds should be determined in a standardized prospective fashion utilizing MRI data in order to draw definite conclusions about the optimal cutoff, or perhaps range, with its associated arrhythmic risk groups.

## Ischemic heart disease, poor excitability and arrhythmogenesis

Prior myocardial infarction leaves a residue of poorly excitable cardiac tissue. Findings from a canine study suggested that disruptions in cell-to-cell electrical continuity may contribute to slow conduction in the infarcted region.[12] In later experiments a persistent reduction of the space constant existed in chronically infarcted canine myocardium 5-8 days after persistent occlusion and reperfusion which is directly related to slow conduction velocity.[13] The investigators hypothesized that these alterations were due to a depression in action potential depolarization, an increase in internal axial resistance (by modification of the low resistance gap junctions, therefore increasing anisotropy) and an increase in the axial resistance of the extracellular space (due to the fibrotic matrix in which surviving cells are distributed within the mottled infarcted myocardium). Furthermore, wavefront-obstacle interactions in a poorly excitable medium may reflect an arrhythmogenic process that permits formation of separate new wavelets which in vivo may lead to flutter, fibrillation, and sudden cardiac death.[23]

Arrhythmias leading to sudden cardiac death are often associated with the presence of inhomogeneities (obstacles) in cardiac tissue and reduced excitability of cardiac cells. Observations of fast arrhythmias in a medium of reduced excitability, combined with medium inhomogeneities provide a substrate for formation of multiple wavelets leading to high-frequency arrhythmias.[11;24-26]

## Device therapy and stimulation threshold

Stimulation thresholds vary immediately following implant due to lead-myocardium maturation and chronically due to changes in underlying myocardium, ischemia, infarction, metabolic state, or drug therapy.[27-30] The present findings suggest that properties of the baseline RV stimulation threshold may be used clinically as an indicator of chronic changes caused by ischemic heart disease, increasing the risk of arrhythmic events requiring ICD therapy and the risk of mortality. A high RV stimulation threshold was used as a marker of the degree of poor myocardial excitability to indirectly indicate potentially arrhythmia-prone conditions. The association was found to be independent of infarction location despite the essentially local measurement position at the RV apex, which implies that the parameter reflects not only a localized effect but rather a sum of effects. In addition, when looking at a small sample of the first 15 patients who received appropriate ICD shocks (and of whom >1 measurement of

the RV threshold was available before the ICD therapy took place), we saw the RV threshold increasing several months before an appropriate shock in 11 patients (increase with as little as 0.2V or with a much as 3V), stay the same in 3 patients and decrease in 1 patient. After the ICD shock it remained the same in 14 patients and decreased in 1. According to this small sample of patients, one may cautiously suggest that there may also be a predictive value in serial measurement of the RV threshold regarding the imminent occurrence of a ventricular arrhythmia requiring appropriate ICD shock. These changes probably also reflect a state of progressing heart failure.

While the cumulative survival analysis was not able to demonstrate a significant difference in mortality incidence between the two study groups (Figure 3), post-implant RV-threshold ≥1V was nevertheless found to be independently associated with a 60% increased hazard of mortality after adjusting for confounders as listed in table 2. Cardiac resynchronization therapy and LVEF were the most important variables influencing the association between RV-threshold and mortality, both to an equal extent. As the association of the RV-threshold with ventricular arrhythmia triggering appropriate shocks was strongest, the risk parameter may be most valuable for the estimation of fast, potentially life-threatening, arrhythmias.

Though the optimal cut-off value of the RV stimulation threshold for its best predictive value may vary slightly in post-MI patient subgroups with different baseline characteristics or for a different moment of baseline measurement, its ability to identify patient with a higher risk of arrhythmic events leading to appropriate ICD therapy and shocks will most likely not be affected. This is supported by results of the multivariate analyses that showed that the effect was independent of other predictors. Antiarrhythmic drugs such as beta-blockers tend to increase the stimulation threshold, but paradoxically in the current study were used more frequently in the group with RV-threshold <1V, suggesting a limited clinical effect. Amiodarone treatment was more prevalent in patients with RV-threshold ≥1V, but whether the type III antiarrhythmic drug has similar effects is as yet unclear. Virtually all antiarrhythmic drugs may influence the pacing threshold but usually become clinically important only at high serum concentrations.[29]



## Limitations

This is a single-center follow-up study based on data of routine clinical practice. Missing data in the enrolled population was seen in less than 1% of patients which limited potential over- or underestimation of findings. The single-center nature of this study was, in this case, an advantage in that it kept the variability between procedure protocol and operators at a minimum.

Guidelines for ICD eligibility might have changed over time, creating a more heterogeneous patient population than in the strict controlled conditions of a clinical trial. Potentially confounding effects of these heterogeneities were limited by using the multivariable Cox

analysis to assess the independent association between stimulation threshold and ventricular arrhythmias.

The electrophysiologists performing the procedure at our centre are trained to look for a RV threshold preferably below 1V, though the number and distribution of pacing sites is not pre-specified or standardized in the clinical protocol. The search for the optimal threshold was at the discretion of the operator. MRI data was not available of patients in this study to assess scar tissue. However, data was available on the culprit vessel, peak troponin levels and perfusion defects post-MI (assessed with gated SPECT) which informed us about location and extensiveness of the myocardial damage. Other reasons led us to believe that the reported association between RV threshold and ICD therapy is valid, despite the study's non-standardized nature.

First, although certainly far from the accuracy of MRI scar tissue data, simply the location of the MI as informed by the mentioned test modalities should have led to substantial confounding of the association between the pacing threshold and the ICD shock rate, certainly when taking into account the relatively large sample size and number of events. However, on the contrary, a very strong relationship was still observed. Considering that it concerned the "optimal achievable pacing threshold (site)" chosen by the operator at the time of implantation this finding suggests that the operator did already take the location of the infarction into account at placement of the lead and avoided it as much as was possible.

Second, despite variation in procedures, due to the law of "regression toward the mean" the eventual result of the threshold cutoff in a large sample size will probably approach the true mean. Patients included in this study were consecutive and non-selected, because the procedure was not done in a standardized trial setting. After reviewing the data of all patients and performing ROC analysis of all the measured thresholds a clear trend was visible with a RV threshold of 1V as the best statistical and clinical cutoff value. Although it is a relatively simple way to analyze the data, we believed it was best not to "over process" the data after documentation, in order to avoid introducing errors in the natural distribution of the values and simply report what we observed, as we did not have the benefit of a standardized controlled study protocol.

In summary, although lack of MRI scar tissue data is a certain limitation of the study, we still believe that the association we found is a true trend that really exists. However, in order to get to the stage of clinical usefulness, the best threshold cutoff should be determined in a standardized prospective fashion in the future utilizing MRI data in order to draw definite conclusions about the ideal cutoff, or perhaps range, and its associated risk group. Of note, clinical usefulness of the stimulation threshold before the implantation of the ICD still remains to be investigated.

Lastly, while appropriate ICD therapy was used as a primary endpoint throughout the current study, it should be noted that it is not a perfect surrogate for life-threatening ventricular arrhythmia or SCD.

## CONCLUSION

In ICD treated patients with a primary prevention indication and ischemic heart disease the RV stimulation threshold at implantation has an independent prognostic value for the prediction of potentially life-threatening ventricular arrhythmia and death.

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# Chapter 11

## Long-term outcome after ablative therapy of post-operative atrial tachyarrhythmias in patients with congenital heart disease and characteristics of atrial tachyarrhythmia recurrences.

Natasja M.S de Groot, Jael Z. Atary, Nico A. Blom, Martin J. Schalij

Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands

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## ABBREVIATIONS

AT= atrial tachyarrhythmias
CHD= congenital heart disease
AFL= atrial flutter
IART= intra-atrial re-entrant tachycardia
FAT= focal atrial tachycardia
AF= atrial fibrillation

## ABSTRACT

### Background

Catheter ablation has evolved as a possible curative treatment modality for atrial tachyarrhythmias (AT) in patients with congenital heart defects (CHD. However, data on long-term outcome is scarce. We examined characteristics of recurrent AT after ablation of post-operative AT during long-term follow-up in CHD patients.

### Methods and Results

CHD patients (N=53, 27 male, 38±15 yrs) referred for catheter ablation of AT were studied during a follow-up period of 5±3 years.

After ablative therapy of the first AT (N=53, 27 atrial flutters (AFL), CL= 288±81 ms; 22 intra-atrial re-entrant tachycardias, (IART), CL= 309±81 ms; 5 focal atrial tachycardias (FAT), CL= 380±147 ms, success rate: 65%), AT recurred (59% within the first year) in 29 patients, 15 underwent repetitive ablative therapy. Mechanisms underlying recurrent AT was similar in 7 patients (IART: 2, AFL: 5). The location of arrhythmogenic substrates of recurrent AT (IART, FAT) was different for all but one patient. After 5±3 yrs, 5 patients died due to heart failure, 3 were lost to follow-up and the remaining patients had sinus rhythm (31), AT (5) or AF (14). Anti-arrhythmic drugs were used by 18 (57%) sinus rhythm patients.

### Conclusion

Successive post-operative AT in CHD patients developing over time may be caused by different mechanisms, including focal and reentrant mechanisms. Recurrent AT originated from different locations suggesting that these new AT were not caused by arrhythmogenicity of previous ablative lesions. Long-term outcome is often complicated by development of AF. Despite frequent need for repeat ablative therapy, most patients are in sinus rhythm.

## INTRODUCTION

Atrial tachyarrhythmias (AT) occurring late after cardiac surgery for congenital heart disease (CHD) or acquired heart disease are associated with hemodynamic deterioration, increased risk of thromboembolism and even cardiac death.[1-5] Management of post-operative AT with anti-arrhythmic drugs is often not successful and accompanied by side effects.[1,5-8] In recent years, catheter ablation has evolved as a feasible curative treatment modality for these AT.[9-16] As the arrhythmogenic substrate in patients with prior cardiac surgery is often complex detailed mapping prior to ablation is essential for successful ablative therapy.[17,18]

The first studies of ablative therapy of post-operative AT described ablation procedures using only fluoroscopy. During these procedures, multiple catheters were often required to comprehend the mechanism of the AT. Technological advancement over the years resulted in introduction of 3-dimensional electro-anatomical mapping techniques such as the CARTO™ system.[19,20] By visualizing the electrical activation of the heart chamber mapped in a 3-dimensional reconstruction, these systems are able to facilitate ablative therapy. Ever since their implementation, numerous articles reported on the outcome of ablative therapy of post-operative AT.[10,12,21-26] However, data of long-term outcome is scarce[25,26] and there is a lack of information about characteristics of successive post-operative AT for individual patients.

The aim of this study was to evaluate long-term outcome after ablation of late post-operative AT and to examine characteristics of recurrent AT in a large cohort of patients with predominantly complex congenital heart defects.

## METHODS

### Study Population

The study population consisted of 53 consecutive patients with congenital heart disease and post-operative, drug refractory AT referred for ablation to our center between 2000 and 2004. Data regarding congenital defects and surgical history were obtained from hospital records. The first visit to the out-patient clinic was 4 weeks after ablation. After this visit, patients were seen every 6 months. Evaluation prior to ablation and during the follow-up period included history, physical examination, ECG, Holter monitoring and echocardiographic examination.

### Mapping Procedure

Mapping was performed using a 3-D electro-anatomical mapping system (CARTO™, Biosense-Webster, Diamond Bar, CA, USA). A detailed description of the underlying technology of electro-anatomical mapping has been given previously.[19,20] A 7F Navistar (4mm tip,

2 bipolar electrode pairs, inter-electrode distance 2 mm, Biosense-Webster, USA) was used for mapping and ablation. Bipolar electrograms were filtered at 10-400Hz. A bipolar atrial electrogram recorded by a 6F diagnostic catheter (Biosense-Webster) positioned in the RA served as a temporal reference. A sensor taped on the back served as a location reference.

If AT was not present at the onset of the procedure, it was induced using programmed electrical stimulation. 3-D bipolar activation and voltage maps were constructed during AT to 1) identify the underlying mechanism, and 2) select target sites for ablation. Stability parameters (variability in cycle length, local activation time and beat to beat difference of the catheter's location) were used to exclude signals with low amplitudes due to poor contact of the catheter's tip with the endocardial wall. The local activation time was determined by automatically marking the maximum amplitude of each bipolar potential.

If necessary, markings were adjusted manually. The peak-to-peak amplitude of bipolar electrograms was used to construct colour coded voltage maps. In case of fractionated potentials, the peak-to-peak amplitude of the largest deflection was measured. Areas of scar were delineated using a cut-off value of 0.1 mV.[18]

## Classification of Atrial Tachycardia

Based on activation maps, three different types of AT were distinguished:

1) typical atrial flutter (AFL): a single (counter)-clockwise, cavo-tricuspid isthmus dependent macro-reentrant circuit, 2) intra-atrial reentrant atrial tachycardia (IART): a macro-reentrant tachycardia involving scar tissue, suture lines or prosthetic materials,

3) focal atrial tachycardia (FAT): electrical activation originating from a small, circumscribed region from where it expands to the remainder of the atria.



## Ablation Procedure

After mapping, a radiofrequency catheter ablation procedure was performed. At each site, radiofrequency current was applied for 60 seconds. In case of non-cooled ablation, tip temperature was set at 70°C and the maximum output at 50W. During ablation using an irrigated-tip catheter (19% of the procedures), temperature was limited to 45-50°C and power to 40-45 W with saline flow of 20 ml/min. Each lesion was tagged on the electroanatomical map. Success was defined as (1) in AFL patients: establishment of a line of conduction block over the cavo-tricuspid isthmus, (2) in IART/FAT patients: termination during ablation.

## Statistical Analysis

Data were expressed as mean value ±SD or median (range). Statistical significance was defined as $P<0.05$. One-way ANOVA test was used to compare fluoroscopy time and procedure time required for ablation of different types of tachycardias. Survival free from arrhythmia recurrence was analyzed by method of Kaplan-Meier with corresponding log-rank test for differences in distribution between the curves. The 2 groups were defined as

patients who underwent a successful ablation procedure and patients in whom ablation was not successful.

## RESULTS

### Characteristics of the study population

The study population consisted of 53 patients (27 male, median age 35 (6-80) yrs). Major common congenital heart defects included transposition of the great arteries (TGA: N=4), univentricular hearts (UVH: N=15), ventricular septal defect (VSD: N=2), coarctation of the aorta (CoA: N=2), atrial septal defect (ASD: N=11), tetralogy of Fallot (ToF: N=10) or valvular heart disease (VHD: N=9). Characteristics of the study population are given in Table 1.

**Table 1.** Characteristics of the study population.

| CHD (number, gender) | Surgical Procedures |
|---|---|
| TGA (N=4, 3M) | Mustard procedure |
| UVH (N=14, 7M) | Fontan procedure (atrio-pulmonary conduit, N=11)<br>Mustard operation followed by Jatene procedure (N=1) |
| Ebstein's anomaly (N=1,M) | Conduit left ventricle –pulmonary artery (N=1)<br>Blalock shunt (N=1)<br>Glenn shunt and ASD closure (N=1) |
| VSD (N=2, 1M) | surgical closure defect |
| CoA (N=2, 2F) | resection stenotic part and interposition of a graft |
| ASD (N=11, 5M) | surgical closure defect |
| ToF (N=10, 5M) | total correction (N=9)<br>closure VSD and creation Blalock-Taussig shunt (N=1) |
| VHD (N=9, 5M) | valve replacement (N=8)<br>surgical valvotomy (N=1) |

CHD= congenital heart defect, N=number of patients, M=male, F=female UVH= univentricular hearts, TGA= transposition of the great arteries, VHD= valvular heart disease, CoA= coarctation of the aorta, ASD= atrial septal defect, VSD= ventricular septal defect, ToF= tetralogy of Fallot

### Time to post-operative atrial tachyarrhythmias and first intervention

Figure 1 shows age at 1) the time of the first surgical procedure, 2) the onset of the AT and 3) the first ablation procedure. Patients are grouped according to major common congenital defect; the groups are ranked according to the earliest averaged age at time of cardiac surgery. Age at time of the first surgical procedure ranged from 0 to 55 (median: 7) years. Median age at onset of AT was 31 (4-73) years; AT developed 18 (6 months to 44) years after the first surgical intervention. The first ablation procedure was performed at the median age of 38 (6-80) years. On average, median time between the onset of AT and the first ablation procedure was 4 years.

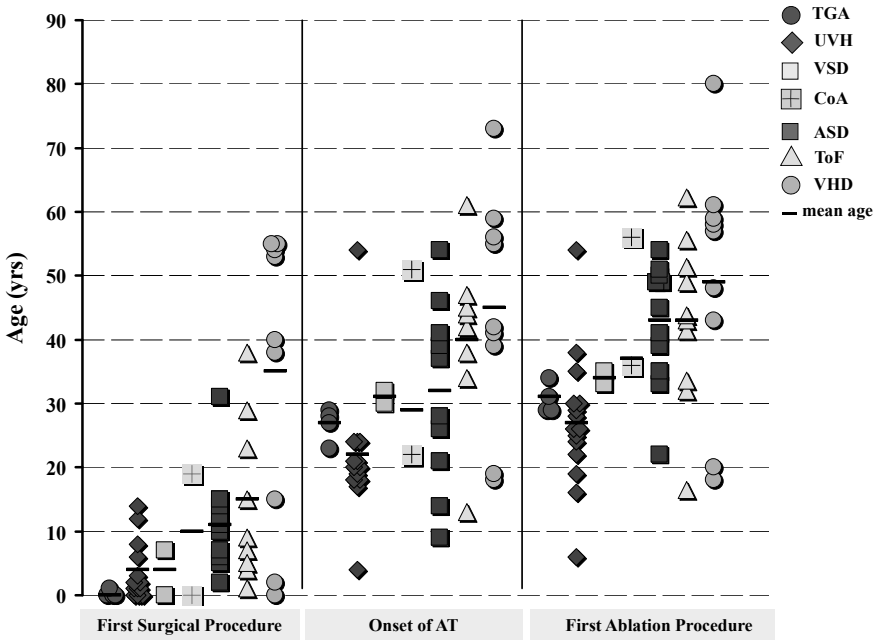


**Figure 1.** Age at the time of the first surgical procedure, onset of the AT and first ablation procedure for each patient separately. Patients are grouped according to major congenital/acquired heart disease and groups are ranked according to the earliest averaged age at time of cardiac surgery.
TGA = transposition great arteries, UVH = univentricular hearts, VSD = ventricular septal defects, CoA = coarctatioa aortae, ASD = atrial septal defect, ToF = tetralogy of Fallot, VHD=valvular heart disease.



## Outcome first ablation procedure

In the entire study population, mapping revealed 27 AFL (cycle length= 288±81 ms), 22 IART (cycle length= 309±81 ms) and 5 FAT (cycle length= 380±147 ms) at the first ablation procedure.

In one patient, 2 AT were eliminated during the same procedure. Successful ablative therapy was achieved in 65% (N=35) of all AT; 20% (N=11) of AT did not terminate and the other AT converted to either another AT (N=4, 7%) or AF (N=4, 7%) during ablation.

In case of AFL, termination during ablation and assessment of a bi-directional conduction block over the cavo-tricuspid isthmus was achieved in 67% (N=18). Despite entrainment demonstrating cavo-tricuspid isthmus dependent conduction, 18% (N=5) of the AFL did not terminate during ablation. Conversion from AFL to AF during ablation occurred in the other 15% (N=4). In those patients, a bi-directional conduction block was assessed after electrical cardioversion to sinus rhythm.

Fifty-five percent of the IART terminated during ablation; conversion from IART to another regular AT or AF occurred in respectively 14% (N=3) and 5% (N=1). Target areas for ablation of IART were located between 1) areas of scar tissue (N=20), 2) scar tissue areas

and the inferior caval vein (N=2). The critical path of the re-entrant circuit was located in the left atrium in only 3 patients. In 27% (N=6), AT did not terminate during ablation despite extensive mapping.

All FAT (N=5) were successfully eliminated by ablation at the site of earliest activation. The majority of the FAT also originated from the right atrium; 1 FAT emerged from the left side of the inter-atrial septum.

## Recurrent atrial tachyarrhythmias

Mean follow-up after the first ablation procedure was 5±3 (2.5-9) years. AT recurred in 29 patients and 15 of them underwent therefore more than one ablation procedure. Time between ablative therapy and recurrences of AT are shown in Figure 2. Recurrences after the second ablation procedure occurred in seven patients. In one patient, 9 different AT were ablated during a follow-up period of 6-years (not shown). As demonstrated in Figure 2, most AT often re-appeared within the first year after ablative therapy.

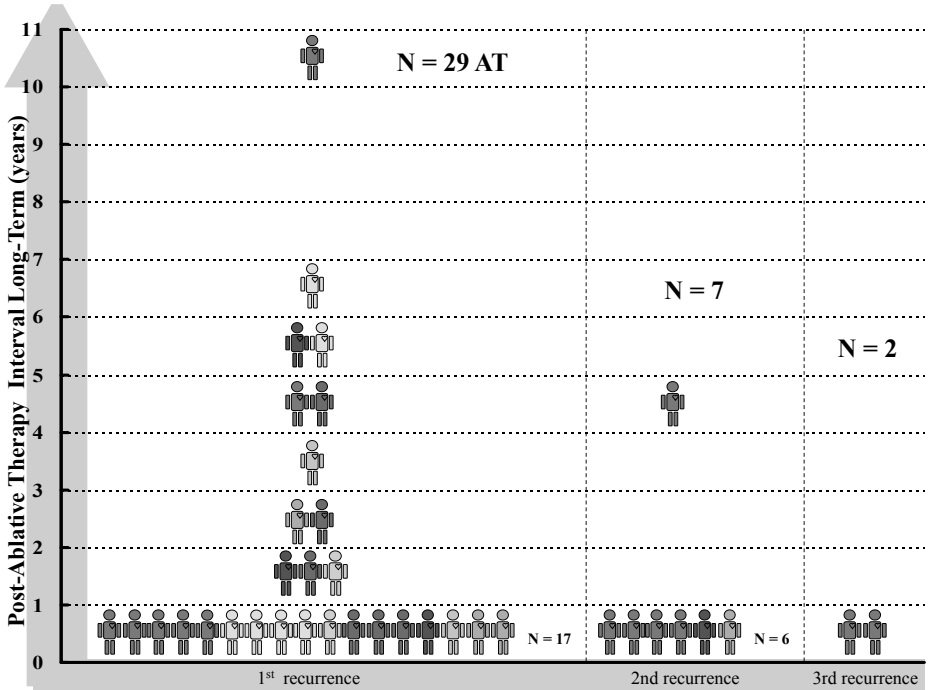


**Figure 2.** Long-term time interval between ablative therapy and recurrences of AT. Twenty-nine patients experienced one or more recurrences.

## Mechanism and location of the arrhythmogenic substrate of recurrent atrial tachyarrhythmias

Figure 3 shows schematic representations of the atria demonstrating the location of the arrhythmogenic substrate of recurrent IART and/or FAT for patients undergoing repetitive ablative therapy (N=15); patients with recurrent AFL (N=5) are not shown. The mechanism underlying the AT is represented by a symbol and the number indicates the order of recurrences. The outcome of the ablation procedure is represented by the colour of the symbol (green: elimination of the AT, red: unsuccessful ablation procedure). In 7 patients with recurrent AT, the underlying mechanism of successive AT was similar, either IART (N=2) or AFL (N=5). Eight patients presented with successive AT caused by different mechanisms, including IART+FAT (N=3), AFL+FAT (N=1), IART+AFL (N=2), AFL+FAT+AF (N=1) or IART+FAT+ AF (N=1). Interestingly, the re-entrant circuit of IART, or the origin of an FAT of consecutive AT was different for the majority of the patients. In one patient, the crucial pathway of the re-entrant circuit of 2 successive IART was located between the inferior caval vein and the atriotomy scar (first patient in the upper panel).

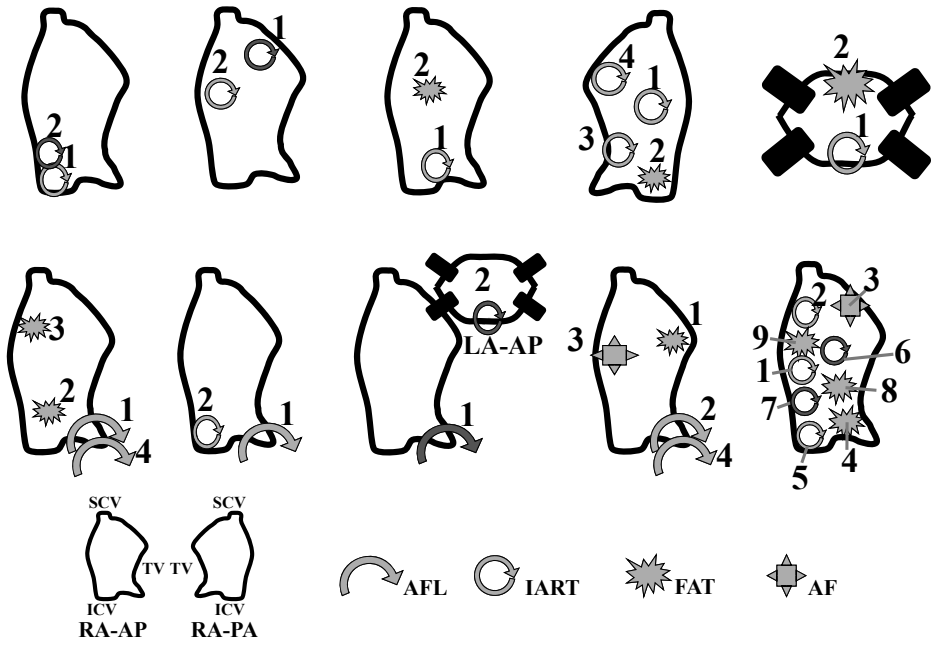


**Figure 3.** Schematic representations of the atria demonstrating the location of the arrhythmogenic substrate of recurrent AT for patients undergoing repetitive ablative therapy. The mechanism underlying the AT is represented by a symbol and the number indicates the order of recurrences. The outcome of the ablation procedure is represented by the colour of the symbol (green: elimination of the AT, red: unsuccessful ablation).

## Long-term outcome

During the follow-up period, a total of 77 catheter ablation procedures were performed. In 4 patients, 2 AT were eliminated during the same procedure. Eighty-one distinct AT (29 incessant) were mapped and treated with ablative therapy. In the entire study population, mapping revealed 34 AFL (CL= 372±99 ms), 32 IART (CL= 275±75 ms), 13 FAT (CL= 307±76 ms) and 2 "focal" AF. Ablative therapy was succesful in 69% of all AT; 19% of AT did not terminate and the other AT converted to either another AT (5%) or AF (7%) during ablation. Fluoroscopy time during mapping and ablation of IART (55±26* minutes) was significantly longer than during AFL (42±27 minutes) or FAT (40±25 minutes) procedures, P =0.03. The

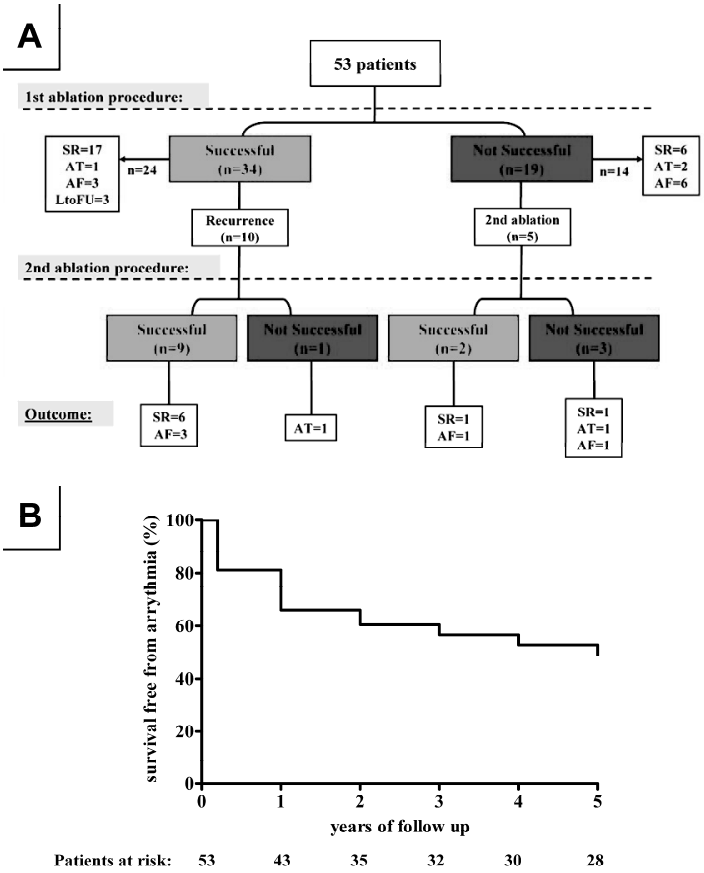


**Figure 4.**

Panel A: Flowchart describing the acute success, recurrences, additional ablation procedures and final outcome in the total patient population. Panel B: Kaplan Meier curve with survival free from arrhythmia for all patients (with and without acutely successful ablation). AF = atrial fibrillation, AFL = atrial flutter, AT = atrial tachycardia, LtoFU = lost to follow up, SR = sinus rhythm.

procedure time required for ablative therapy of IART was also longer (300±100* minutes, compared to AFL: 229±76 minutes, FAT: 211±66 minutes, P=0.001).

The relation between the results of the ablation procedure and long-term outcome is demonstrated in Figure 4. During last follow-up visit of the 50 patients excluding 3 subjects lost for follow-up, they had either sinus rhythm (N=31, 59%), a regular AT (N=5, 9%) or AF (N=14, 26%). Five patients died due to progressive heart failure 34±28 months after the ablation procedure; rhythm prior to death was sinus rhythm (N=2) and AF (N=3).

Paroxysms of AT were recorded in 12 sinus rhythm patients who underwent a successful ablation procedure. Anti-arrhythmic drugs were used by 18 patients with sinus rhythm. Persistent AF developed during the follow-up period in 14 patients. Seven patients had AF despite a successful ablation; in the other 7 patients, AF resulted from progression of AT to AF. Eleven of the 19 patients with an unsuccessful ablative therapy had persistent AT at the onset of the ablation procedure. Surprisingly, 7 patients who had one or more unsuccessful ablation procedures (no termination during ablation, conversion to AF or another AT) remained in sinus rhythm during the follow-up period.

## DISCUSSION



This study reports on characteristics of recurrent AT after ablative of late post-operative AT during long-term follow-up in a large cohort of patients with predominantly complex congenital heart defects.

The majority of the ablation procedures were guided by 3-dimensional electro-anatomical mapping techniques enabling accurate localization of the arrhythmogenic substrate. The key findings of our study are that though ablative therapy of post-operative AT is most often successful, a large number of patients presented with recurrent AT. However, repeated ablative therapy of recurrent AT was effective in maintaining sinus rhythm in most of the patients. As the arrhythmogenic substrate of patients who had multiple ablation procedures was located at different atrial sites it is most likely that recurrent AT are the result of diffuse electro-pathological alterations of atrial tissue and/or progressive atrial myopathy instead of arrhythmogenicity of prior ablative lesions. Despite recurrent AT in many patients, the majority of the study population was in sinus rhythm at the end of the follow-up period.

### Atrial tachyarrhythmia mechanism

The mechanism underlying late post-operative AT in our study population was variable; often AFL and IART, less frequently FAT and rarely focal AF. In a large number of patients, different mechanisms gave rise to successive AT.

Consistent with other reports on the mechanism underlying post-operative AT in patients with congenital heart disease, IART and AFL were most often observed.[8,27]

FAT were less frequently observed. We previously demonstrated that FAT arise mainly from areas where conduction is abnormal.[28,29] The atria of patients with CHD contain areas of fibrotic tissue giving rise to local dissociation in conduction and hence favor development of focal activity.[30,31] Reports on focal AF in CHD patients are rare and the mechanism underlying this AT in our patient population has recently been described in detail.[28,29]

## Ablative therapy

Most ablation procedures performed in this study population were guided by a 3-dimensional electro-anatomical mapping system. Triedman et al. demonstrated the beneficial effect of an electro-anatomical mapping system over a conventional, fluoroscopy based mapping technique on the outcome of ablative therapy of post-operative AT. [32] However, compared to their ablation results, in our study 28% of the IART did not terminate during ablation despite the use of a 3-dimensional electro-anatomical mapping technique. This outcome emphasizes that ablation of IART remains very difficult despite facilitating mapping techniques.

Crucial pathways of the reentry circuit of most IART were located between areas of scar tissue, indicating necessity of accurate delineation of low voltage areas. [18] In patients who had multiple ablation procedures, target sites for ablation of successive AT were located at different atrial sites suggesting that new AT were not caused by arrhythmogenicity of previous ablative lesions. Most recurrences occurred in the first year after ablative therapy.

As the reentry circuit of post-operative AT in patients with CHD often consist of multiple re-entrant pathways a new reentry circuit may develop after ablation giving rise to early recurrences. Also, these new AT may simply be the result of diffuse electro-pathological alterations of the atrial tissue. Late recurrences also indicate progression of atrial myopathy.

After successful elimination of the AT, we did not induce other AT. It can be hypothesized that the incidence of redo-procedures can be reduced by additionally ablating other inducible AT. However, low voltage areas and prosthetic materials are present throughout the atria and multiple reentry circuits may therefore be possible. Extensive ablation at different sites in the atria would be required to eliminate additional IART (with unknown clinical relevance). This might increase the chance of constructing incomplete lesions which may in turn be pro-arrhythmic.

Another interesting finding is that in some patients who had several ablation procedures mapping revealed different mechanism underlying the AT; e.g. an IART during the first ablation procedure and a FAT in the next procedure. To our knowledge, the presence of different mechanisms underlying consecutive AT in patients with CHD has so far not been reported.

Surprisingly, despite some unsuccessful ablation procedures (no termination or conversion to another AT or AF) patients converted to sinus rhythm after the ablation procedure and remained in sinus rhythm during the follow-up period.

### Atrial Fibrillation

At the end of the follow-up period, 26% of the patients had AF. Kirsh et al. demonstrated that AF is not an uncommon AT in CHD patients.[33] In some of our patients, AF resulted from progression of recurrent AT. Experimental mapping studies have demonstrated that a single macro-reentrant circuit may degenerate to AF if atrial tissue can not be activated at a high activation rate and fibrillatory conduction occurs consequently. [34] In line with these experiments, we have previously reported on focal activity giving rise to fibrillatory conduction in two patients with CHD. However, AF developed in 7 patients despite successful elimination of the AT by ablative therapy suggesting that different mechanisms causing AF in this patient group may be involved. Further studies in larger populations are required in order to gain insight into the mechanism of AF in this patient group.

### Limitations

Holter monitoring was not consistently performed in every patient in order to determine the incidence of AT after ablative therapy. However, the majority of the CHD patients with an AT recurrence immediately visited the hospital because of symptoms. Data in this study are based on only 15/29 patients with recurrent AT who underwent more than one ablation procedure.

During the mapping procedure, crucial pathways of reentrant circuits were mainly selected by analyzing electro-anatomical activation maps. Entrainment techniques could not always be used as pacing in low voltage areas was often difficult and frequently resulted in conversion to another AT. When one AT was successfully ablated, we did not try to induce other AT.

When one AT converted to another AT, we did not target this AT as well. Consequently, we do not know whether ablation of multiple AT during one ablation procedure could have prevented future recurrences. In addition, irrigated tip ablation was performed in only a minority of the patients and 8 mm tip catheters were not used. Hence, the applied mapping and ablation techniques may account for a number of recurrences observed in this study.



## CONCLUSION

Focal and reentrant mechanisms underlie late post-operative AT in patients with CHD.

Successive AT developing over time may be caused by different mechanisms. The complexity of the reentrant circuit is associated with the complexity of the CHD and corresponding extensiveness of surgical procedures. In patients who had multiple ablation procedures, the AT originated from different atrial sites suggesting that these new AT were not caused by arrhythmogenicity of previous ablative lesions. Recurrent AT occurred frequently after successful ablation and occurred mainly in the first year after treatment. The long-term outcome is often complicated by development of AF. However, the majority of the patients were in sinus rhythm.

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# Chapter 12

## Long-term clinical outcome after radiofrequency ablation of cavotricuspid isthmus dependent atrial flutter and risks of atrial fibrillation occurrence.

Jael Z. Atary, Natasja M.S. de Groot MD, Jeroen Jansson, Marianne Bootsma, Martin J. Schalij

Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands

## ABSTRACT

### Objective

To assess long-term (median 40 months) outcome of cavotricuspid isthmus ablation in terms of atrial flutter (AFL) recurrence and particularly in terms of atrial fibrillation (AF) occurrence in a clinical population with electrocardiographically documented isthmus dependent AFL with or without a history of AF.

### Methods

From 1995 to 2006 149 patients underwent radiofrequency ablation procedures for AFL. Of these patients, 87 patients had a known history of paroxysmal AF (87/149, 58%) and were assigned to group 1. The remaining patients were defined as group 2.

### Results

A total of 133/149 patients had an initially successful AFL ablation. In 85% (113/133) of procedures bidirectional isthmus block was achieved (others were defined as successful due to noninducibility). Patients in group 1 had a significantly higher cumulative incidence rate of AF occurrence than patients in group 2 (p=0.0007): The cumulative incidence of AF occurrence was 60% at 1 year (95%CI 48%-72%) and 81% at 5 years (95%CI 71%-92%). AF occurrence in group 2 at 1 year was 28% (95%CI 14%-43%) and at 5 years 57% (95%CI 39%-75%). However, the large difference between groups 1 and 2 reflected primarily the much higher rate of AF occurrences in group 1 during the first 1.5 year post-ablation.

### Conclusion

Despite the efficacy of cavotricuspid isthmus RF ablation in the treatment of AFL, most patients cannot be considered completely cured, particularly with regard to AF occurrences. Patients with a preablation history of AF and high diastolic blood pressure were at significantly higher risk and should be monitored more closely and treated more aggressively for hypertension. However, preablation AF did not lead to an increased long-term (>1.5 year) risk after AFL ablation. Patients in this subgroup therefore may expect the same long-term risk of AF as patients without pre-existing AF.

## INTRODUCTION

Catheter ablation of the inferior vena cava–tricuspid isthmus is an established treatment modality for typical atrial flutter (AFL). Though ablative therapy of AFL has proven to be efficacious, long-term outcome of ablation may be complicated by the occurrence of atrial fibrillation (AF), either preexisting or developing de novo[1-3]. Studies investigating factors predictive of AF arising after ablation of AFL showed that there is a high risk of developing AF particularly in a subgroup of patients with a history of paroxysmal AF[1-6]. Despite the seemingly pessimistic outlook for this patient subgroup, several follow-up studies including patients with both AFL and AF, showed that ablation of the right atrial isthmus for typical AFL in combination with previously ineffective antiarrhythmic drug (AAD) therapy was found to result in longer arrhythmia-free intervals in a large proportion of patients[7;8]. It has therefore been suggested that patients with preexisting AF may benefit from isthmus ablation of AFL in terms of less recurrences of AF and better effect of medication on previously therapy-resistant AF [7;8]. The purpose of this retrospective study was to assess the long-term (median 40 months) outcome of cavotricuspid isthmus ablation in terms of AFL recurrence and particularly in terms of AF occurrence in a population of "real-practice" patients with electrocardiographically documented isthmus dependent AFL with or without a preablation history of AF.

## METHODS

### Patient population

Consecutive patients referred between June 1995 and Aug 2003 for ablative therapy of electrocardiographically documented isthmus dependent atrial flutter were included in the current retrospective study. Patients were divided into 2 groups: Group 1 were patients with isthmus dependent AFL and documented coexisting paroxysmal AF and group 2 consisted of patients with AFL who had no history of AF. Patients with congenital heart disease were excluded from this study.

### Electrophysiology study and ablation procedure

Linear ablation of the right atrial isthmus was guided by either fluoroscopy only or with 3-D electro-anatomical mapping techniques. In case of conventional mapping, the right atrial pattern of activation was studied with a 7F 20-electrode steerable catheter (Halo catheter, Cordis-Webster, Diamond Bar, California, USA) or a 8F 64-electrode collapsible Basket catheter (Cardiac Pathways, Sunnyvale, California, USA).

Three-dimensional electro-anatomical mapping techniques used included the CARTO™ (Biosense-Webster, Diamond Bar, California, USA), the Real time position management

system (RPM, Cardiac Pathways, Sunnyvale, California, USA) or the Ensite system (Endocardial Solutions Inc., St. Paul, Minnesota, USA). Detailed description of the underlying technology and use of these various electro-anatomical mapping techniques has been given previously by others.[9-11]

For induction of AFL, programmed electrical stimulation applying up to three extrastimuli or burstpacing at 2 times diastolic threshold (pulse width 2 ms) was performed with a constant current stimulator (Medtronic, Minneapolis, MN, USA). Ablation was performed with either a non-cooled or cooled 7F 4 mm Navi-star catheter (Biosense-Webster, Diamond Bar, California, USA), a 7F 4mm tip steerable cooled ablation catheter (Cardiac Pathways, Sunnyvale, California, USA) or a standard 7F 4 mm steerable ablation catheter.

At each site, radiofrequency current was applied for 60 seconds. In case of non-cooled ablation, tip temperature was set at 70°C and the maximum output at 50W. During ablation using an irrigated-tip catheter, temperature was limited to 50°C and power to 45W with saline flow of 17 ml/hour (4 ml/min). Each lesion was tagged on the electro-anatomical right atrial map when using a 3-D electro-anatomical mapping system.

During the procedure, heparin was administered intravenously to maintain an anti-clotting time of 2.5-3 times the control value for adequate anti-coagulation. If necessary, patients were intravenously sedated with midazolam and fentanyl. Acute procedural success was initially defined as termination of AFL during ablation and non-inducibility, and later in time as establishing bidirectional conduction block over the cavo-tricuspid isthmus.[3;12]



## Definitions

Some patients underwent more than one AFL ablation procedure. The first successful AFL ablation procedure is defined as the first of several AFL ablation procedures during which acute procedural success was achieved. The last successful AFL ablation procedure is defined as the last of several AFL ablation procedures during which acute procedural success was achieved.

AFL or AF episodes at follow-up were documented by either electrocardiographic or 24-hour Holter recordings and by repeat electrophysiology study if repeat ablation was clinically indicated.

## Follow-up

Follow-up was conducted at the out patient clinic initially at 3 months post-ablation and subsequently continued at the arrhythmia clinic or at the patients' referring physician at 6 month intervals except when patients remained entirely free of symptoms. In the event of a recurrence, symptomatic or documented, patients were referred back to the arrhythmia clinic for re-analysis.

### Statistical Analysis

Continuous data are expressed as mean (±standard deviation [SD]), or as median (interquartile range [IQR]), and dichotomous data are presented as numbers and percentages. Differences between categorical data were tested for statistical significance using a Pearson chi-square test using continuity correction where appropriate. Continuous normally distributed data were tested by student t-tests or in the case of a non-Gaussian distribution by a nonparametric test for independent samples. One way analysis of variance (ANOVA) was performed when comparing normally distributed data between more than two independent groups. Normal distribution was tested using the Kolmogorov-Smirnov test. Survival was analyzed by method of Kaplan-Meier with corresponding log-rank test for differences in distribution between the curves. Univariate and multivariate Cox regression analysis was performed to determine a relation between potential risk factors at baseline and the occurrence of AF. All variables with an unadjusted p value of <0.10 entered the multivariate regression model. Adjusted Hazard Ratio (HR) is reported in the text with the corresponding 95% confidence interval (CI). All tests were two-sided, a p-value of <0.05 was considered significant.

## RESULTS

### Patients

Between June 1995 and July 2006 149 patients underwent a total of 210 radiofrequency ablation procedures for isthmus dependent atrial flutter. Baseline characteristics are shown in table 1 for the total patient population and for group 1 and 2 separately. Of the total patient population, 87 patients had a known history of paroxysmal AF (87/149, 58%) and were therefore assigned to group 1.

Patients in group 2 were younger than patients in group 1 (61 ± 13 years vs. 66 ± 11 years, p=0.015) and used more Class 1C antiarrhythmic drugs (20% vs. 5%, respectively, p=0.009). Eighty patients (80/149, 54%) had at least one kind of structural heart disease, the majority being valvular heart disease (n=63), which was in most cases mitral valve insufficiency (54/63, 86%). The incidence of structural heart disease was similar between the two patient groups as well as the cardiovascular risk profile.

Figure 1 illustrates the distribution of symptoms reported by patients in group 1 and 2. Overall, symptoms reported by patients were similar. Palpitations was the most frequently reported complaint (>70%) in both groups. Ten percent of all patients were asymptomatic at the time of enrolment. Significantly fewer patients in group 2 had complaints of dyspnea when compared to patients in group 1 (24% vs. 40%, p=0.041; Figure 1).

**Table 1.** Baseline characteristics.

| | Total (n=149) | Group 1 (n=87) | Group 2 (n=62) | p-value |
|---|---|---|---|---|
| Men | 116 (78%) | 72 (83%) | 44 (71%) | 0.09 |
| Age (years ± SD) | 64 ± 12 | 66 ± 11 | 61 ± 13 | 0.015* |
| Structural heart disease | | | | |
| Dilating cardiomyopathy | 16 (11%) | 9 (10%) | 7 (11%) | 0.85 |
| Hypertrophic cardiomyopathy | 6 (4%) | 4 (5%) | 2 (3%) | 1.00 |
| Valvular heart disease | 63 (42%) | 41 (47%) | 22 (36%) | 0.16 |
| Coronary artery disease | 16 (11%) | 11 (13%) | 5 (8%) | 0.37 |
| Coronary bypass surgery | 12 (8%) | 9 (10%) | 3 (5%) | 0.36 |
| Congenital heart disease | - | - | - | - |
| Body Mass Index (± SD) | 26.0 ± 3.9 | 26.1 ± 4.8 | 25.9 ± 3.0 | 0.80 |
| Hypertension | 37 (25%) | 24 (28%) | 13 (21%) | 0.36 |
| Diabetes | 13 (9%) | 7 (8%) | 6 (10%) | 0.73 |
| Hypercholesterolemia | 29 (20%) | 21 (24%) | 8 (13%) | 0.09 |
| Thyroid disease | 13 (9%) | 8 (9%) | 5 (8%) | 0.81 |
| Antiarrhythmic drugs | | | | |
| Class IA | 1 (0.7%) | 1 (1.6%) | 0 | 0.86 |
| Class IB | 1 (0.7%) | 1 (1.6%) | 0 | 0.86 |
| Class IC | 20 (13%) | 3 (5%) | 17 (20%) | 0.009* |
| Class II | 19 (13%) | 14 (16%) | 5 (8%) | 0.15 |
| Class III | 80 (54%) | 49 (56%) | 31 (50%) | 0.45 |
| Class IV | 21 (14%) | 13 (15%) | 8 (13%) | 0.72 |
| Lanoxin | 29 (20%) | 18 (21%) | 11 (18%) | 0.65 |
| Left atrial size (mm ± SD) | 44.1 ± 0.8 | 45.5 ± 0.8 | 42.4 ± 0.7 | 0.055 |



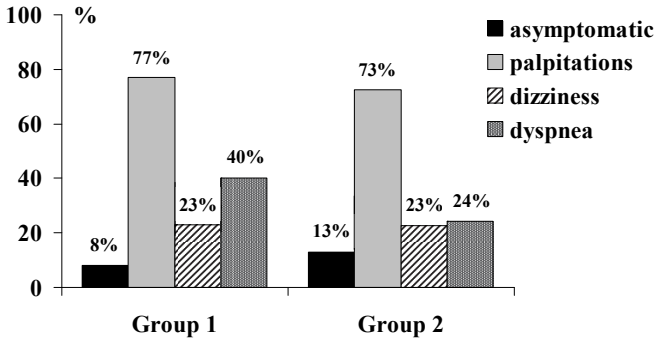


**Figure 1.** Symptom characteristics.

## Procedure

Procedural characteristics are summarized in table 2. Of the 210 AFL ablation procedures 173 (83%) were considered acutely successful, either by achieving termination of AFL with noninducibility (13%) or by the confirmation of a line of conduction block (87%). The proportion of patients with procedural success was not significantly different between the groups. In terms of patients, 133 of 149 patients (89%) underwent at least one ablation procedure that was considered acutely successful. Eleven patients required more than one ablation procedure (11/133, 8%) to achieve this result. In the remaining patients, a bidirectional conduction block was not achieved despite extensive ablation.

Patients in group 2 had a shorter AFL cycle length than patients in group 1 (240 ± 45ms vs 259 ± 42ms, p=0.013) and acute success was more often defined by noninducibility than by bidirectional isthmus block when compared to patients in group 1 (19% vs 9%, p=0.042).

**Table 2.** Procedure characteristics.

| | Total (n=149) | Group 1 (n=87) | Group 2 (n=62) | p-value |
|---|---|---|---|---|
| Procedures (n) | 210 | 123 | 87 | |
| Patients with >1 RFA of AFL (n) | 47/149 (32%) | 30/87 (35%) | 17/62 (27%) | 0.36 |
| Acute procedural success achieved | 133/149 (89%) | 80/87 (92%) | 53/62 (86%) | 0.21 |
| Acute success after 1st RFA | 122/149 (82%) | 74/87 (85%) | 48/62 (77%) | 0.23 |
| Initial rhythm during study | | | | |
| Sinus | 110/210 (52%) | 59/123 (48%) | 51/87 (59%) | |
| AFL | 71/210 (34%) | 36/123 (29%) | 35/87 (40%) | <0.001* |
| AF | 29/210 (14%) | 28/123 (23%) | 1/87 (1%) | |
| AFL cycle length (ms ± SD) | 249 ± 44 | 259 ± 42 | 240 ± 45 | 0.013* |
| Acute success of RFA of AFL | 173/210 (83%) | 105/123 (85%) | 68/87 (78%) | 0.18 |
| Criteria of successful RFA | | | | |
| Noninducibility | 22/173 (13%) | 9/105 (9%) | 13/68 (19%) | |
| Bidirectional conduction block | 151/173 (87%) | 96/105 (91%) | 55/68 (81%) | 0.042* |
| Rhythm at procedure end | | | | |
| Sinus rhythm | 176/210 (84%) | 105/123 (85%) | 71/87 (82%) | |
| Conversion to AF | 30/210 (14%) | 17/123 (14%) | 13/87 (15%) | 0.37 |
| AFL | 4/210 (2%) | 1/123 (1%) | 3/87 (3%) | |
| Procedure time (min ± SD) | 201 ± 72 | 199 ± 70 | 203 ± 75 | 0.82 |
| Fluoroscopy time (min ± SD) | 34 ± 19 | 34 ± 17 | 35 ± 21 | 0.97 |
| RFA guiding technique | | | | |
| Conventional | 51/210 (24%) | 27/123 (22%) | 24/87 (28%) | |
| CARTO | 134/210 (64%) | 79/123 (64%) | 55/87 (63%) | |
| Ensite | 14/210 (7%) | 9/123 (7%) | 5/87 (6%) | |
| RPM | 11/210 (5%) | 8/123 (7%) | 3/87 (3%) | 0.62 |

## Ablation techniques

Ablation procedures were guided with conventional techniques (24%), or the CARTO™ (64%), the RPM (5%) or ENSITE (7%) system (Table 2). Overall, procedure time did not differ significantly between the 4 ablation techniques (overall mean procedure time: 201 ± 72 minutes, one-way ANOVA test: p=0.52). Fluoroscopy time was for the most part similar between the different ablation techniques (overall mean fluoroscopy time: 34 ± 19 min), but a significant difference in fluoroscopy times was found between the 4 techniques due to the shorter fluoroscopy times in the subgroup guided with the CARTO™ system (32 ± 18min) when compared to the Ensite system (47 ± 22min, one-way ANOVA test: p=0.005). No significant differences were observed in procedure-, or fluoroscopy time between consecutive ablation procedures.

## Follow-up: AFL recurrence rate

Figure 2 illustrates the estimated cumulative rate of freedom from AFL recurrence in patients with and without a history of AF from the moment of the last successful AFL ablation procedure (median follow-up: 34 months, IQR 2-62 months). As mentioned earlier, this was achieved in 133 patients (table 2). Of these patients, 43 (32%) underwent >1 AFL ablation procedure (26/80, 33% in group 1 and 17/53, 32% in group 2). As initial success was not yet based on bidirectional isthmus block in the earliest procedures performed in this study, the last successful AFL ablation procedure was chosen as starting point from which AFL recurrence rate was evaluated (Figure 2). In 89% (119/133) of these last procedures immediate success was defined by bidirectional isthmus block.

The cumulative incidence rate of AFL recurrence in patients of group 1 at 1 year was 23% (95%CI 12%-33%) and at 4 years 34% (95%CI 22%-47%). For patients in group 2

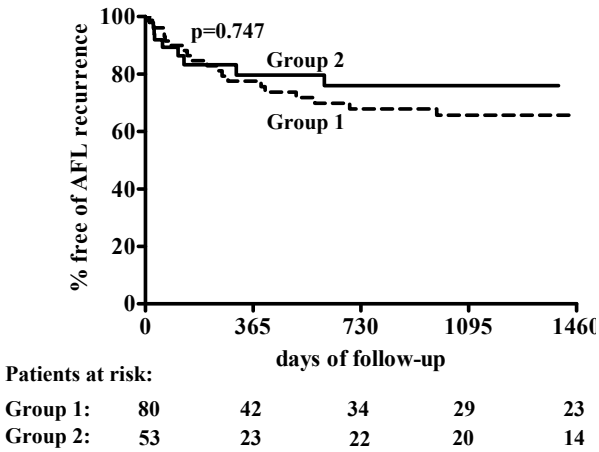


**Figure 2.** Recurrence of atrial flutter after the last successful AFL ablation procedure (32% of these patients underwent >1 AFL ablation procedure).

the cumulative incidence of AFL recurrence was similar: At 1 year 20% (95%CI 7%–34%) and at 4 years 24% (95%CI 9.7%–38%).

## Follow-up: AF occurrence rate

Figure 3 demonstrates the estimated cumulative rate of freedom from AF in patients in groups 1 and 2 from the moment of the first successful AFL ablation procedure (n=133, median follow-up: 40 months, IQR 5-70 months). In 85% (113/133) of these early initially successful procedures bidirectional isthmus block was achieved (the rest was defined as successful due to noninducibility of AFL). Not surprisingly, patients with a known history of AF (group 1) had a significantly higher cumulative incidence rate of AF occurrence than patients in group 2 (log-rank test: p=0.0007). The cumulative incidence rate of AF occurrence in group 2 at 1 year was 28% (95%CI 14%-43%) and at 5 years 57% (95%CI 39%-75%). For patients in group 1 the cumulative incidence of AF occurrence was 60% at 1 year (95%CI 48%-72%) and 81% at 5 years (95%CI 71%-92%). However, figure 4 demonstrates that the large difference between groups 1 and 2 reflects primarily the much higher rate of AF occurrences in group 1 during the first 1.5 year post-ablation. This difference was highly significant (log-rank p=0.0006). After 1.5 year the cumulative incidence of first AF episodes in the group of patients with a history of AF was similar to the group of patients without a history of AF.

Multivariate Cox regression analysis (table 3) revealed that a known history of AF and a diastolic blood pressure ≥90 mmHg (measured at hospital admission for the ablation procedure) were independently associated with a 2-fold increased risk of AF occurrence at follow-up.

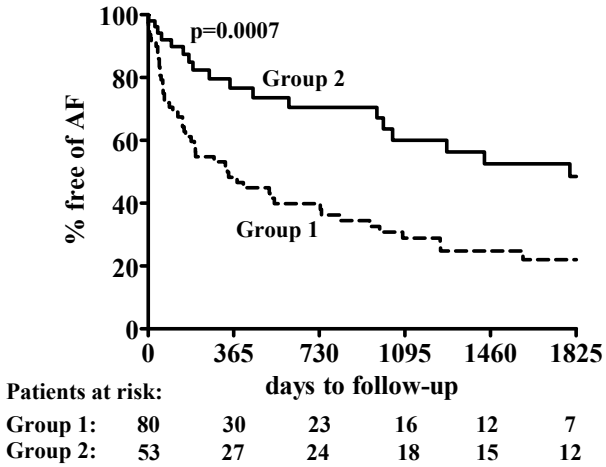


**Figure 3.** Occurrence of atrial fibrillation after initially successful ablation of typical AFL.

**Table 3.** Multivariable Cox Regression Analysis.

| | AF occurrence after successful AFL ablation | | | |
|---|---|---|---|---|
| | Unadjusted HR (95% CI) | p-value | Adjusted HR (95% CI) | p-value |
| Age † | 1.02 (1.00-1.04) | 0.036* | 1.01 (0.99-1.03) | 0.456 |
| Sex (male) | 1.03 (0.59-1.80) | 0.919 | | |
| Preablation AF † | 2.24 (1.33-3.77) | 0.002* | 2.17 (1.24-3.79) | 0.006* |
| Syst. blood pressure ≥140 mmHg | 0.98 (0.61-1.58) | 0.932 | | |
| Diast. blood pressure ≥90 mmHg † | 2.02 (1.23-3.33) | 0.006* | 2.00 (1.21-3.31) | 0.007* |
| Coronary artery disease | 1.71 (0.69-4.26) | 0.248 | | |
| Diabetes Mellitus | 0.55 (0.25-1.20) | 0.134 | | |
| Thyroid disease | 0.77 (0.31-1.94) | 0.579 | | |
| Bidirectional isthmus block † | 0.41 (0.17-1.03) | 0.058 | 0.66 (0.24-1.86) | 0.435 |
| ACE-inh/AT2-antag. at discharge | 0.75 (0.46-1.21) | 0.237 | | |
| Sotacor at discharge | 0.91 (0.53-1.56) | 0.743 | | |
| Flecainide at discharge | 0.68 (0.38-1.20) | 0.184 | | |
| Amiodarone at discharge | 0.84 (0.45-1.58) | 0.596 | | |
| Verapamil at discharge | 0.86 (0.43-1.74) | 0.678 | | |
| Statin at discharge | 0.80 (0.45-1.41) | 0.432 | | |
| Recurrence of AFL | 1.21 (0.72-2.04) | 0.474 | | |
| Left atrial diameter | 1.02 (0.98-1.06) | 0.340 | | |
| AF at procedure end | 0.60 (0.26-1.40) | 0.240 | | |
| RFA without use of 3D-electroanatomical mapping † | 2.08 (1.08-3.99) | 0.028* | 1.90 (0.92-3.96) | 0.085 |

Only variables with an unadjusted p-value of <0.10 were included in multivariable analysis (indicated with †). Unadjusted and adjusted Hazard Ratio (HR) is reported with the corresponding 95% confidence interval (CI). * p<0.05





## Long-term treatment course

Figure 4 shows prevalence of AAD treatment in patients who underwent a successful AFL ablation procedure (n=133). The percentage of patients on AAD therapy at baseline is shown next to the percentage of patients on AAD treatment by the end of follow-up (median 40 months). There was no significant change in AAD use for patients in group 1 when compared to baseline AAD use: Fifteen percent (n=12/80) of patients in group 1 used no AAD at all at the end of follow-up versus 11% (9/80) at baseline (p=0.48)

Similarly, in group 2 the proportion of patients that did not require AAD treatment by the end of follow-up was comparable to the percentage of patients without AAD therapy at baseline (baseline: 26%, 14/53, versus follow-up: 36%, 19/53; p=0.29). However, there was a significant change in AAD treatment class. Significantly fewer patients in group 2 were on Class III AAD treatment at follow-up (baseline: 49%, 26/53, vs follow-up: 30%, 16/53; p=0.047). Of the 26 patients who were on Class III AAD's at baseline, seven patients needed no AAD treatment by the end of follow-up, 3 patients were treated with only rate-control

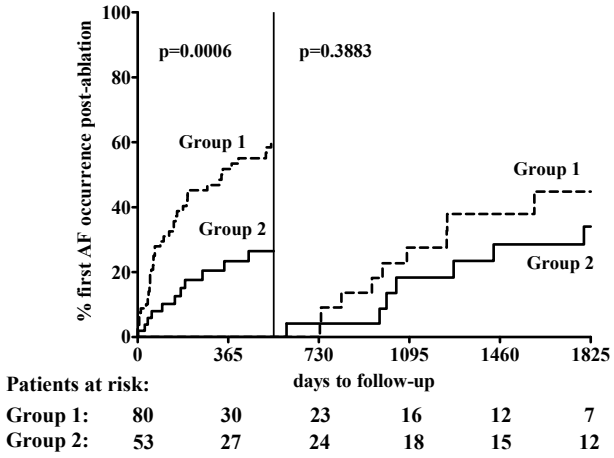


**Figure 4.** Landmark incidence estimates for AF occurrence after successful AFL ablation.

(beta-blockers) at follow-up and 3 patients were switched to a Class IC AAD. Slightly more patients in group 2 appeared to be on Class IC AAD therapy by the end of follow-up when compared to baseline (baseline: 6%, 3/53, vs follow-up: 17%, 9/53; p=0.066), but this was not statistically significant.

Ten patients (10/80, 13%) in group 1 underwent pulmonary vein isolation for AF during follow-up. In group 2 only one patient (1/53, 2%, p=0.049) was treated for AF with pulmonary vein isolation during follow-up. His bundle ablation was performed in 11% of patients of group 1 (n=9/80) versus 6% of patients in group 2 (3/53, p=0.43).

## DISCUSSION

Key findings of this study are that: (1) The cumulative incidence of AF after successful AFL ablation procedures was high, with 57% during 5 year follow-up even in the patient group without preexisting AF (group 2), (2) that after 1.5 year post-AFL ablation patients with a history of AF had a similar AF occurrence rate compared to patients without a history of AF, and (2) a twofold and highly significant risk of AF occurrence was observed for patients with a diastolic blood pressure ≥90mmHg, independent of a pre-ablation history of AF.

### AFL recurrence

Earlier studies of RF ablation of the cavotricuspid isthmus for typical AFL yielded disappointing results with immediate procedural success rates as low as 78% and short-term recurrence rates as high as 41%.[13] Since the introduction of complete bidirectional isthmus block as a procedural end-point, the success rate has risen to ≥90%.[6;14-16] In accordance,

acute ablation success in this study was achieved in 89% (133/149) of patients, in >80% of patients by means of bidirectional conduction block as confirmation of success. With a 1-year recurrence rate of 22% (average of group 1 and 2) and a 4-year rate of 29% (average), recurrence of typical AFL was a relatively common problem in this series. In the early part of this series, conduction block in the isthmus was not tested as an endpoint after ablation and predominantly non-cooled catheter tips were used for ablation. It is possible that therefore analysis of recurrence is limited compared to other series where bidirectional block was used as endpoint and cooled catheter tips were used for isthmus ablation in all patients. Results are relatively comparable to other early observational studies with similar time period related experience, and procedural conditions.[4;17]

## Coexistence between AFL and AF

Atrial flutter and atrial fibrillation, which are both intra-atrial reentrant arrhythmias with differing complexity in their activation pattern and mechanisms, are frequently seen to cooexist in clinical practice. This was reflected in the present study by the fact that more than half of the unselected and consecutive patients referred for AFL ablation presented with a history of AF (87/149, 58%). Undoubtedly, the electrophysiological basis of the interrelation between AFL and AF needs further elucidation. The association generally reflects a similar arrhythmogenic substrate. One mechanism of AF occurrence is the electrical remodeling in the atrium induced by atrial flutter that predisposes to development of AF.[18-20] Another mechanism may be that AF is the primary arrhythmia that precedes the onset of AFL because formation of a functional line of block between the vena cava during AF leads to the development of cavotricuspid isthmus dependent AFL.[21] AF is then unmasked by elimination of the AFL substrate and continues to progress after AFL ablation.

Other theories include that AF development is part of the natural course of atrial flutter in these patients, as atrial flutter is occasionally observed to spontaneously disorganize into atrial fibrillation in the electrophysiology laboratory. The right atrial flutter circuit is postulated to play a critical role in the initiation and maintenance of atrial fibrillation in some patients.[22] These observations may explain the absence of recurrent atrial fibrillation in some patients with pre-ablation AF.

## New-onset AF after AFL ablation

AF occurrence after RF ablation for AFL, either preexisting or de novo, is a phenomenon well documented in literature, with incidences ranging from 8%-82%.[1;3;15;23;24]. Though catheter ablation is an effective treatment for AFL and has become common, it is unclear if ablation is able to affect the risk for future AF development. Findings of a study by Halligan et al. all demonstrated that 56% of patients with AFL naturally developed new-onset AF after an average of 5 ± 6 years after the diagnosis of AFL in the absence of a preceding AFL ablation.[25;26] This rate is very similar to the 5-year cumulative incidence rate of new-onset

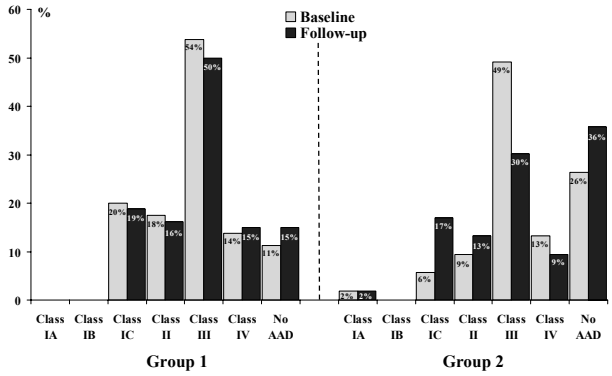


**Figure 5.** Antiarrhythmic drug use at baseline and at the end of follow-up.

AF found in the present study (57%, group 2). Ellis et al. reported a cumulative incidence of new-onset AF as high as 82% in patients with AFL after mean follow-up of 39 ± 11 months post-cavotricuspid isthmus ablation.[24] These results suggest that the long term (≥5 years) risk of developing AF is already high for patients with "lone" AFL, and may not be affected by AFL ablation.

## AF recurrence after AFL ablation

Should ablation be then undertaken in patients with AFL who also have AF? The answer to that question at present seems to be yes as there is ample evidence that ablation of AFL in patients who have both AFL and AF is associated with reduced incidence of subsequent atrial fibrillation by approximately 50%.[1;2;16;27;28] It is suggested that, at least in a proportion of patients, reentry around a stable anatomical pathway such as the tricuspid annulus might serve as the underlying mechanism for maintaining AF.[7]

The present study found a high 5-year cumulative incidence of AF recurrence of 82% in the group with pre-existing paroxysmal AF (group 1). A recent observational study by Moubarak et al reported very similar results after AFL ablation, with an AF recurrence rate of 86% in patients with preexisting AF and a rate of new-onset AF of 62% after median follow-up of 7.8months in 135 patients who underwent successful isthmus-dependent AFL ablation.[26]

Is transisthmus ablation a definite cure for patients with AFL then, or can their follow up be characterized by the occurrence of other atrial arrhythmia, particularly in patients with a history of AF? Many studies have tried to answer these questions.[1;4] The high and mostly unchanged number of patients receiving AADs at the end of follow-up in this study highlights the importance of the arrhythmic burden independent of the relapse of AFL. Despite the relatively pessimistic results of the current study for this subgroup of patients, further data analysis (figure 4) demonstrated a particularly pronounced difference in the

incidence rate of AF occurrence between groups 1 and 2 in the first 1.5 year post-ablation, after which cumulative first events of AF occurrence appeared to happen at a similar rate between the groups. In addition, a limited percentage of patients (19%) with preablation AF (group 1) still had no (documented) recurrence of AF after 5 years of follow-up. It is possible that cavotricuspid isthmus ablation to some extent had a positive effect on the clinical course of AF in these patients. However, at the same time it is also possible that AF recurrence rates were underestimated because of asymptomatic episodes that may not have been documented. Nevertheless, in the 40% of patients of group 1 who were still free of AF 1.5 years after successful AFL ablation, the risk of AF recurrence was comparable to the risk of developing new-onset AF in the group without a history of AF (group 2) (Figure 4). These patients probably benefited from the ablation of isthmus-dependent AFL in terms of AF recurrences.

## Hypertension as additional treatment focus

Hypertension is frequently complicated by the development of AF though the mechanisms of this link are not completely understood. In a recent ovine study by Lau et al, investigators demonstrated that even short-duration hypertension (4-7weeks) may lead to significant atrial remodeling characterized by atrial enlargement/dysfunction, interstitial fibrosis, inflammation, slowed/heterogeneous conduction, increased ERP, and greater propensity for AF.[29] Multivariate analysis in the present study revealed that a high diastolic blood pressure (≥90mmHg) predisposed patients to twice the risk of AF occurrence after AFL ablation, independent of preexisting AF. Results shows that aggressive treatment of hypertension should be a prime focus of attention after successful AFL ablation, especially when considering the long-term risk of new-onset AF is >50% for patients with only AFL.



## Limitations

Our study population was classified into 2 groups on the basis of documentation of AFL alone or in combination with AF. The exact incidence and burden of arrhythmia episodes, (i.e. asymptomatic episodes, or in- or decrease of AF burden post-ablation), is not known and may have affected our classification and the evaluation of clinical improvement regarding arrhythmia burden. Elimination of flutter may have resulted in symptomatic improvement and facilitated better pharmacological control of atrial arrhythmia. Thus, the results should not be interpreted as lack of utility of transisthmic ablation in patients with coexisting AF and AFL; rather they show that transisthmic ablation cannot completely cure AF in this subgroup of patients.

Although every procedure involved a right atrial isthmus ablation, the ablation protocol and the criteria for procedural success have changed over the study period in keeping with advances in our knowledge. A complete bidirectional isthmus block at the conclusion of

a successful procedure was not obtained in all patients. This has obvious implications for analysis of arrhythmia recurrences.

Only 30% of the study population used no AAD at the end of follow-up. Thus, in these patients results should be interpreted as the consequence of the combination of RF ablation and AAD therapy rather than RF ablation alone.

## CONCLUSION

Despite the efficacy of cavotricuspid isthmus RF ablation in the treatment of AFL, most patients cannot be considered completely cured, particularly with regard to AF occurrences. Patients with a preablation history of AF and high diastolic blood pressure were at significantly higher risk and should be monitored more closely and treated more aggressively for hypertension. However, preablation AF did not lead to an increased long-term (>1.5 year) risk after AFL ablation, and patients in this subgroup therefore may expect the same long-term risk of AF as patients without pre-existing AF.

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# Summary

## Summary and conclusions

Cardiovascular disease remains the leading cause of mortality in the western World, but significant improvements have been made in its treatment and prevention. This thesis shows that consistent implementation of a structured regional treatment and prevention program for acute myocardial infarction patients is feasible when health professionals of various disciplines collaborate (**Chapter 2**). Guideline-recommended time-to-treatment intervals were achieved for the entire region of Hollands-Midden.

PCI in the setting of AMI significantly reduces mortality. The introduction of DES has significantly improved one-year outcomes among patients undergoing elective PCI, primarily by reducing the need for repeat revascularization. Although DES are commonly used in AMI, there has been significant debate in the clinical community regarding their true efficacy and long-term safety. In **Chapter 3** results of the randomized MISSION!-intervention study demonstrates that safety of SES is comparable to BMS three years after the index event, in terms of death, stent thrombosis and nonfatal recurrent MI. The study also showed that the greatest efficacy of SES (compared to BMS) was achieved in the first year of follow-up after the AMI, by significantly reducing target vessel revascularizations. A similar need for target vessel revascularizations in SES and BMS treated patients was seen in the two subsequent years. It must be kept in mind though, that these results were achieved in the setting of the structured MISSION! AMI treatment protocol which ensured optimal treatment adherence and follow-up of patients.

In **Chapter 4** an effort was made to relate plaque characteristics at stent edges to clinical outcome at 9 months post PCI in 40 AMI patients by utilizing virtual histology intravascular ultrasound imaging (VH-IVUS). The technique allows for identification of four plaque components: fibrous, fibro-fatty, necrotic core and dense calcium. Plaque composition at 9 months follow-up was believed to be different in SES treated patients when compared to BMS treated patients due to the potent antiproliferative effects of sirolimus. However, against expectations, the study did not demonstrate any significant changes in plaque composition at stent edges after 9 month follow-up in either SES or BMS treated patients. At the same time an effect of sirolimus on vascular lumen dimensions at the distal stent edge and neointima volume inside the stent was clearly present. Because of the relatively small patient sample size and perhaps too short follow-up, it is not possible to definitely conclude that no differences exists in plaque composition between SES and BMS at stent edges, but it may be possible that these changes are of smaller magnitude than anticipated. Also, the complexity of the VH-IVUS analysis technique in the setting of a follow-up study may have made it difficult to detect such small changes at the present time.

It is thought that routine thrombus aspiration prior to DES implantation in STEMI may improve clinical outcome after such procedures. Given the association between large thrombus burden in STEMI and late stent thrombosis, debulking thrombus burden could reduce the occurrence of residual thrombus and stent malapposition. In the study presented in **Chapter 5**, a strategy of adjunctive thrombus aspiration before primary PCI in AMI patients

in combination with early (pre-hospital/in-ambulance) abciximab administration, was associated with a significant improvement in post-procedural ST segment resolution and with a lower mortality at one year follow-up.

In **Chapter 6** we evaluated the frequency and distribution of culprit lesions in patients presenting with ST-segment elevation myocardial infarction. This simple study demonstrated that the majority of occlusions occur in the proximal parts of the LAD and RCA with worse post-procedural LV-function in particular for LAD and LCX culprit lesions. The study shows that plaques in the proximal parts of the LAD and RCA are more prone to rupture. Knowledge of the distribution of vulnerable plaques may help in the identification of patients at risk of coronary events.

**Chapter 7** aimed to provide more insight into the clinical profile, treatment delays, medication compliance and 12 month outcome of treatment in the elderly AMI patient population (≥ 75 years). Results showed that older AMI patients had significantly less modifiable risk factors of coronary artery disease than younger patients and had a significantly higher in-hospital mortality rate despite similar post-procedural TIMI flow grades. Most importantly, the study showed that after surviving the first 3 months post AMI, elderly patients had a similar potential for favorable clinical outcomes at 12 months to their younger counterparts when they were treated with equal consistency and intensity

In recent years heart rate has been described as an increasingly important risk factor for reinfarction, revascularization and heart failure in patients with left ventricular dysfunction. The study presented in **Chapter 8** investigated clinical relevance of resting heart rate in post AMI patients who were treated with primary percutaneous intervention and a relatively preserved LV-function. During a mean follow-up of 20 months a baseline heart rate (first electrocardiogram at admission) of 72bpm or higher was associated with a significantly increased risk of the composite endpoint of all-cause mortality, nonfatal reinfarction, coronary revascularization, and hospitalization for heart failure. In addition every 5bpm increase in baseline heart rate was associated with a further increase in risk for every one of those endpoints. Results of this study suggest that targeting heart rate in the currently growing population of post-AMI patients with preserved LV-function may also be of significant clinical importance.

**Chapter 9** demonstrates that (1) left ventricular function can be preserved using an evidence-based protocol to manage AMI; (2), with preservation of left ventricular function, the proportion of post-MI patients fulfilling criteria for implantable cardioverter defibrillator (ICD) implantation is small; and (3), that relatively few of those patients who received ICDs receive appropriate ICD therapy delivery during follow-up. This last observation brings into question the current guidelines for the selection of patients for ICD implantation as primary prophylaxis against sudden cardiac death and should prompt a review of the evidence on which these guidelines are based.

Findings of the study described in **Chapter 10** suggest that properties of the baseline stimulation threshold may be used clinically as an indicator of chronic changes caused by ischemic heart disease which increase the risk of arrhythmic events requiring ICD therapy and risk of mortality. A high right ventricular stimulation threshold was used as a marker of potentially arrhythmia-prone conditions. Although the simple uncontrolled measurement method in this retrospective observational study is by no means sufficient to suggest routine clinical use for assessment of arrhythmia risk or ICD eligibility at this time, the results indicate future potential in measuring and utilizing stimulation thresholds in a standardized prospective fashion, as clinical predictors for these patients.

**Chapter 11** aimed to provide more long-term (mean 5±3 years) data on the characteristics of recurrent atrial tachyarrhythmias (AT) after ablation of post-operative AT in 53 patients with congenital heart defects (CHD). A number of conclusions could be drawn from the findings of this observational study: First, the data demonstrated that successive post-operative AT in CHD patients may be caused by different mechanisms, including focal and reentrant mechanisms. The complexity of the reentrant circuit was associated with the complexity of the underlying CHD and the extensiveness of the corresponding surgical procedure. Second, as recurrent AT originated from different locations, it seems unlikely that these new AT were caused by arrhythmogenicity of previous ablative lesions. Third, the long-term outcome was often complicated by development of atrial fibrillation. Finally, despite frequent need for repeat ablative therapy, most patients were in sinus rhythm by the end of follow-up.

The purpose of the observational study presented in **Chapter 12** was to provide more insight into long-term (median 40months) outcome of cavotricuspid isthmus ablation in terms of atrial flutter (AFL) recurrence and particularly in terms of atrial fibrillation (AF) occurrence in "real-practice" patients with electrocardiographically documented isthmus-dependent AFL with or without a preablation history of AF. The study provided several interesting findings. (1) The cumulative incidence of AF after successful AFL ablation procedures was high, with 57% during 5 year follow-up even in the patient group without preexisting AF (group 2), (2) that after 1.5 year post-AFL ablation patients with a history of AF had a similar AF occurrence rate compared to patients without a history of AF, and (2) a twofold and highly significant risk of AF occurrence was observed for patients with a diastolic blood pressure ≥90mmHg, independent of a pre-ablation history of AF.

## Conclusions

Standardized protocols like the multidisciplinary MISSION! program contribute to improved adherence to evidence-based medicine in routine clinical practice and to the uniform implementation of structured care for patients with AMI. It is clear that a good collaboration between general practitioner, ambulance services and hospital is essential in achieving well-coordinated prevention, acute care and rehabilitation of (potential) AMI patients. Results

demonstrated in this thesis demonstrate the efficacy of a pre-hospital protocol in achieving predefined targets, stressing the importance of close collaboration with all partners. In a later stage of this thesis, it is additionally shown that by the rigorous adherence to this kind of AMI protocol, development of severe LV dysfunction post-MI can be prevented by focusing on minimal treatment delays, aggressive reperfusion therapy and the use of early and consistent optimal pharmacological therapy. This way, only a very small percentage of AMI patients eventually become candidates for primary prevention ICD implantation according to current guidelines which also helps contain the strain on financial resources.

Sirolimus-eluting stent implantation in acute ST-elevation myocardial infarction is associated with a significant benefit (compared to bare-metal stents) at 1 year follow-up in terms of target vessel revascularizations, but declines thereafter to some extent due to more similar target vessel revascularization rates during the 2 subsequent years. Rates of death and non-fatal recurrent MI remain comparable.

There is a trend towards positive remodeling at the distal stent edges in SES patients and a significant inhibition of neointimal hyperplasia within the stented segment at follow-up as compared to BMS treated patients. The effect on the distal stent edge suggests a down-stream effect of sirolimus elution, despite the fact that an effect on plaque composition is not visible with virtual histology IVUS at 9-months follow-up.



Among STEMI patients treated with primary PCI and receiving early (in-ambulance) abcix-imab, it appears that the adjunctive use of manual thrombectomy significantly improves post-procedural ST-segment resolution, and may be associated with a lower clinical event rate. Therefore, although no benefit was observed regarding the enzymatic infarct size or LV function as assessed by Gated-SPECT, it appears that a selective strategy of thrombus aspiration still has an additive benefit, even with adjunctive early abciximab administration. This needs further confirmation in appropriately powered randomized trials.

Patients with ST-segment elevation AMI who are candidates for primary PCI are more likely to have a RCA or LAD culprit lesion that tends to be clustered in the proximal or mid vessel segments.

Older patients surviving the first 3 months post-MI have similar outcomes to younger patients in terms of cardiac function. Age was not a significant risk factor of 1-year mortality in survivors three months after MI. Therefore, though conservative treatment may be the adequate choice for some patients, many older patients have the potential to gain significant advantage from aggressive and invasive AMI treatment which suggests that age alone should not preclude intensive treatment after an MI.

In patients after AMI treated with primary PCI and preserved left ventricular function, resting heart rate at admission is a strong independent risk factor for all-cause mortality, reinfarction, revascularization and hospitalization for heart failure. This emphasizes that achieving a lower heart rate should be a priority in the care for the currently growing population of post-AMI patients with preserved left ventricular function.

In a cohort of ICD treated patients with a primary prevention indication and ischemic heart disease the RV stimulation threshold at implantation has an independent prognostic value for the prediction of potentially life-threatening ventricular arrhythmia and death.

It may also have a predictive value when measured serially, but this requires further investigation in future studies.

Focal and reentrant mechanisms underlie late post-operative atrial tachycardia in patients with congenital heart disease (CHD). Successive atrial tachycardias developing over time may be caused by different mechanisms. The complexity of the reentrant circuit is associated with the complexity of the CHD and corresponding extensiveness of surgical procedures. In patients who had multiple ablation procedures, the atrial tachycardia originated from different atrial sites suggesting that these new atrial tachycardias were not caused by arrhythmogenicity of previous ablative lesions. Recurrent atrial tachycardia occurred frequently after successful ablation and occurred mainly in the first year after treatment. The long-term outcome is often complicated by development of atrial fibrillation. However, the majority of the patients are in sinus rhythm.

Despite the efficacy of cavotricuspid isthmus radiofrequency ablation in the treatment of atrial flutter, most patients cannot be considered completely cured, particularly with regard to atrial fibrillation (AF) occurrences. Patients with a preablation history of AF and high diastolic blood pressure are at significantly higher risk and should be monitored more closely and treated more aggressively for hypertension. However, preablation AF did not lead to an increased long-term (>1.5 year) risk after atrial flutter ablation. Patients in this subgroup therefore may expect the same long-term risk of AF as patients without pre-existing AF.

## CURRICULUM VITAE

Jael Z. Atary, was born on August 25th 1982 in Petach-tikva, a small town near Tel Aviv, Israel. At 1 year of age her family moved to Germany where she went to elementary school. Her high school years were spent in Israel, the United Kingdom and the Netherlands, at the end of which she graduated from the Maascollege Atheneum in Maassluis, the Netherlands, in 2000. She went on to study Medicine at the University of Leiden, obtaining her medical degree in 2006. After working for six months as a resident at the department of cardiology in the HAGA hospital (location Leyenburg) in The Hague and another three months at the cardiology department in the Leiden University Medical Center in Leiden, she started in June 2007 with her research for the studies described in this thesis under the supervision of Prof. M.J. Schalij and Prof. E.E. van der Wall. During this time she represented young cardiology residents in a national society of residents in training for a medical specialty (*Landelijke Vereniging voor Medisch Specialisten in Opleiding*, LVAG). Through this position she was able to provide residents with up to date information on developments in their field concerning employment conditions, and the quality and development of their traineeships. She participated as an instructor in two subsequent ECG training courses for residents in the Erasmus Medical Center in Rotterdam and is currently working there as a resident at the department of cardiology.