



**Universiteit
Leiden**
The Netherlands

Improving acute and long-term myocardial infarction care : bridging the gap between science and practice

Liem, S.S.

Citation

Liem, S. S. (2009, April 23). *Improving acute and long-term myocardial infarction care : bridging the gap between science and practice*. Retrieved from <https://hdl.handle.net/1887/13751>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/13751>

Note: To cite this publication please use the final published version (if applicable).

Improving Acute and Long-term Myocardial Infarction Care

Bridging the gap between Science and Practice

Su-San Liem

COLOPHON

The studies described in this thesis were performed at the department of Cardiology of the Leiden University Medical Center, Leiden, The Netherlands

Copyright © Su-San Liem, The Hague, The Netherlands. All rights reserved. No part of this book may be reproduced or transmitted, in any form or by any means, without prior permission of the author.

Cover after a painting by Su-San Liem, and ECG by Arie Maan

Lay out Optima Grafische Communicatie, Rotterdam

Printed by Optima Grafische Communicatie, Rotterdam

ISBN 978-90-8559-512-0

Improving Acute and Long-term Myocardial Infarction Care

Bridging the gap between Science and practice

PROEFSCHRIFT

ter verkrijging van

de graad van Doctor aan de Universiteit Leiden,
op gezag van de Rector Magnificus prof. mr. P.F. van der Heijden,
volgens besluit van het College van Promoties
te verdedigen op donderdag 23 april 2009
klokke 13.45 uur

door

Su-San Liem

geboren te Tegelen
in 1976

PROMOTIECOMISSIE

Promotores	Professor Dr. E.E. van der Wall Professor Dr. M.J. Schalij
Referent	Dr. W. Jaarsma (St. Antonius Ziekenhuis, Nieuwegein)
Overige leden	Prof. Dr. J.W. Jukema Dr. S.C. Cannegieter Dr. P.V. Oemrawsingh (Medisch Centrum Haaglanden, Den Haag)

Financial support by the Netherlands Heart Foundation and the Bronovo Research Fund for the publication of this thesis is gratefully acknowledged.

TABLE OF CONTENTS

Chapter 1	7
General introduction and outline of the thesis	
Chapter 2	27
MISSION!: optimization of acute and chronic care for patients with acute myocardial infarction. <i>Am Heart J. 2007; 153: 14.e1-11.</i>	
Letter to the editor <i>Am Heart J 2007; 153: e33</i>	49
Response to the letter to the Editor by van de Werf <i>Am Heart J 2007; 153: e35</i>	51
Chapter 3	55
Optimization of acute and long-term care for patients with an acute myocardial infarction: The Leiden MISSION! project <i>Submitted for publication</i>	
Chapter 4	75
Does left ventricular dyssynchrony immediately after acute myocardial infarction result in left ventricular dilatation? <i>Heart Rhythm. 2007; 4: 1144-8.</i>	
Chapter 5	87
Left ventricular dyssynchrony acutely after myocardial infarction predicts left ventricular remodeling. <i>J Am Coll Cardiol. 2007; 50: 1532-40.</i>	
Chapter 6	107
Sirolimus-eluting stents versus bare-metal stents in patients with ST-segment elevation myocardial infarction: 9-month angiographic and intravascular ultrasound results and 12-month clinical outcome results from the MISSION! Intervention Study. <i>J Am Coll Cardiol. 2008; 51: 618-26.</i>	

Chapter 7	129
Cardiovascular Risk in Young Apparently Healthy Descendents from Asian Indian Migrants in the Netherlands: The SHIVA study	
<i>Accepted Netherlands Heart Journal</i>	
Chapter 8	
Role of calcified spots detected by intravascular ultrasound in patients with ST-segment elevation acute myocardial infarction.	147
<i>Am J Cardiol. 2006; 98: 309-13.</i>	
Summary, conclusions and future perspectives	157
Samenvatting, conclusies en toekomstperspectieven	167
List of publications	179
Curriculum Vitae	183

CHAPTER 1

General introduction and outline of the thesis

S.S. Liem

I Epidemiology and burden

9

Cardiovascular diseases are the number one cause of death and are projected to remain so for the next decades.(1) An estimated 17.5 million people died from cardiovascular diseases in 2005, representing 30% of all global deaths.(1) Of these deaths, 7.6 million were due to ischaemic heart disease. In the Netherlands, rates are comparable: of the 136.553 people who died in 2004, 33% were due to a cardiovascular disease, of whom 31% due to ischaemic heart disease.(2) In comparison, in the beginning of the 20th century only 9% of all death were the result of a cardiovascular disease. During the last century however degenerative diseases became more common as the incidence of infectious pandemics decreased. The peak of cardiovascular related mortality was reached in the seventies. In those years cardiovascular disease related mortality was responsible for 45% of all death in the Netherlands.(3) Since then cardiovascular mortality declined steadily. The impressive reduction in mortality rates of 54% among men and 44% among women for ischemic heart disease can be explained by development and introduction of better prevention and treatment strategies, as natural history and pathophysiology of ischaemic heart disease became more clear.(2) The introduction of the coronary care unit in the beginning of the seventies of the last century alone resulted in a decline of in-hospital mortality of acute myocardial infarction (AMI) patients by 50% due to a major reduction of fatal arrhythmic events.(4,5) The introduction of fibrinolytic therapy(6), aspirin (7-9) and ACE-inhibitors (10-12) reduced short-term infarct related mortality further to 15%. Due to fibrinolytic therapy it became possible to open the infarct related artery in a significant number of patients by resolving the thrombus, which resulted in a reduction of the extent of myocardial necrosis.(6) The latest major improvement, mechanical revascularization therapy by Percutaneous Coronary Interventions in the acute phase of the myocardial infarction, further reduced mortality rates to 5-15% at 12 months follow-up.(13-16) Since the majority of patients presenting in a hospital with an AMI became survivors, long-term treatment strategies to prevent a second heart attack or complications of the initial heart attack (such as ventricular arrhythmias or heart failure) became more important. Secondary prevention by aspirin (9,17,18) and statins reduced the relative risk of a second myocardial infarction by more than 30%. Beta-blockers (19,20), ACE-inhibitors(10-12,21), AT-II blockers(22), and aldosterone blockers (23) improved long-term prognosis by improving ventricular function. Beta-blockers (19,20) and Implantable Cardioverter Defibrillators (24-26) have reduced the risk for sudden cardiac death. Moreover, favorable modification of classical risk factors, like tobacco use (27), unhealthy eating patterns (28) and physical inactivity

(29,30) reduced the rate of coronary events. In addition, participation in a cardiac rehabilitation program post-AMI helps the patient to establish and maintain these healthy lifestyles.(29,30) With the widespread application of coronary interventions, fibrinolytic agents, antithrombotic therapy and secondary prevention, the overall 1-year mortality was reduced to 4-6%, at least in those who participated in the latest large-scale randomized trials.(31,32) Despite these positive results, mortality rates in registries remain higher compared to the mortality rates in trials. Moreover, cardiovascular diseases are still the leading causes of mortality worldwide.

II Pathophysiology of ischaemic heart disease

Ischemic heart disease is caused by atherosclerosis. Atherosclerosis represents a chronic inflammatory response to the stress imposed by various risk factors, i.e. male sex, tobacco use, psychosocial stress, unhealthy diet, diabetes, hypertension, obesity and physical inactivity.(33) These stimuli induce a cascade of pathophysiological and patho-anatomical processes in the coronary artery. A schematic overview of the development of atherosclerosis is given in Figure 1.(34) Endothelial dysfunction of the artery wall is considered to be the first step in the development of atherosclerosis, which leads to hyper-adhesiveness of leucocytes, enhanced perme-

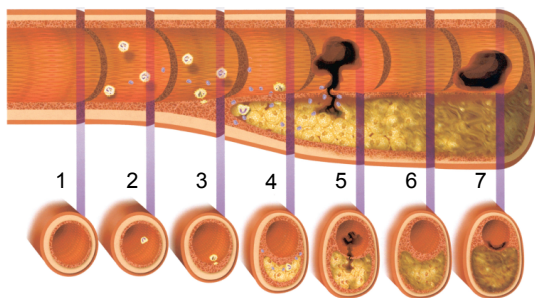


Figure 1. Development and complications of a human atherosclerotic plaque.

On top. The development of the atherosclerotic lesion is depicted in time from normal artery (1) to atheroma that caused clinical manifestations (5-7). **On the bottom.** Cross sections of different stages of the atherosclerotic lesion **1.** Normal artery. **2.** Endothelial dysfunction and recruitment of leucocytes resulting in lipid accumulation in the intimal space. **3.** Evolution to fibrofatty stage due to foam cell formation and amplification of leukocyte recruitment, smooth muscle cell migration and proliferation. **4.** Expression of tissue factor resulting in weakening of the fibrous cap. **5.** Rupture of fibrous cap resulting in thrombus formation. **6.** Thrombus resorbs and the lesion evolves to an advanced fibrous and calcified plaque. **7.** Thrombus formation due to erosion of the endothelial layer. See text for further explanation. Adapted from Libby, et al. (34)

ability of lipoproteins, functional imbalance between pro- and anti-thrombotic factors, imbalance between growth stimulators and inhibitors and vasoactive substances.

Atherosclerosis can become clinically manifest as stable angina pectoris, an acute coronary syndrome (i.e. unstable angina, non-ST segment elevation or ST-segment elevation myocardial infarction) and/or sudden cardiac death. In acute coronary syndromes, rupture or erosion of the atherosclerotic lesion causes partial or total occlusion of the coronary artery by forming a luminal thrombus.(34) This thrombotic response can be explained by several factors: the content of the exposed atherosclerotic plaque is highly thrombogenic as a result of ongoing inflammation, expression of tissue factors by macrophages and the lipid core containing active tissue factors. After plaque rupture, these contents are exposed directly to the circulating blood. High shear stress forces promote arterial thrombosis, probably via shear stress induced platelet activation. Subsequently, fibrin plays an important role to stabilize the initial and fragile platelet thrombus. Of note, the thrombotic response to plaque rupture is dynamic: thrombosis and thrombolysis tend to occur simultaneously, often in association with vasospasm, causing intermittent flow obstruction and distal embolization.(35)

For the optimal treatment of myocardial infarctions, several issues have to be kept in mind:

1. Irreversible myocardial damage occurs already after 15 to 20 minutes of occlusion of the coronary artery, and progresses from the subendocardium to the subepicardium in a time dependent fashion ("the wave-front phenomenon").(36)
2. The extent of myocardial damage is inversely related to the time of onset of the coronary artery occlusion (start symptoms) and the restoration of blood flow. Maximal damage occurs within the first 4 to 6 hours of sustained occlusion, however most damage arises already in the first 2 or 3 hours.(36-38)
3. Of those who die, approximately half do so within 2 hours after onset of symptoms, before reaching the hospital.(39)
4. Most early deaths are related to ventricular arrhythmias.
5. Most myocardial infarctions originate from atherosclerotic lesions who, prior to the event, were mildly to moderately stenotic. Hence, not the extent of plaque burden, but the biological state, predicts whether or not rupture of the atherosclerotic lesion and myocardial infarction will occur.(40)
6. As AMI is an acute exacerbation of a chronic process, interventions have to focus not only on the acute event, but also on reduction of the burden of atherosclerosis and the complications of AMI during follow-up. Furthermore, to prevent AMI it is important to identify and treat patients at high risk.

III Guidelines and implementation

To optimize care and outcome of AMI patients many organizations, e.g. the European Society of Cardiology, the American College of Cardiology with the American Heart Association, and The Netherlands Society of Cardiology, have published guidelines for the treatment of patients with AMI.(41-44) Guidelines are systematically developed statements to assist practitioners and patients in making evidence-based decisions about appropriate health care for specific clinical conditions.(45) These AMI guidelines advocate early and aggressive reperfusion strategies, recommend the use of a combination of evidence-based medicine and support programs to stimulate a healthier lifestyle. Compliance to these guidelines is proven beneficial. Shiele et al. demonstrated that the degree of guideline compliance is independently correlated with the one-year mortality after AMI.(46) In this study, a risk score based on initial presentation, and a compliance index based on patient characteristics, type of myocardial infarction, in-hospital management (including revascularization strategies and use of recommended drugs) were established. Mortality was found independently related to three variables: type of myocardial infarction, risk score and compliance index. After stratification for risk score and type of infarction the relationship between extent of guideline compliance and mortality remained strong. These findings were confirmed by the recently published report of the GRACE registry, which analyzed the in-hospital management of 44372 myocardial infarction patients enrolled at 113 hospitals in 14 countries from 1999 to 2005.(47) A clear trend was shown towards an increased use of guideline-recommended medication and interventional strategies over the course of this study. These changes were accompanied by a significant decrease in in-hospital death, cardiogenic shock, recurrent myocardial infarction, and the development of heart failure independent of the risk status of the patient at presentation.

Registries are of major importance to provide clear insights in day-to-day practice, effectiveness of treatment and to determine the actual implementation level of guidelines in the real world. Beside the fact that these registries revealed a global effort to improve day-to-day practice, they also identified substantial opportunities for improvement. For example, in the Grace registry, still one third of all AMI patients did not receive any reperfusion therapy; a similar number (36%) was found in the second Euro Heart survey.(48,49) Median door-to-balloon time remained relatively constant from 1999 to 2005: i.e. between 75 and 84 minutes.(48) Even worse is the situation after the acute phase: modifiable risk factors were often not controlled and optimal medication is often not prescribed.(50,51) Also confirmed by the recent

registries, but also reported in prior surveys, guidelines were applied less thoroughly in highest risk patients, for example patients of older age, patients with prior myocardial infarction or patients with diabetes.(46,48,52) Moreover, women overall are less adequately treated compared to men.(46,48,52-54) In conclusion, over the years treatment of AMI patients has improved significantly, however, still a large number of patients is treated far from optimal. Therefore, all efforts should be addressed to elevate the standard of care to a level that all patients benefit from optimal therapy. This can be accomplished by changing the system of care delivery. Herein, money might seem an obstacle; however in the Western world it seems more a question of the correct allocation of money and how to overcome bureaucratic organizational barriers.

IV Barriers of guideline implementation

Lack of implementation of guidelines can be explained by several factors: the guidelines themselves, patient- and physician's constraints, and organizational barriers.(55)

- Guidelines: First, the number of guidelines dealing with at least partly the same patient population makes it difficult to implement the different, sometimes even conflicting recommendations into clinical practice; Second, most guidelines consist of numerous pages (for example the American Heart Organization/American College of Cardiology guidelines for management of ST-elevation myocardial infarction patients contains 212 pages) making it less likely that physicians have knowledge of the complete contents of all guidelines.(41) Third, the basis of these guidelines ranges from randomized clinical trials to expert panel opinions.(56) The "generalisability" of trial data are sometimes questionable due to the often highly selected study populations enrolled in these randomized trials. Additionally, statements are classified by level of evidence making interpretation of the guidelines complex.

- Physicians' constraints: Not all physicians are familiar with the guidelines.(57) Moreover, physicians' awareness of the guidelines is not similar as reaching the recommended treatment goals in patients. For example, 95% of the physicians were aware of the cholesterol recommendations as written in the National Education Cholesterol Program, however only 38% of the patients achieved adequate cholesterol levels.(54) Some physicians judge guidelines as oversimplified, "cookbook" medicine, too rigid to apply to individual patients and a threat for the autonomy of the physicians.(57)

- Patients' factors: Patients play a central role in the success of therapy. It takes a lot of effort, time and money to adopt and maintain a healthier behavior and to use all prescribed drugs. Factors that appear to influence compliance include patient's knowledge, confidence in the ability to follow recommended behavioral changes, perception of health and benefits of therapy or behavior, availability of social support, and complexity of the regimen.(58-60) Of importance, reinforcement on a regular basis is crucial to maintain a healthier lifestyle.(55)

- Organizational barriers: optimal treatment of AMI patients should be a continuum-of-care; it should include acute and long-term care.(41,43,44) Therefore, regional ambulance services, general physicians, regional hospitals, cardiologist, nurses and rehabilitation centers should work all together. Guidelines of the different professionals should be aligned to make smooth transition from one setting to the other possible. Besides optimizing care processes, political, economical and financial issues have to be overcome. A mental switch has to be established from self-interest to community-interest.

V Bridging the gap between science and practice

The question is how to bridge the gap between science and practice? Translational research refers to translating research into practice: i.e. ensuring that new diagnostics and treatment modalities actually reach the patients or population for whom they are intended, and that they are implemented in a correct manner.(61) Registries confirm that passive diffusion of guideline recommendations into clinical practice is not sufficient.(41,47,49,50,62) A more active approach is therefore needed, focusing on changing the system of care delivery to accomplish a high and uniform standard of care for all patients.(63) The Cooperative Cardiovascular Project was one of the first quality improvement programs for patients with AMI.(64) This project started in 1992 with the aim to improve the quality of care for patients with AMI by data feedback and the use of predefined quality indicators. By doing so, better performance was achieved in prescription of aspirin during hospitalization and beta-blockers at discharge. This resulted in a reduction of both in-hospital and one-year mortality. Data feedback remains a crucial step in the cycle of continuous quality improvement (figure 2).(65, 66)

Various quality improvement programs followed the Cooperative Cardiovascular Project: for example, Get with the Guidelines, Guidelines Applied in Practice and Crusade.(67-68) In addition to the data feedback these programs created a system

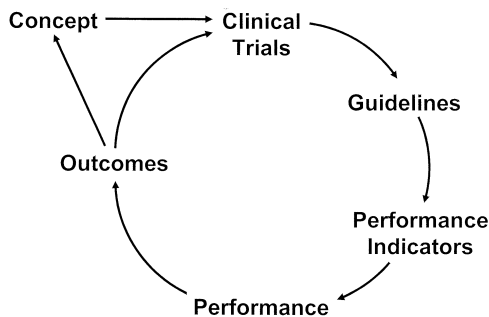


Figure 2. The cycle of continuous quality improvement. Adapted from Califf et al. (66)

of reminders (e.g. care-tools) in the form of standard orders, discharge forms and information forms for patients. The extent of the use of these care-tools was correlated to the degree of following the guidelines.(63) Nowadays it is clear that care improvement only can be accomplished when it is embedded into a system of reminders. Memory is fallible, and the more we can do to assure patients of the consistent application of knowledge at the highest level, the better.(70)

On the other hand, optimal AMI care should cover both acute and long-term care. The above mentioned projects mainly focused on acute cardiac care and secondary prevention strategies during the index hospitalization phase only. In the last few years, more and more projects installed pre-hospital care systems: networks of collaborating emergency medical services, community hospitals and interventional cardiac centers to foster early reperfusion therapy in acute AMI patients.(71-74) Pre-hospital triage is effective in limiting myocardial damage and improving outcome. (72,74) Moreover, “a well-functioning regional system of care... and fast transport to the most appropriate facility is the *key* to the success of the treatment”, as stated in the most recent published guidelines for AMI patients of the European Society of Cardiology of 2008.(43) Although, as addressing systematically one phase of AMI care improves outcome significantly, it can be expected that further improvement of care and outcome can be achieved by maximizing the use of evidence-based therapy during all essential phases of AMI care. Therefore, in 2004 an all-phases integrated guideline-implementation program for patients with AMI: the MISSION! protocol was designed and implemented in daily clinical practice. The aim of MISSION! was to improve AMI care by implementation of the most recent international guidelines in all essential phases of AMI care, i.e. the pre-hospital, in-hospital and outpatient phase up to one-year after AMI, thereby maximizing the use of evidence-based medicine in real life.

VI Aim and outline of the thesis

The aim of this thesis was to evaluate the design, and subsequent implementation of the MISSION! protocol in daily AMI care. The rationale, design and implementation of the MISSION! protocol is described in **Chapter 2** MISSION! is a framework for clinical decision making and treatment to improve acute and long-term AMI care. MISSION! was a multifaceted intervention, and lessons learned from prior quality improvement programs were incorporated in the MISSION! protocol. To our knowledge, this all-phases integrated approach is unique, and implicates a close collaboration among all health care professionals in the “Hollands-Midden” region in The Netherlands.

Chapter 3 presents the results of the MISSION! protocol on AMI care. Using a before (n=84) and after implementation cohort of AMI patients (n=518) we assessed the impact of MISSION! by performance indicators.

In **Chapter 4** and **5** we evaluated the relation between LV dyssynchrony early after AMI and the occurrence of long-term LV dilatation. One out of 6 AMI patients develops LV dilatation (defined as an increase of left ventricle end-systolic volume of $\geq 15\%$).⁽⁷⁵⁾ LV dilation is associated with adverse long-term prognosis.⁽⁷⁶⁾ Early identification of patients prone to LV remodeling is needed to optimize therapeutic management.

Chapter 6 describes the outcome of the MISSION! Intervention Study, a prospective randomized control trial comparing the efficacy and safety of sirolimus-eluting stents and bare-metal stents in patients with ST-elevation AMI. Eligible patients from the MISSION! protocol were included in this intervention study.

In **Chapter 7** the results of the SHIVA study is described. Asian Indian migrants in the Western world are highly susceptible for ischemic heart disease (IHD).^(77,78) Until now, most IHD risk studies were performed in 1st and 2nd generation Asian Indian expatriates.⁽⁷⁹⁻⁸³⁾ For optimal prevention, knowledge of the cardiovascular risk profile of younger generations is crucial. In this study we assessed the prevalence of conventional IHD risk factors and Framingham risk score in asymptomatic 3rd to 7th generation Asian Indian descendants, compared to Europeans. Asymptomatic was defined as not being familiar with IHD, diabetes, hypertension or high cholesterol, nor receiving any form of treatment for any of these conditions.

Chapter 8 describes the results of a study investigating the distribution, arc and location of calcified spots in AMI related coronary artery of patients with ST-elevation myocardial infarction. From Electron Beam Computed Tomography studies it is known that the extent of intracoronary calcium is related to the risk of coronary events.⁽⁸⁴⁻⁸⁸⁾ In this study we investigated the degree of intracoronary calcium by the use of gray-scale images.

Finally, a general summary, conclusions and future perspectives are described in English and Dutch respectively.

REFERENCES

1. World Health Organization. Cardiovascular diseases, fact sheet n° 317. 2007. World Health Organization. <http://www.who.int/mediacentre/factsheets/fs317/en/index.html>
2. Koek H.L., Engelfriet-Rijk C.J.M., Bots ML. Hart- en vaatziekten in Nederland 2006. In: Jager-Geurts MH, Peters RJG, van Dis SJ, Bots ML, editors. Hart- en vaatziekten in Nederland 2006. Den Haag: Nederlandse Hartstichting, 2006.
3. Kromhout D, van Dis I, Verschuren M. Een vermijdbare kwaal? Een eeuw hart- en vaatziekten in Nederland. Nederlandse Hartstichting, Nederlandse Vereniging voor Cardiologie i.s.m. Waanders Uitgevers Zwolle, 2004: 35-47.
4. Julian D.G., Valentine P.A., Miller G.G. Disturbance of rate, rhythm and conduction in acute myocardial infarction: a prospective study of 100 consecutive patients with the aid of electrocardiographic monitoring. *Am J Med* 1964; 37:915-927.
5. Goble AJ, Sloman G, Robinson JS. Mortality reduction in a coronary care unit. *Br Med J* 1966; 1(5494):1005-1009.
6. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet* 1994; 343(8893):311-322.
7. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS- 2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988; 2(8607):349-360.
8. ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. *Lancet* 1992; 339(8796):753-770.
9. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; 324(7329):71-86.
10. Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000; 355(9215):1575-1581.
11. Danchin N, Cucherat M, Thuilleux C, Durand E, Kadri Z, Steg PG. Angiotensin-converting enzyme inhibitors in patients with coronary artery disease and absence of heart failure or left ventricular systolic dysfunction: an overview of long-term randomized controlled trials. *Arch Intern Med* 2006; 166(7):787-796.

12. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. *Circulation* 1998; 97(22):2202-2212.
13. Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. *Lancet* 2006; 367(9510):579-588.
14. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003; 361(9351):13-20.
15. Dalby M, Bouzamondo A, Lechat P, Montalescot G. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. *Circulation* 2003; 108(15):1809-1814.
16. Zijlstra F, Hoorntje JC, de Boer MJ, Reijfers S, Miedema K, Ottervanger JP et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1999; 341(19):1413-1419.
17. Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. *JAMA* 1999; 282(21):2058-2067.
18. Collaborative overview of randomised trials of antiplatelet therapy—I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *BMJ* 1994; 308(6921):81-106.
19. Olsson G, Wikstrand J, Warnold I, Manger C, V, McBoyle D, Herlitz J et al. Metoprolol-induced reduction in postinfarction mortality: pooled results from five double-blind randomized trials. *Eur Heart J* 1992; 13(1):28-32.
20. Freemantle N, Cleland J, Young P, Mason J, Harrison J. beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999; 318(7200):1730-1737.
21. Teo KK, Yusuf S, Pfeffer M, Torp-Pedersen C, Kober L, Hall A et al. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. *Lancet* 2002; 360(9339):1037-1043.
22. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; 349(20):1893-1906.
23. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; 348(14):1309-1321.

24. Wilber DJ, Zareba W, Hall WJ, Brown MW, Lin AC, Andrews ML et al. Time dependence of mortality risk and defibrillator benefit after myocardial infarction. *Circulation* 2004; 109(9):1082-1084.
25. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; 346(12):877-883.
26. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004; 351(24):2481-2488.
27. Aberg A, Bergstrand R, Johansson S, Ulvenstam G, Vedin A, Wedel H et al. Cessation of smoking after myocardial infarction. Effects on mortality after 10 years. *Br Heart J* 1983; 49(5):416-422.
28. Mead A, Atkinson G, Albin D, Alphey D, Baic S, Boyd O et al. Dietetic guidelines on food and nutrition in the secondary prevention of cardiovascular disease - evidence from systematic reviews of randomized controlled trials (second update, January 2006). *J Hum Nutr Diet* 2006; 19(6):401-419.
29. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. *Eur Heart J* 2007; 28(19):2375-2414.
30. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med* 2004; 116(10):682-692.
31. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006; 367(9510):569-578.
32. Armstrong PW, Granger CB, Adams PX, Hamm C, Holmes D, Jr., O'Neill WW et al. Pexelizumab for acute ST-elevation myocardial infarction in patients undergoing primary percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2007; 297(1):43-51.
33. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med* 1999; 340(2):115-126.
34. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. *Circulation* 2001; 104(3):365-372.
35. Davies MJ. The pathophysiology of acute coronary syndromes. *Heart* 2000; 83(3):361-366.
36. Reimer KA, Jennings RB. The “wavefront phenomenon” of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. *Lab Invest* 1979; 40(6):633-644.

37. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996; 348(9030):771-775.
38. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation* 2004; 109(10):1223-1225.
39. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. *Lancet* 1999; 353(9164):1547-1557.
40. Fuster V, Moreno PR, Fayad ZA, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque: part I: evolving concepts. *J Am Coll Cardiol* 2005; 46(6):937-954.
41. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 2004; 110(9):e82-292.
42. Van de Werf F, Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KA et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2003; 24(1):28-66.
43. Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2008; 29(23):2909-2945.
44. Guidelines acute myocardial infarction with ST-elevation. 2003. The Netherlands Society of Cardiology. <http://www.nvvc.nl/UserFiles/Richtlijnen/Richtlijnen.htm>
45. Field MJ, Lohr KN. Clinical Practice Guidelines: Directions for a New Program. Washington: National Academy Press, 1999.
46. Schiele F, Meneveau N, Seronde MF, Caulfield F, Fouche R, Lassabe G et al. Compliance with guidelines and 1-year mortality in patients with acute myocardial infarction: a prospective study. *Eur Heart J* 2005; 26(9):873-880.
47. Fox KA, Steg PG, Eagle KA, Goodman SG, Anderson FA, Jr., Granger CB et al. Decline in rates of death and heart failure in acute coronary syndromes, 1999- 2006. *JAMA* 2007; 297(17):1892-1900.

48. Eagle KA, Nallamothu BK, Mehta RH, Granger CB, Steg PG, Van de WF et al. Trends in acute reperfusion therapy for ST-segment elevation myocardial infarction from 1999 to 2006: we are getting better but we have got a long way to go. *Eur Heart J* 2008; 29(5):609-617.
49. Mandelzweig L, Battler A, Boyko V, Bueno H, Danchin N, Filippatos G et al. The second Euro Heart Survey on acute coronary syndromes: Characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. *Eur Heart J* 2006; 27(19):2285-2293.
50. Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. EUROASPIRE I and II Group. European Action on Secondary Prevention by Intervention to Reduce Events. *Lancet* 2001; 357(9261):995-1001.
51. Burwen DR, Galusha DH, Lewis JM, Bedinger MR, Radford MJ, Krumholz HM et al. National and state trends in quality of care for acute myocardial infarction between 1994-1995 and 1998-1999: the medicare health care quality improvement program. *Arch Intern Med* 2003; 163(12):1430-1439.
52. Peterson ED, Shah BR, Parsons L, Pollack CV, Jr., French WJ, Canto JG et al. Trends in quality of care for patients with acute myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. *Am Heart J* 2008; 156(6):1045-1055.
53. Yusuf S, Flather M, Pogue J, Hunt D, Varigos J, Piegas L et al. Variations between countries in invasive cardiac procedures and outcomes in patients with suspected unstable angina or myocardial infarction without initial ST elevation. OASIS (Organisation to Assess Strategies for Ischaemic Syndromes) Registry Investigators. *Lancet* 1998; 352(9127):507-514.
54. Pearson TA, Laurora I, Chu H, Kafonek S. The lipid treatment assessment project (LTAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med* 2000; 160(4):459-467.
55. Miller NH, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: recommendations for a call to action. A statement for healthcare professionals. *Circulation* 1997; 95(4):1085-1090.
56. Gibbons RJ, Smith S, Antman E. American College of Cardiology/American Heart Association clinical practice guidelines: Part I: where do they come from? *Circulation* 2003; 107(23):2979-2986.
57. Tunis SR, Hayward RS, Wilson MC, Rubin HR, Bass EB, Johnston M et al. Internists' attitudes about clinical practice guidelines. *Ann Intern Med* 1994; 120(11):956-963.
58. Robertson D, Keller C. Relationships among health beliefs, self-efficacy, and exercise adherence in patients with coronary artery disease. *Heart Lung* 1992; 21(1):56-63.

59. Richardson MA, Simons-Morton B, Annegers JF. Effect of perceived barriers on compliance with antihypertensive medication. *Health Educ Q* 1993; 20(4):489-503.
60. Schmid TL, Jeffery RW, Onstad L, Corrigan SA. Demographic, knowledge, physiological, and behavioral variables as predictors of compliance with dietary treatment goals in hypertension. *Addict Behav* 1991; 16(3-4):151-160.
61. Woolf SH. The meaning of translational research and why it matters. *JAMA* 2008; 299(2):211-213.
62. McNamara RL, Herrin J, Bradley EH, Portnay EL, Curtis JP, Wang Y et al. Hospital improvement in time to reperfusion in patients with acute myocardial infarction, 1999 to 2002. *J Am Coll Cardiol* 2006; 47(1):45-51.
63. Mehta RH, Montoye CK, Faul J, Nagle DJ, Kure J, Raj E et al. Enhancing quality of care for acute myocardial infarction: shifting the focus of improvement from key indicators to process of care and tool use: the American College of Cardiology Acute Myocardial Infarction Guidelines Applied in Practice Project in Michigan: Flint and Saginaw Expansion. *J Am Coll Cardiol* 2004; 43(12):2166-2173.
64. Marciniak TA, Ellerbeck EF, Radford MJ, Kresowik TF, Gold JA, Krumholz HM et al. Improving the quality of care for Medicare patients with acute myocardial infarction: results from the Cooperative Cardiovascular Project. *JAMA* 1998; 279(17):1351-1357.
65. Roe MT, Ohman EM, Pollack CV, Jr., Peterson ED, Brindis RG, Harrington RA et al. Changing the model of care for patients with acute coronary syndromes. *Am Heart J* 2003; 146(4):605-612.
66. Califf RM, Peterson ED, Gibbons RM, et al. Integrating quality into the cycle of therapeutic development. *J Am Coll Cardiol* 2002;40: 1895–1901.
67. Eagle KA, Montoye CK, Riba AL, Defranco AC, Parrish R, Skorcz S et al. Guideline-based standardized care is associated with substantially lower mortality in medicare patients with acute myocardial infarction: the American College of Cardiology's Guidelines Applied in Practice (GAP) Projects in Michigan. *J Am Coll Cardiol* 2005; 46(7):1242-1248.
68. Lewis WR, Peterson ED, Cannon CP, Super DM, LaBresh KA, Quealy K et al. An organized approach to improvement in guideline adherence for acute myocardial infarction: results with the Get With The Guidelines quality improvement program. *Arch Intern Med* 2008; 168(16):1813-1819.
69. Peterson ED, Roe MT, Mulgund J, DeLong ER, Lytle BL, Brindis RG et al. Association between hospital process performance and outcomes among patients with acute coronary syndromes. *JAMA* 2006; 295(16):1912-1920.
70. Dans PE. Credibility, cookbook medicine, and common sense: guidelines and the college. *Ann Intern Med* 1994; 120(11):966-968.

71. Jacobs AK, Antman EM, Faxon DP, Gregory T, Solis P. Development of systems of care for ST-elevation myocardial infarction patients: executive summary. *Circulation* 2007; 116(2):217-230.
72. Kalla K, Christ G, Karnik R, Malzer R, Norman G, Prachar H et al. Implementation of guidelines improves the standard of care: the Viennese registry on reperfusion strategies in ST-elevation myocardial infarction (Vienna STEMI registry). *Circulation* 2006; 113(20):2398-2405.
73. Krumholz HM, Bradley EH, Nallamothu BK, et al. A campaign to improve the timeliness of primary percutaneous coronary intervention: door-to-balloon: an alliance for quality. *J Am Coll Cardiol Intv* 2008; 1:97-104.
74. Ortolani P, Marzocchi A, Marrozzini C, Palmerini T, Saia F, Serantoni C et al. Clinical impact of direct referral to primary percutaneous coronary intervention following pre-hospital diagnosis of ST-elevation myocardial infarction. *Eur Heart J* 2006; 27(13):1550-1557.
75. Giannuzzi P, Temporelli PL, Bosimini E, Gentile F, Lucci D, Maggioni AP et al. Heterogeneity of left ventricular remodeling after acute myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-3 Echo Substudy. *Am Heart J* 2001; 141(1):131-138.
76. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 1987; 76(1):44-51.
77. Enas EA, Yusuf S, Mehta JL. Prevalence of coronary artery disease in Asian Indians. *Am J Cardiol* 1992; 70(9):945-949.
78. Balarajan R. Ethnic differences in mortality from ischaemic heart disease and cerebrovascular disease in England and Wales. *BMJ* 1991; 302(6776):560-564.
79. Anand SS, Yusuf S, Vuksan V, Devanesen S, Teo KK, Montague PA et al. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE). *Lancet* 2000; 356(9226):279-284.
80. Bhatnagar D, Anand IS, Durrington PN, Patel DJ, Wander GS, Mackness MI et al. Coronary risk factors in people from the Indian subcontinent living in west London and their siblings in India. *Lancet* 1995; 345(8947):405-409.
81. Bhopal R, Unwin N, White M, Yallop J, Walker L, Alberti KG et al. Heterogeneity of coronary heart disease risk factors in Indian, Pakistani, Bangladeshi, and European origin populations: cross sectional study. *BMJ* 1999; 319(7204):215-220.

82. Cappuccio FP, Cook DG, Atkinson RW, Strazzullo P. Prevalence, detection, and management of cardiovascular risk factors in different ethnic groups in south London. *Heart* 1997; 78(6):555-563.
83. McKeigue PM, Ferrie JE, Pierpoint T, Marmot MG. Association of early-onset coronary heart disease in South Asian men with glucose intolerance and hyperinsulinemia. *Circulation* 1993; 87(1):152-161.
84. Wayhs R, Zelinger A, Raggi P. High coronary artery calcium scores pose an extremely elevated risk for hard events. *J Am Coll Cardiol* 2002; 39(2):225-230.
85. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol* 2000; 36(4):1253-1260.
86. Raggi P, Callister TQ, Cooil B, He ZX, Lippolis NJ, Russo DJ et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 2000; 101(8):850-855.
87. Pohle K, Ropers D, Maffert R, Geitner P, Moshage W, Regenfus M et al. Coronary calcifications in young patients with first, unheralded myocardial infarction: a risk factor matched analysis by electron beam tomography. *Heart* 2003; 89(6):625-628.
88. Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. *Radiology* 2003; 228(3):826-833.

CHAPTER 2

MISSION!: Optimization of acute and chronic care for patients with acute myocardial infarction

Su-San Liem
Barend L. van der Hoeven
Pranobe V. Oemrawsingh
Jeroen J. Bax
Johanna G. van der Bom
Jan Bosch
Eric P. Viergever
Cees van Rees
Iman Padmos
Meredith I. Sedney
Henk J. van Exel
Harriette F. Verwey
Douwe E. Atsma
Enno T. van der Velde
J. Wouter Jukema
Ernst E. van der Wall
Martin J. Schalij

ABSTRACT

Background

Guideline implementation programs for patients with acute myocardial infarction (AMI) enhance adherence to evidence-based medicine (EBM) and improve clinical outcome. Although undertreatment of patients with AMI is well recognized in both acute and chronic phases of care, most implementation programs focus on acute and secondary prevention strategies during the index hospitalization phase only.

Hypothesis

Implementation of an all-phase integrated AMI care program maximizes EBM in daily practice and improves the care for patients with AMI.

Aim

The objective of this study is to assess the effects of the MISSION! program on adherence to EBM for patients with AMI by the use of performance indicators.

Design

The MISSION! protocol is based on the most recent American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for patients with AMI. It contains a prehospital, in-hospital, and outpatient clinical framework for decision making and treatment, up to 1 year after the index event. MISSION! concentrates on rapid AMI diagnosis and early reperfusion, followed by active lifestyle improvement and structured medical therapy. Because MISSION! covers both acute and chronic AMI phase, this design implies an intensive multidisciplinary collaboration among all regional health care providers.

Conclusion

Continuum of care for patients with AMI is warranted to take full advantage of EBM in day-to-day practice. This manuscript describes the rationale, design, and preliminary results of MISSION!, an all-phase integrated AMI care program.

Coronary heart disease is the leading cause of death in the western world, with an estimated 3.8 million men and 3.4 million women dying each year worldwide.(1) Furthermore, 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. This imposes a significant socioeconomic burden on society.(1)

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.(2,3) 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. For example, despite the fact that there is clear evidence that reperfusion therapy in the acute phase improves survival of patients with AMI, registries show that only 56% to 76% of the eligible patients actually receives this form of therapy.(4-6)

Furthermore, a recent publication of 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.(7) Even worse is the situation after the acute phase: modifiable risk factors are often not controlled and optimal medication is often not prescribed.(4,8) Consequently, a significant number of patients with AMI is treated less than optimal.

Schiele et al.(9) demonstrated that the degree of guideline compliance is independently correlated with the 1-year mortality after AMI. 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.(10-12) 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.(10,13) Therefore guideline implementation programs are of paramount importance to optimize AMI care.

Still, most quality improvement programs only focus on acute care and secondary prevention strategies during the index hospitalization phase, whereas it is known that the prehospital and chronic phase is also important. Thus, to improve AMI care, we have to maximize the diffusion of EBM into daily clinical practice across practical

setting. Therefore, we developed and implemented an all-phase integrated AMI care program in the region “Hollands-Midden” The Netherlands: MISSION!.

METHODS

Study design

MISSION! is designed according to a quasi-experimental approach.⁽¹⁴⁾ The MISSION! protocol is developed based on the most recent American College of Cardiol-

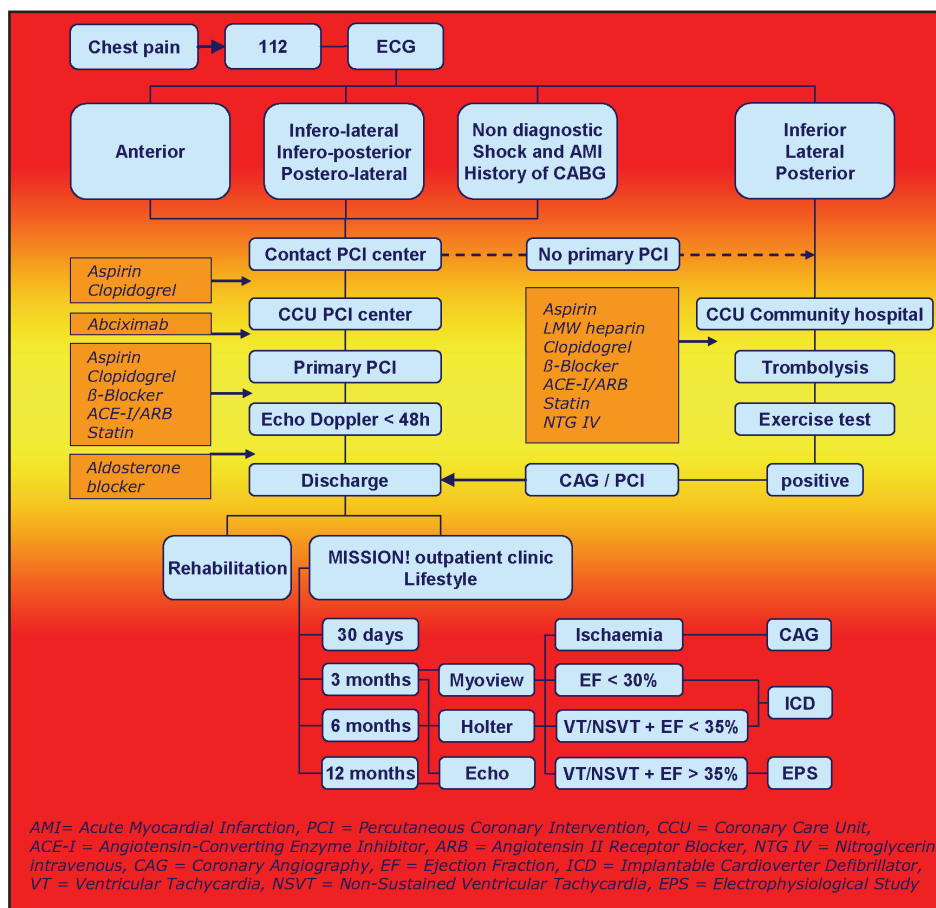


Figure 1.

The MISSION! flowchart presents the clinical framework for decision making and treatment. The flowchart covers all phases of AMI care: the prehospital and in-hospital phase, followed by a structured outpatient program, up to 1 year after the index infarction.

ogy/American Heart Association and European Society of Cardiology guidelines for AMI.(2,3) It contains a prehospital, in-hospital, and outpatient clinical framework for decision making and treatment, up to 1 year after the index event (Figure 1). The MISSION! goals, addressing all aspects of AMI care, are summarized in Figure 2. The Hollands-Midden region has 750.000 inhabitants and covers an area of approximately 50 x 25 miles. Based on historical data, it is estimated that approximately 1000 patients within the area will suffer from an AMI annually. An intensive collaboration has been established among primary care physicians, the regional ambulance service, 3 community hospitals (without PCI facilities), 3 cardiac rehabilitation centers, and the Leiden University Medical Center, Leiden, The Netherlands (serving as the primary PCI facility), to align AMI care. To provide insight into the rationale of the MISSION! program, we described the 3 MISSION! care phases and MISSION! care tools.

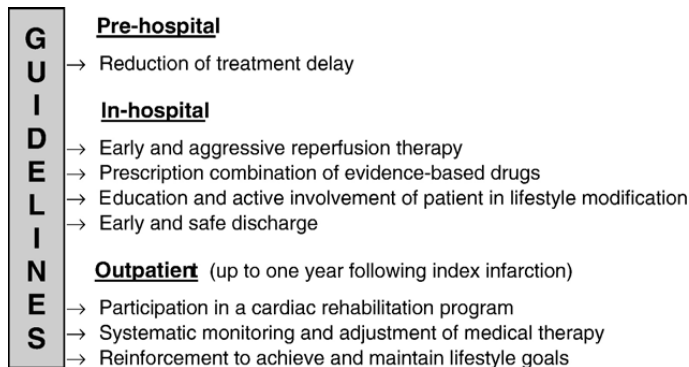


Figure 2.

The MISSION! goals, addressing all phases of AMI care, are summarized in this figure.

Prehospital phase

As advocated by the different guidelines, the cornerstones of optimal prehospital AMI care are rapid diagnosis, early risk stratification to identify patients who benefit from early intervention, minimal treatment delay, and aggressive reperfusion strategies. Prehospital triage by 12-lead electrocardiogram (ECG) in the field, thereby allowing early AMI diagnosis and rapid access to an intervention or community center, can reduce the treatment delay significantly.(15) Thereupon, primary PCI or thrombolysis prevents unnecessary infarct extension and saves lives.(16,17)

All these aspects are incorporated in the prehospital MISSION! protocol: in patients with chest pain, trained paramedics obtain a high-quality 12-lead ECG at the patient's

home (Lifepak 12 Defibrillator/Monitor Series; Medtronic, Redmond, WA). If the ECG fulfills the positive identification criteria as shown in the prehospital MISSION! standard order form (Figure 3), the ECG is transmitted directly to the computer network of the PCI hospital (Lifenet RS system; Medtronic). Trained coronary care unit (CCU) nurses analyze the ECG for determining patient's eligibility for primary PCI, based

Name:		Date of birth:		Location:	
Times Start symptoms hr:min Call for medical-help : Arrival general physician : Arrival ambulance : First ECG : Departure ambulance : Arrival hospital :		Medical history 		Current medication 	
		Clinical examination Weight ____ KG BP ____/____ Heartbeats ____/ min Rhythm SR/AF/VT/VF			

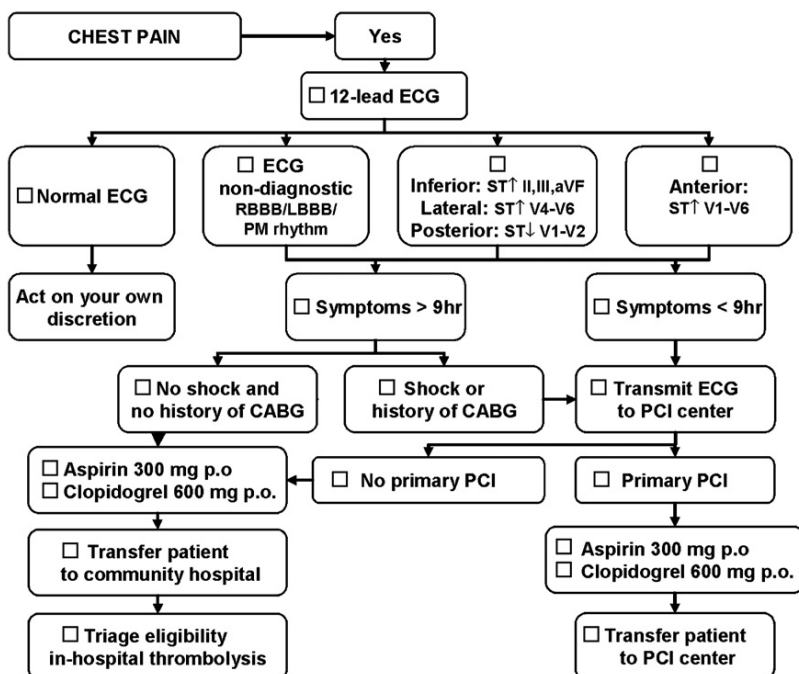


Figure 3.

Prehospital triage of patients with AMI is performed according to clinical and ECG criteria shown in this standard order: to determine the patient's eligibility for PCI or thrombolysis and to allow rapid access to the appropriate center for early and aggressive reperfusion therapy.

MISSION! COMMUNICATION FORM AMBULANCE-CCU			
Date:		Time call:	
		Ambulance number:	
Patient's information			
Last name, initials			
Date of birth			
Weight			
Time start symptoms			
Medical history			
Estimated duration to arrive at CCU?			
Contra-indications for abciximab ?			
Hemorrhagic disease?		Yes	No
Liver function disturbances?		Yes	No
Kidney function disturbances?		Yes	No
Blood loss in the last 3 months?		Yes	No
Operation in the last 3 months?		Yes	No
Trauma in the last 3 months?		Yes	No
TIA/CVA in the last 6 months?		Yes	No
Is the patient pregnant or does she menstruate at this moment ?		Yes	No
If patient is accepted			
Office-hours		Evening / Night / Weekend	
Call Cath Lab. Ask for the person who makes the schedule for today Tel 2018		Call first the interventional cardiologist in charge	
Call the trainee *9157		Call the Cath Lab laboratory worker in charge	
Prepare abciximab		Call the trainee *9157	
		Prepare abciximab	
After patient's arrival			
Enter patient in the hospital information system/ask the secretary to do			
Call the trainee *9157			
Call the Cath Lab and tell that the patient is arrived Tel 2018			
Admission according to MISSION! Protocol, see nurse standard order			

Figure 4.

This communication form is used by the CCU nurses, when they call the ambulance personal immediately after receiving the ECG of the primary PCI candidate.

on predefined criteria. If the patient is eligible for PCI, and after confirmation by phone, the ambulance paramedic administers clopidogrel and aspirin and the patient is transferred directly to the PCI center (Figures 3 and 4). Meanwhile, the CCU is prepared and the catheterization staff is informed. The catheterization laboratory is operational within 20 minutes, 24 hours/d, 7 days/wk.

If the ECG does not fulfill the criteria for primary PCI, but the patient may be a candidate for thrombolysis, prehospital triage for in-hospital thrombolysis is performed (Figure 5). These patients also receive clopidogrel and aspirin. The patient is transferred to the nearest community hospital directly, which never exceeds 10 mi in this region, allowing rapid access.

MISSION! Standard order eligibility thrombolysis		
Is the patient older than 80yrs?	Yes	No
Duration of symptoms >6hrs?	Yes	No
Does the pain consistently stay away after NTG s.l.?	Yes	No
History of CABG?	Yes	No
Decreased consciousness?	Yes	No
Is the patient paralyzed at this moment?	Yes	No
Systolic blood pressure >180 mmHg?	Yes	No
Does the patient suffer from a hemorrhagic disease?	Yes	No
Did the patient fall or bump his/her head today ?	Yes	No
Is there a chance to be pregnant?	Yes	No
Does the patient menstruate at this moment?	Yes	No
Did the patient ever suffer from a TIA/CVA?	Yes	No
	Yes	No
In the last 3 months, did the patient		
- have had a severe accident?	Yes	No
- have had a big operation?	Yes	No
- have coughed blood?	Yes	No
- have suffered from a stomach ulcer or hemorrhage?	Yes	No
- have lost blood in urine or stool?	Yes	No
- have suffered from abnormal vaginal blood loss?	Yes	No
<i>If all questions are answered with "NO", consult with the Central Post Ambulance (CPA) where to present the patient. The CPA will announce the CCU that a potential thrombolysis patient is arriving.</i> 		

Figure 5.

This form is used to determine patient's eligibility for thrombolysis.

Inhospital phase

The patient with AMI is directly admitted to the CCU, bypassing the emergency department, where all PCI patients receive abciximab (dose abciximab, 0.25 mg/kg bolus followed by an infusion of 0.125 Ag/kg per minute during 12 hours) in the absence of contraindications, and a PCI is performed (Figure 6). Likewise, thrombolysis patients receive fibrinolytic therapy immediately on arrival at the CCU of the community hospital. This approach minimizes inhospital delay as much as possible.

After reperfusion therapy, the patient stays for 24 hours at the CCU. Electrocardiogram and hemodynamic monitoring are performed continuously. According to protocol, all patients receive supplemental oxygen (3 L/min or more, according to the oxygen need) for the first 6 hours. If no contraindications exist, β -blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins are administered within 24 hours of admission. Reasons for not prescribing these drugs are documented. Respective drugs are titrated to control heart rate (target heart rate, 60-70 beats/min) and blood pressure (target level, <140/90 mm Hg or <130/80 mm Hg for patients with diabetes or chronic renal disease).

LUMC cardiology	MISSION!	NURSE STANDARD ORDER
1. Admission CCU ☐ Connect patient to the ECG monitor ☐ Obtain a 12-lead ECG ☐ Insert 2 intravenous catheters ☐ Nasal O₂ at 3L/min ☐ Check if clopidogrel and aspirin are administered in the ambulance ☐ Start Abciximab Time start Abciximab: ____/____ ☐ Print patient's labels to the Cath Lab ☐ Transfer the patient immediately to the Cath Lab with ECG monitoring ☐ Bring blood-tubes to the Cath Lab to obtain blood for laboratory studies 2. After primary PCI ☐ Connect patient to the ECG monitor ☐ Obtain a 12-lead ECG ☐ Chest X-ray ☐ Nasal O₂ at 3L/min for minimal 6h and according to patients needs. ☐ Control vital parameters, insertion side and medication. ☐ Stop abciximab after 12 hrs. Time stop Abciximab: ____/____ ☐ Medication: clopidogrel, aspirin, metoprolol, statin, perindopril, pantoprazol ☐ Start enoxaparin after finishing abciximab ☐ Complete MISSION! standard order set (<i>application forms for laboratory tests, echo, physiotherapist, id.</i>) ☐ Remove the sheath 4 hrs after prim PCI and apply Safeguard™. Time removal sheath: ____/____ ☐ 2 hours after applying Safeguard™ deflate and inflate Safeguard™, according to protocol. Time: ____/____ ☐ 4 hours after applying Safeguard™ deflate Safeguard™. Inspection of the insertion side by MD. Time: ____/____ ☐ When Angio-Seal is used: 2 hours bedrest in a lying position of 30°. Time: ____/____ ☐ After these 2 hrs: remove bandage and inspection of the insertion side by MD Time: ____/____ ☐ If no clinical contra-indications: start telemetry and mobilization scheme. ☐ After 12-24 hours: stable patient to Cardiac Stepdown Unit <u>ECG and laboratory test scheme</u> ☐ 6 hrs after admission: ECG Time: ____/____ Studies: CK, Troponin-T ☐ 12 hrs after admission: ECG Time: ____/____ Studies: CK, ASAT, ALAT, LDH, K, Ureum, Creat, Troponin-T, Hb, Htc, Trombo ☐ 18 hrs after admission: ECG Time: ____/____ Studies: CK, Troponin-T ☐ 24 hrs after admission: Studies: CK, according to this protocol until CK have reached the highest value Time: ____/____ CK max.....U/L Troponin-T max.....µg/L ☐ After CK have reached the highest value: CK once daily, till the 3rd day after prim. PCI ☐ ECG once daily ☐ Echo heart within 48 hrs after admission ☐ MISSION! talk by MISSION! MD ☐ Educate patient to fill in his/her MISSION! brochure and stimulate patient to keep it up-to-date. ☐ Weight patient: ____ Kg. (Instruct patient to fill his/her weight into his/her patient brochure) ☐ Educate the patient the benefit of drug compliance, the possibility to reduce his/her risk by changing unhealthy lifestyles and draw patient's attention to existing resources to succeed in these lifestyle changes 3. Discharge When Angio-seal is used: ☐ Give discharge instructions ☐ Give Angio-Seal patient card ☐ MISSION! outpatient visits arranged by secretary ☐ Check if MISSION! brochure is completely filled in by patient: medication list, cholesterol, blood pressure id. ☐ Give discharge letter ☐ Give Medication prescriptions		

Figure 6.

This order function as a check for nurse to maximize EBM in practice. Adequate feedback can be given by the use of check boxes.

Patients free of recurrent ischemic symptoms, symptoms of heart failure, or hemodynamically compromising arrhythmias start a mobilization program within 12 hours

postreperfusion (supervised by a physiotherapist) and are transferred to a stepdown unit within 24 hours. In the presence of complications, the patient remains at the CCU until clinical stable.

Resting 2-dimensional echocardiography is performed within 48 hours after admission, and left ventricular ejection fraction (LVEF) is calculated to evaluate the need for aldosterone inhibition (ie, LVEF <40% and existence of either symptomatic heart failure or diabetes) (Figure 1).

An important part of the inhospital MISSION! protocol is to educate and involve the patient actively in changing the lifestyle (smoking cessation, healthy diet, exercise, and weight management) and to emphasize the need for drug compliance. This secondary prevention program is provided by a multidisciplinary team (physicians, nurses, and a nurse practitioner) and is continued in the outpatient cardiac rehabilitation program and during follow-up.

Furthermore, in an era of growing economic pressure in health care, attention is paid to early and safe discharge of the uncomplicated patient. Patients without complications are discharged at day 3. Complications include stroke, reinfarction, ischemia, cardiogenic shock, heart failure (Killip class >1), bypass surgery, balloon pumping, emergency cardiac catheterization, or need for cardioversion or defibrillation. Although the risk of uncomplicated patients to develop adverse events after discharge is low, the strategy of early discharge inquires the possibility of rapid access to medical help.(18) Therefore, we provide a network: first, before discharge, patient and family members are informed how to recognize acute cardiac symptoms and how to take appropriate actions in response (ie, calling the emergency number 1-1-2); second, the general practitioner is informed concerning the diagnosis and treatment at discharge; third, all patients are contacted by phone within 1 week after discharge; and fourth, all patients are offered an outpatient rehabilitation program starting within 2 weeks after discharge.

Outpatient phase

The patient visits the MISSION! outpatient clinic 4 times during the first year after AMI. According to the protocol, a number of functional tests are obtained during these visits. If necessary, further tests/interventions are performed (Figure 1). The achieved medical and lifestyle goals are monitored, and if required, the physician and nurse practitioner emphasize the principles of secondary prevention. Each patient receives the appointment schedule for the first year at discharge to stress the importance of active participation of the patient.

After 1 year of follow-up, patients are referred either to the general practitioner (asymptomatic patients and an LVEF > 45%), to a regional cardiologist (patients with symptoms or an LVEF between 35% and 45%), or to the outpatient clinic of the university hospital (LVEF < 35%, after implantation of a device or in case of serious symptoms).

MISSION! care tools

We created guideline-oriented care tools for each phase of the MISSION! protocol. These care tools were developed to facilitate adherence to the MISSION! protocol and function as a check for physician, nurses and patients to maximize EBM in practice.(10) The following MISSION! care tools are customized and implemented: standard orders with check boxes for each clinical decision-making step and medical

The screenshot displays the EPD-Vision 6.01 software interface. The main window is titled "EPD-Vision [Visit data]" and includes a menu bar with "File", "Module", "Guidelines", and "Help". Below the menu bar, there are fields for "Name", "Patient ID", "Birth date", and "Age". To the right of these fields are buttons for "Results after last visit", "Echo", "Pace FU", "Ergometry", "Holter", "Shortstay", and "Cathlab study". A "Select Image" button is also present, which is linked to a "Select Image" dialog box showing four medical images. The main content area is divided into two tabs: "General" and "Letter". The "General" tab is active, showing a "History" section with a list of symptoms (Angina Pectoris, Dyspneu, Palpitations, Collaps) and a "Clinical examination" section with a list of options (Lenght, Weight, BMI, Waist circumference, Heart rate, Blood pressure left, right, General appearance, CVP, Lung, Heart). The "Letter" tab is also visible, showing a "Dear Colleague" letter template with fields for "Reason of visit", "Cardiac History", "General Medical History", "Risk factors", and "Anamnesis". The "Clinical examination" section is expanded, showing a list of options for "Lenght", "Weight", "BMI", "Waist circumference", "Heart rate", "Blood pressure left", "right", "General appearance", "CVP", "Lung", and "Heart". The "General appearance" section includes checkboxes for "Healthy", "Sick", "Dyspneic", "Pale", and "Cyanotic". The "CVP" section includes checkboxes for "Elevated", "Not elevated", and "Not assessable". The "Lung" section includes checkboxes for "Normal breath sounds", "Prolonged expiration", "Rales", "Rhonchi", and "Wheezes". The "Heart" section includes a checkbox for "Heart".

Figure 7.

EPD-VISION 6.01 is the electronic patient file and data management system that is used to store all the information of each patient, using a unique identification number. After applying the medical information in the inhospital and outpatient setting, this system produces automatically a letter concerning the diagnosis and treatment, which is electronically sent to the patient's primary care physician.

intervention (Figures 3-6), a guideline-based electronic patient file and data management system (EPD-VISION 6.01, Leiden University Medical Center) (Figure 7), a personal digital assistant (PDA) MISSION! protocol, chart stickers, patients' brochures, posters with lifestyle advices, and a MISSION! website for patients and professionals. Physicians and nurses are trained to use these care tools. The use of these care tools is guaranteed by handing out as standard order sets for each patient and the use of EPD-VISION in hospital and in the outpatient setting.

Patients

Patients who comply with the predefined criteria mentioned in the prehospital flow-chart are included in the prehospital MISSION! protocol (Figure 3). In hospital, the AMI diagnosis is confirmed by the presence of an unstable coronary lesion on acute angiography and/or the presence of enzymatic myocardial damage, defined as an increase in cardiac biomarker(s) above normal level(s). Also, patients who are presenting without typical ST-elevation in hospital, but with elevated cardiac biomarker(s), are diagnosed as patients with AMI. Based on this "a posteriori" diagnosis, patients with AMI follow the subacute in hospital and outpatient MISSION! program. Patients who need mechanical ventilation at the time of index event are excluded for the prehospital and in hospital MISSION! protocol. However, these patients are treated according to the outpatient MISSION! protocol after discharge.

No specific age threshold for exclusion is defined. Nevertheless, carefulness is needed in elderly patients, given the relative low number of studies and lack of consensus of optimal treatment strategies in this group. Elderly people with severe preexisting comorbidities are excluded. No informed consent is required, whereas MISSION! is the standard AMI care regimen in the region Hollands-Midden, The Netherlands.

Control group

MISSION! data are compared with data of AMI, patients treated with primary PCI at the Leiden University Medical Center from January 2003 until December 2003. This historical group was treated just before implementation of MISSION!, thereby limiting the effect of changes in, for example, drug regimen and/or technical aspects of PCI procedures. Although a randomized design to compare the effects of MISSION! with routine care would have been better, this was considered unethical. The patients of the historical group were selected by using the code for "primary PCI" in EPD-VISION. We retrospectively included only those with an "a posteriori" AMI diagnoses by using the same criteria as in the MISSION! patients' group. After

approval by the institutional ethical committee, all patients of the control group gave written informed consent.

Data collection

Data are systematically collected for each MISSION! patient in EPD-VISION, using a unique identification number. This database includes patient's medical history, symptoms on arrival, electrocardiographic examination, medication at the time of index, index times (ie, time onset symptoms, time call for medical help, time of first medical contact, time arrival hospital, needle time, time of first balloon inflation), in-hospital treatment and events, clinical examination at admission and discharge, discharge treatment, clinical examination at follow-up, follow-up treatment and events, laboratory measurements, functional tests, achieved lifestyle changes and the use of prescribed drugs. Similar data were extracted retrospectively from the hospitals' patient files in the historical patients with AMI group treated in 2003.

Data analysis

To assess the impact of MISSION!, we developed performance indicators (Table 1). The MISSION! performance indicators are based on key indicators used in previous studies, but in an extended version in accordance with the most recent guidelines. (19) This extended version creates the opportunity to assess the quality of care of all phases of the MISSION! protocol. For each performance indicator, a target level of improvement is given. We extracted these target levels from the Euro Heart Survey and EuroAspire registry.(6,20,21) For performance indicators without prior predefined target levels, we determined target levels that we considered reasonable and achievable based on clinical experiences, prior performance data, and prevalence rates of risk factors.(6,20-23) The indicators will be calculated for both levels of eligibility, in "eligible" patients and "ideal" patients, as reported in previous studies. (19) Although not the main object, we also measure clinical end points, that is, all-cause mortality and reinfarction, at 30 days, at 6 months, and at 1 year. Analyses are only performed in those patients with an "a posteriori" diagnosis of AMI. The efficacy of the MISSION! guideline implementation program is assessed in the first 300 patients with AMI. This sample size was calculated based on Dutch performance and cardiovascular risk factors' prevalence data and the predefined targets levels of improvement for each performance indicator.(6,20-23) Sample comparisons are made using a χ^2 test for categorical variables and a paired t test for continuous variables. All P values will be 2 tailed with an α of .05. All data will be analyzed in SPSS 12.0.1 (SPSS Inc, Chicago, IL).

Performance indicators	Time points of measurement						TARGET
	<24 hours	Discharge	30 days	6 months	12 months		
Primary PCI	X						> 75%
Door-to-Balloon <90 min							
Abciximab before PCI	X						> 90%
Thrombolysis	X						> 75%
Door-to-Needle <30 min							
Aspirin	X	X	X	X	X		> 90%
Clopidogrel	X	X	X	X	X		> 90%
Beta-blocker	X	X	X	X	X		> 75%
Angiotensin-Converting enzyme inhibitor / Angiotensin-II receptor blocker	X	X	X	X	X		> 75%
Statin	X	X	X	X	X		> 90%
Bloodpressure < 140/90 mm Hg		X	X	X	X		> 90%
Total cholesterol < 4.5 mmol/L (180 mg/dl)			X	X	X		> 90%
LDL cholesterol < 2.5 mmol/L (100 mg/dl)			X	X	X		> 90%
Complete smoking cessation			X	X	X		> 50%
Moderate physical activity minimal 3 X 30 min/week			X	X	X		> 75%
BMI < 27 Kg/m ²			X	X	X		> 60%
Waist circumference women < 88 cm, men < 102 cm			X	X	X		> 60%
Participation cardiac rehabilitation program			X	X	X		> 75%

Table 1. MISSION! Performance indicators, time points of measurement and targets. PCI = Percutaneous Coronary Intervention, LDL Cholesterol = Low Density Lipoprotein Cholesterol, BMI = Body Mass Index

PRELIMINARY RESULTS

MISSION! is a multifaceted intervention. Figure 8 shows the timeline of implementation of the MISSION! protocol. The development of the MISSION! protocol started in October 2003. The first patients were enrolled in February 2004. Until now, 300

patients are included in the in-hospital and outpatient MISSION! protocol. The communication between a limited number of ambulances and the PCI center started as a pilot in September 2004. Since January 2005, all ambulances are participating.

Baseline characteristics are shown in Table 2. The MISSION! patients were more often diabetics, were less known with hyperlipidemia, and exhibited higher blood pressures at the time of presentation compared with the historical group. In the MISSION! group, 56% presented with an anterior infarction compared with 70% in the historical group ($P = .02$). No significant difference in treatment strategy could be observed (96% vs 95% primary PCI, $P = 1$) (Table 3). After implementation of the prehospital MISSION! protocol, more patients were treated within the recommended 90-minute door-to-balloon time (80% vs 63%, $P = .01$), and a significant reduction of door-to-balloon time of 16 minutes was observed (67 ± 38 minutes [$n = 106$] vs 83

Baseline characteristics	Historical group 2003 n=100	MISSION! n=300	P-value
Demographics			
Male	77 (77%)	233 (78%)	1
Age (years)	58.8 ± 11.5 (33-81)	60.1 ± 11.8 (28-84)	0.3
Non-white	8 (8%)	25 (8%)	0.9
Medical history			
Diabetes	5 (5%)	37 (12%)	0.06
Hyperlipidemia	30 (30%)	56 (19%)	0.02
Hypertension	32 (32%)	86 (29%)	0.6
Current smokers	53 (53%)	148 (49%)	0.6
Ischaemic heart disease	13 (13%)	22 (7%)	0.1
Family history	43 (43%)	129 (43%)	0.9
Clinical			
Blood pressure (mm Hg)			
Systolic	125 ± 3 (60-190)	136 ± 26 (60-233)	<0.001
Diastolic	74 ± 2 (20-125)	79 ± 17 (30-120)	0.01
Killip class at admission			
I	93 (93%)	270 (90%)	0.5
II	4 (4%)	17 (5.7%)	0.7
III or IV	3 (3%)	13 (4.3%)	0.8
Body Mass Index (kg/m ²)	27.2 ± 3 (18-38)	26.5 ± 4 (18-46)	0.3
Anterior myocardial infarction	70 (70%)	167 (56%)	0.02

Table 2.

Baseline characteristics of the historical group and the MISSION! patients

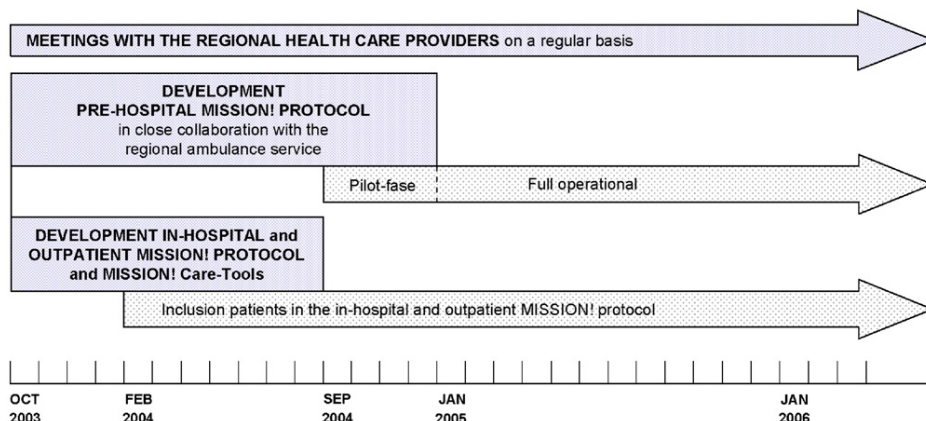


Figure 8.

MISSION! is a multifaceted intervention. The timeline of implementation of the MISSION! protocol is given.

± 33 minutes, $P < .01$). The MISSION! patients received more frequently β -blocker (83% vs 64%, $P < .001$) and ACE-inhibitor therapy (85% vs 34%, $P < .001$) within 24 hours after admission, and more patients were discharged with an ACE inhibitor (96% vs 73%, $P < .01$). MISSION! patients were discharged earlier compared with the historical group (3.9 ± 2.8 vs 7.3 ± 8.2 days, $P < .001$).

DISCUSSION

The treatment of patients with AMI has expanded and improved tremendously over the last 2 decades. However, widespread dissemination of EBM in daily practice is still lacking, and a significant number of patients with AMI is undertreated.(4-8) Prior AMI guideline implementation programs succeeded to increase the uptake of guidelines in daily care.(10,11,13) However, these programs mainly focus on in-hospital AMI care, whereas it is known that the prehospital and chronic care for patients with AMI is equally important. Therefore, we developed and implemented an all-phase integrated AMI care program, MISSION!. The aim of MISSION! is to maximize the use of EBM across practical settings and thereby to further improve the care for patients with AMI in real life.

MISSION! is a multifaceted intervention. Lessons learned from prior studies are incorporated in the MISSION! program.(24) Changing routine care into a systematic process of care is essential to improve AMI care in real life.(24) Furthermore, imple-

	Historical group 2003 n=100	MISSION! n=300	P-value
Primary PCI	96 (96%)	286 (95%)	1
Door-to-Balloon time < 90 min (%)	63	80*	0.01
Abxiximab before PCI (%)	90	91*	0.9
Medical therapy <24 h (%)			
Aspirin	97	95	0.6
Clopidogrel	98	97	0.9
Statin	98	96	0.5
Beta-blocker	64	83	<0.001
ACE-inhibitor	34	85	<0.001
Medical therapy at discharge (%)			
Aspirin	96	98	0.5
Clopidogrel	100	98	0.3
Statin	98	100	0.3
Beta-blocker	94	90	0.3
ACE-inhibitor	73	96	<0.001
Blood pressure < 140/90 mm Hg at discharge (%)	89	94	0.1
Length of stay (days)	7.3 ± 8.2 (1-44)	3.9 ± 2.8 (1-18)	<0.001
In-hospital mortality	5 (5%)	7 (2.3%)	0.3

Table 3. In-hospital performance and outcome

* % out of n=106 patients, since the pre-hospital MISSION! protocol started January 2005

mentation of guideline-orientated care tools makes this consistent and structural approach of patients with AMI possible and thereby enhances adherence of EBM. (24)

During the development and implementation of MISSION!, we encountered the following problems. First, financial resources are mandatory to build and implement such a comprehensive project as MISSION!. Therefore, we developed a clear statement of the intended improvements. We obtained financial support from the Dutch Heart Foundation and The Netherlands Society of Cardiology. Second, because MISSION! covers all phases of AMI care, an intensive collaboration among all regional healthcare providers had to be established. Before MISSION!, these settings operated as distinct independent institutions with their own policies, (financial) interests, and individual guidelines resulting in a dispersion of AMI care. The university center served as a key initiator. We organized meetings for all healthcare providers concern-

ing AMI care in our region. In addition, we enraptured leaders in each practical setting to create a MISSION! working group. These working groups are responsible for the implementation of MISSION! and monitoring of the care processes. Furthermore, these groups provide educational activities at a regular basis. Short- and long-term feedback is given and received to optimize the care process. When necessary, the protocol is adjusted and updated according to new evidence, taking into account that quality improvement is a continuous process.(25) It takes a lot of effort to establish such a project. However, taking responsibility and persuasively underscoring the need for alignment of regional AMI care are the way to accomplish patient-centered care and improve AMI care in real life.

The preliminary data of the first 300 MISSION! patients are promising. Baseline characteristics among the historical and MISSION! group differ (Table 2). However, prior studies have shown that patients with AMI who actually receive reperfusion therapy in routine care are less likely diabetic, are more known with hyperlipidemia and are more often present with an anterior AMI.(5) A shift in these variables is observed between the 2 groups. Hence, it can be concluded that MISSION! succeeded in changing the care system into a system in which more eligible patients benefit from EBM in real life than in the past. Implementation of the prehospital MISSION! protocol resulted in a significant reduction of door-to-balloon time compared with the historical group and an increase of patients treated within the recommended 90 minutes. Although the historical performance in the prescription of evidence-based drugs was good, MISSION! improved the performance in early use of β -blockers and ACE inhibitors, and discharge ACE inhibitors. It is known that prescription of medication before discharge increases the compliance during follow-up.(13) Moreover, Mukherjee et al(26) demonstrated marked survival advantage in patients with acute coronary syndromes, if a combination of evidence-based drugs were prescribed. Finally, MISSION! decreased the length of in-hospital stay in low-risk patients with AMI. In an era of increasing economic pressures in health care, the efficient use of medical resources is mandatory.

CONCLUSIONS

MISSION! adds a new dimension in the field of AMI quality improvement initiatives, by integrating all AMI care phases in 1 structured patient-centered care program. The aim of MISSION! is to improve AMI care by implementing the most recent AMI guidelines across practical settings in real life. The preliminary results of MISSION!

are promising. If this integrated approach of AMI care proves to work, MISSION! may function as a guideline implementation program beyond our region.

REFERENCES

1. Sans S, Kesteloot H, Kromhout D. The burden of cardiovascular diseases mortality in Europe. Task Force of the European Society of Cardiology on Cardiovascular Mortality and Morbidity Statistics in Europe. *Eur Heart J*. 1997;18:1231-1248.
2. Antman EM, Anbe DT, Armstrong PW et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation*. 2004;110:e82-292.
3. Van de Werf, Ardissino D, Betriu A et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J*. 2003;24:28-66.
4. Burwen DR, Galusha DH, Lewis JM et al. National and state trends in quality of care for acute myocardial infarction between 1994-1995 and 1998-1999: the medicare health care quality improvement program. *Arch Intern Med*. 2003;163:1430-1439.
5. Barron HV, Bowlby LJ, Breen T et al. Use of reperfusion therapy for acute myocardial infarction in the United States: data from the National Registry of Myocardial Infarction 2. *Circulation*. 1998;97:1150-1156.
6. Hasdai D, Behar S, Wallentin L et al. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin; the Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). *Eur Heart J*. 2002;23:1190-1201.
7. Nallamothu BK, Bates ER, Herrin J et al. Times to treatment in transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NORMI)-3/4 analysis. *Circulation*. 2005;111:761-767.
8. Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. EUROASPIRE I and II Group. European Action on Secondary Prevention by Intervention to Reduce Events. *Lancet*. 2001;357:995-1001.
9. Schiele F, Meneveau N, Seronde MF et al. Compliance with guidelines and 1-year mortality in patients with acute myocardial infarction: a prospective study. *Eur Heart J*. 2005;26:873-880.
10. Eagle KA, Montoye CK, Riba AL et al. Guideline-based standardized care is associated with substantially lower mortality in medicare patients with acute myocardial infarction: the American College of Cardiology's Guidelines Applied in Practice (GAP) Projects in Michigan. *J Am Coll Cardiol*. 2005;46:1242-1248.

11. LaBresh KA, Ellrodt AG, Gliklich R et al. Get with the guidelines for cardiovascular secondary prevention: pilot results. *Arch Intern Med.* 2004;164:203-209.
12. Ohman EM, Roe MT, Smith SC, Jr. et al. Care of non-ST-segment elevation patients: insights from the CRUSADE national quality improvement initiative. *Am Heart J.* 2004;148:S34-S39.
13. Fonarow GC, Gawlinski A, Moughrabi S et al. Improved treatment of coronary heart disease by implementation of a Cardiac Hospitalization Atherosclerosis Management Program (CHAMP). *Am J Cardiol.* 2001;87:819-822.
14. Krumholz HM, Peterson ED, Ayanian JZ et al. Report of the National Heart, Lung, and Blood Institute working group on outcomes research in cardiovascular disease. *Circulation.* 2005;111:3158-3166.
15. Canto JG, Rogers WJ, Bowlby LJ et al. The prehospital electrocardiogram in acute myocardial infarction: is its full potential being realized? National Registry of Myocardial Infarction 2 Investigators. *J Am Coll Cardiol.* 1997;29:498-505.
16. Boersma E, Maas AC, Deckers JW et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet.* 1996;348:771-775.
17. De Luca G, Suryapranata H, Ottervanger JP et al. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation.* 2004;109:1223-1225.
18. Kaul P, Newby LK, Fu Y et al. International differences in evolution of early discharge after acute myocardial infarction. *Lancet.* 2004;363:511-517.
19. Marciniak TA, Ellerbeck EF, Radford MJ et al. Improving the quality of care for Medicare patients with acute myocardial infarction: results from the Cooperative Cardiovascular Project. *JAMA.* 1998;279:1351-1357.
20. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries; principal results from EUROASPIRE II Euro Heart Survey Programme. *Eur Heart J.* 2001;22:554-572.
21. Simoons ML, Boer de M.J, Boersma E et al. Continuously improving the practice of cardiology. *Netherlands Heart Journal.* 2004;12:110-116.
22. Jager-Geurts MH, Peters RJ, van Dis SJ et al. Cardiovascular diseases in The Netherlands, 2006. Nederlandse Hartstichting, The Hague, The Netherlands, 2006.
23. Scholte op RW, de Swart E, De Bacquer D et al. Smoking behaviour in European patients with established coronary heart disease. *Eur Heart J.* 2006;27:35-41.

24. Montoye CK, Eagle KA. An organizational framework for the AMI ACC-GAP Project. *J Am Coll Cardiol*. 2005;46:1-29.
25. Roe MT, Ohman EM, Pollack CV, Jr. et al. Changing the model of care for patients with acute coronary syndromes. *Am Heart J*. 2003;146:605-612.
26. Mukherjee D, Fang J, Chetcuti S et al. Impact of combination evidence-based medical therapy on mortality in patients with acute coronary syndromes. *Circulation*. 2004;109:745-749.

LETTER TO THE EDITOR

49

Dear Sir, I read with interest the article on the MISSION! program on adherence to guidelines and evidence-based medicine in patients with an ST-elevation acute myocardial infarction by Liem et al.(1) The authors must be congratulated with this initiative aiming at improving daily clinical practice. The authors have developed a nice clinical framework for decision making in the acute phase. They provide criteria for selecting primary percutaneous coronary intervention versus thrombolytic therapy. However, they do not mention prehospital thrombolysis as a reperfusion option. If the decision to give thrombolytic therapy is taken, it is to the benefit of the patient that this treatment is started already in the ambulance even if the distance to the hospital is relatively short. Traffic jams and overwork at the emergency department of the hospital may significantly delay the start of thrombolytic treatment. Randomized trials have shown a 17% reduction in inhospital mortality if fibrinolytic therapy is started in the ambulance compared with inhospital administration.(2) Also, the recent ASSENT-3 PLUS trial showed an almost 50-minute earlier onset of treatment with ambulance administration of fibrinolytic therapy.(3) Figure 5 of the article indirectly suggests that age of >80 years is an exclusion criterion for fibrinolytic therapy. There are no data in the literature indicating that thrombolytic therapy is ineffective or particularly harmful for age of >80 years. On the contrary, the SENIOR PAMI trial results suggest that thrombolytic therapy may even be slightly better than primary percutaneous coronary intervention in the very elderly (>80 years).(4) I would suggest that the authors incorporate these remarks in their otherwise excellent protocol.

Frans van de Werf, MD, PhD

Department of Cardiology

University Hospital Gasthuisberg

Leuven, Belgium

Am Heart J 2007;153:e33

REFERENCES

1. Liem SS, van der Hoeven BL, Oemrawsingh PV, et al. MISSION!: optimization of acute and chronic care for patients with acute myocardial infarction. *Am Heart J* 2007;153:14.e1-14.e11.
2. Morrison LJ, Verbeek PR, McDonald AC, et al. Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis? *JAMA* 2000;283:2686 - 92.
3. Wallentin L, Goldstein P, Armstrong PW, et al. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. *Circulation* 2003;108:135 -442 [electronic publication 2003 Jul 7].
4. Grines C. SENIOR PAMI, a prospective randomized trial of primary angioplasty and thrombolytic therapy in elderly patients with acute myocardial infarction. Results presented at the TCT 2005 meeting, Washington DC. Available at www.theheart.org.

RESPONSE TO THE LETTER TO THE EDITOR BY VAN DE WERF

51

Dear Sir, It is with interest that we read the “Letter to the Editor” and the stimulating comments by van de Werf referring to our recently published article, which presented the study design of MISSION!, an all-phases integrated guideline implementation program for patients with an acute myocardial infarction in the region of Holland-Midden, The Netherlands.(1) Van de Werf critically remarked that we use inhospital fibrinolysis instead of prehospital fibrinolysis despite the benefit of earlier administration and the evidence of reduction of inhospital mortality when choosing the latter.(2,3) Indeed, we fully agree that prehospital fibrinolysis is preferred to inhospital fibrinolysis, looking at the available outcome data. However, we have chosen inhospital fibrinolysis for several reasons: 1) implementation of such a comprehensive protocol requires a lot of coordination and efforts; all regional health care providers across practical settings (ie, primary physicians, ambulance personnel, cardiologists, and coronary care unit nurses) are involved and collaborate closely to establish this program. Therefore, we tried to keep our MISSION! prehospital protocol as simple, manageable, and workable as possible. 2) In line with this, timely and efficient administration of prehospital fibrinolysis demands experience and practice. Although, most of our patients (>90%) are treated with primary percutaneous coronary intervention (PCI) according to our predefined criteria.(1) Hence, we primarily focused on training the ambulance personnel to perform high-quality 12-lead electrocardiogram in the field and what to do afterward to get rapid access to the appropriate center. 3) Finally, as van de Werf mentioned, benefit of prehospital administration of fibrinolysis would probably remain even if distances are relatively short as is in our region, for example, because of overwork at the emergency department. We tried to avoid the last by paging the coronary care unit of the nearest community hospital already en route to the hospital and directly transferring the fibrinolysis candidate to the coronary care unit, thereby bypassing the emergency department.

With regard to the exclusion of patients >80 years for fibrinolysis, consensus of optimal reperfusion therapy in this subpopulation, a population which exhibits high risk for mortality and severe bleeding complications, is still lacking.(3-6) This is caused by the systematic exclusion of these patients from large clinical trials, and if they are included they are often underrepresented.(4) In the beginning of MISSION!, we used >80 years as an exclusion criterion for primary PCI. However, we are confronted with elderly patients who are vital and do not have any contraindications for PCI. Therefore, >80 years per se is not an exclusion criterion anymore. With regard to fibrinolysis use, the threshold of >80 years is defined to be rather too

cautious than too aggressive. However, if an eligible patient >80 years is presented at the nearest emergency department by the ambulance, fibrinolysis indeed remains an option. MISSION! is not written and designed "as if", but demands individual assessment and tailoring, specially in a subpopulation in whom best practice is still a subject of debate. Moreover, as quality improvement is an ongoing process, clearly targeted large-scale clinical trials are needed to evaluate the relative merits of available reperfusion strategies in the elderly with ST-segment elevation myocardial infarction.(4,5,7)

Su San Liem

J. Wouter Jukema

Martin J. Schalij

Department of Cardiology

Leiden University Medical Center

Leiden, The Netherlands

Am Heart J 2007;153:e35.

REFERENCES

53

1. Liem SS, van der Hoeven BL, Oemrawsingh PV, et al. MISSION!: optimization of acute and chronic care for patients with acute myocardial infarction. *Am Heart J* 2007;153:14.e1-14.e11.
2. Morrison LJ, Verbeek PR, McDonald AC, et al. Mortality and prehospital thrombolysis for acute myocardial infarction: a metaanalysis. *JAMA* 2000;283:2686 - 92.
3. Wallentin L, Goldstein P, Armstrong PW, et al. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. *Circulation* 2003;108:135 - 42.
4. Mehta RH, Granger CB, Alexander KP, et al. Reperfusion strategies for acute myocardial infarction in the elderly: benefits and risks. *J Am Coll Cardiol* 2005;45:471 -8.
5. Sinnaeve PR, Huang Y, Bogaerts K, et al. Age, outcomes, and treatment effects of fibrinolytic and antithrombotic combinations: findings from Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT)-3 and ASSENT-3 PLUS. *Am Heart J* 2006;152:684.e1 -9.
6. Ahmed S, Antman EM, Murphy SA, et al. Poor outcomes after fibrinolytic therapy for ST-segment elevation myocardial infarction: impact of age (a meta-analysis of a decade of trials). *J Thromb Thrombolysis* 2006;21:119 - 29.
7. Roe MT, Ohman EM, Pollack CV Jr3, et al. Changing the model of care for patients with acute coronary syndromes. *Am Heart J* 2003;146:605 -12.

CHAPTER 3

Optimization of acute and long-term
care for acute myocardial infarction
patients: The Leiden MISSION! project

Su San Liem
Barend L. van der Hoeven
Sjoerd A. Mollema
Jan Bosch
Johanna G. van der Bom
Eric P. Viergever
Cees van Rees
Marianne Bootsma
Enno T. van der Velde
J. Wouter Jukema
Ernst E. van der Wall
Martin J. Schalij

ABSTRACT

Aim

We developed an all-phases comprising regional AMI guideline implementation program (MISSION!) to optimize the use of evidence-based medicine (EBM) in clinical practice.

Background

Under treatment of acute myocardial infarction (AMI) patients occurs in both the acute and the chronic phase, however most quality improvement programs focus on the index hospitalization only.

Methods

MISSION! contains a pre-hospital, in-hospital, and outpatient clinical framework for decision making and treatment of AMI patients. Using a before (n=84) and after implementation cohort of AMI patients (n=518) the impact of MISSION! was assessed using predefined performance indicators.

Results

The use of primary PCI increased (94% historical vs. 99% MISSION!; $p<0.001$); pre-hospital triage reduced median door-to-balloon time (81 min. vs. 55 min.; $p<0.001$), and more patients were treated within the guideline-recommended 90-minutes door-to-balloon time (66% vs. 79%; $p=0.04$). More patients received beta-blockers (64% vs. 84%; $p<0.001$) and ACE-inhibitors (40% vs. 87%; $p<0.001$) within 24 hours after admission, and ACE-inhibitors at discharge (70% vs. 98%; $p<0.001$). At one-year follow-up more patients used clopidogrel (72% vs. 94%; $p<0.001$), beta-blockers (81% vs. 90%; $p=0.046$), and ACE-inhibitors (66% vs. 98%; $p<0.001$). Target total cholesterol levels <4.5 mmol/L were achieved more frequently in MISSION! (58% vs. 80%; $p<0.001$).

Conclusion

An all-phases integrated AMI care program is a strong tool to enhance adherence to evidence based medicine and is likely to improve clinical outcome in AMI patients.

INTRODUCTION

Guidelines for the treatment of patients with acute myocardial infarction (AMI) have been developed to increase knowledge and to promote the use of best practice in daily AMI care.(1-3) However, widespread dissemination in clinical practice is still lacking, resulting in under treatment of significant numbers of AMI patients; both in the acute and chronic phase.(4-7)

Prior guideline implementation programs demonstrated that a more systematic approach of AMI care delivery increases adherence to evidence-based medicine (EBM).(8-11) Even more important, enhanced adherence results in improved outcome of AMI patients.(8,10,11) However, these programs mainly focused on acute cardiac care and secondary prevention strategies during the index hospitalization only. Moreover, initiatives to foster early reperfusion therapy by pre-hospital triage also seem to be effective in limiting myocardial damage and improving outcome. (12,13) Although, addressing systematically one phase of AMI care may improve outcome significantly, it can be expected that further improvement of care and outcome can be achieved by maximizing the use of evidence-based therapy during all phases of AMI care. Therefore, a regional guideline implementation AMI care program was developed to improve not only acute care, but long-term care also. (14) MISSION! contains a pre-hospital, in-hospital, and outpatient clinical framework for decision making and treatment, up to one year after the index event.(14) The design of the MISSION! protocol is unique in its kind and implicates an intensive collaboration among all healthcare providers of the Netherlands "Hollands-Midden" region.(14) The results of the first 518 patients enrolled in the MISSION! program are reported.

METHODS

Design

The MISSION! study design has been described previously.(14) In brief, MISSION! is designed according to a quasi-experimental approach. The MISSION! protocol is based on the current American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for AMI.(1-3) It contains a pre-hospital, in-hospital, and outpatient framework for decision-making and treatment, up to one year following the index event (Figure 1). To accomplish this, an intensive collaboration was established between primary care physicians, regional ambulance service,

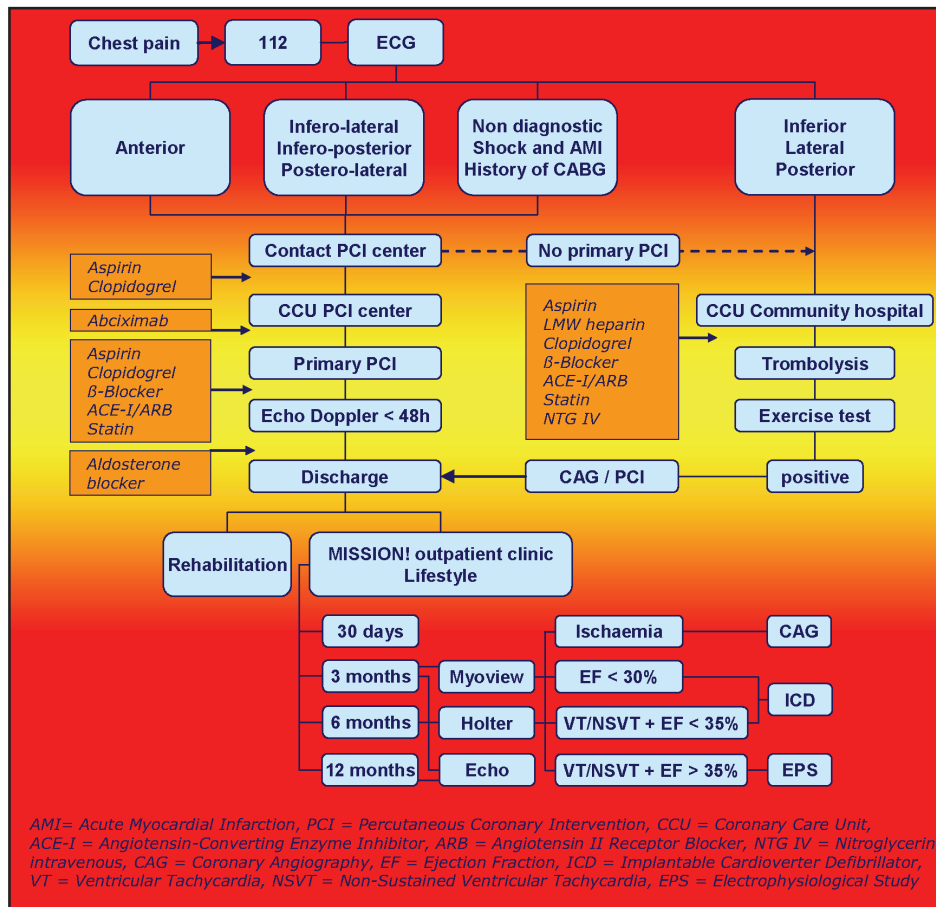


Figure 1.

The MISSION! flowchart, see text for further explanation.

four community hospitals (without percutaneous coronary intervention (PCI) facilities), three rehabilitation centers and the Leiden University Medical Center (serving as regional PCI facility).

The pre-hospital protocol focuses on reduction of treatment delay by pre-hospital triage; a twelve-lead ECG is obtained at the patient's home by trained ambulance personnel. Patients eligible for PCI (according to predefined criteria as shown in Figure 1) are transported directly to the PCI center, and the catheterization laboratory is activated while the patient is transported to the hospital. Candidates for thrombolytic therapy are transported to the Coronary Care Unit (CCU) of the nearest community hospital. If no contraindications exist, aspirin 300 mg and clopidogrel 600 mg are

administrated in the ambulance. PCI patients receive abciximab prior to PCI (0,25 mg/kg bolus followed by an infusion of 0,125 microgram/kg/min during 12 hours).

The in-hospital protocol focuses on early reperfusion therapy, and administration of evidence-based drugs (i.e. beta-blocker, ACE-inhibitor, and statin) within 24 hours of admission (Figure 1). Furthermore, patients are educated and involved in the principles of secondary prevention by a multidisciplinary team (i.e. the need for smoking cessation, healthy diet, exercise, weight control and drug compliance). Patients without complications are discharged within three days.

In the outpatient program, patients visit the outpatient clinic four times during the first year after index hospitalization. During follow-up a number of tests are obtained, medical and lifestyle targets are monitored and therapy is adjusted if necessary (Figure 1). To facilitate adherence, guideline-oriented care-tools were created for each phase of the MISSION! protocol.(14)

Both in-hospital and outpatient programs are located at the university hospital. After one year follow-up, patients are referred either to their general practitioner (asymptomatic patients with a left ventricular ejection fraction (LVEF) >45%), to a regional cardiologist (patients with symptoms or a LVEF between 35% and 45%), or to the outpatient clinic of the university hospital (LVEF <35%, after implantation of a device or in case of serious remaining symptoms).

Patients

Consecutive patients, fulfilling the predefined criteria mentioned in the pre-hospital phase of the flowchart, were included in the pre-hospital MISSION! protocol (Figure 1). In-hospital, AMI diagnosis was confirmed by the presence of an unstable coronary lesion on angiography and/or the presence of enzymatic myocardial damage, defined as an increase in cardiac biomarker(s) above normal level(s).(15) Also patients, presenting without typical ST-elevation in-hospital, but with ischemic symptoms and elevated cardiac biomarker(s), were diagnosed as AMI patients and included in the program.(15) Patients on mechanical ventilation at the time of index event admission were excluded for the pre-hospital and in-hospital MISSION! protocol. However, these patients were treated according to the outpatient MISSION! protocol after discharge. No age threshold for exclusion was defined.

For the current study, MISSION! data were compared with data of a historical reference group, i.e. a 50% random sample of patients with an acute AMI treated at the Leiden University Medical Center just before implementation of MISSION! in 2003. These patients were included by using the same criteria as in the MISSION! patients' group. Analyses were only performed in those patients with an "a

posteriori" diagnosis of AMI. Hence, of 140 historical patients studied 84 patients were included in the current study after written informed consent was obtained (approved by the institutional ethical committee). 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).(14)

Measurement of the quality of care and statistical methods

The change of quality of pre-hospital, in-hospital and outpatient care induced by the MISSION! program was assessed by using predefined performance indicators in both the historical and the MISSION! population.(14) To examine the impact of the pre-hospital triage protocol, MISSION! patients were divided in subgroups according to the timeline of implementation of the pre-hospital protocol (Figure 2). Moreover, to reveal the impact of pre-hospital triage, we sub-analyzed the data of all MISSION! patients treated since January 2005 (after implementation of the pre-hospital MISSION! protocol); patients treated according to the protocol (i.e. after pre-hospital triage directly referred to the CCU of the PCI center) and patients who were not treated according to pre-hospital protocol (i.e. first (self-) presentation at one of the (regional) emergency rooms and then referred for primary PCI). Door-to-balloon time indicates the time window between first presentation at CCU or (regional) emergency room and first balloon deployment. For assessment of the performance in the outpatient phase, we used the data of the historical group per indicator recorded/obtained within 18 months after the index event and closest to one year follow-up. These data were compared with the one-year follow-up of the MISSION! group.

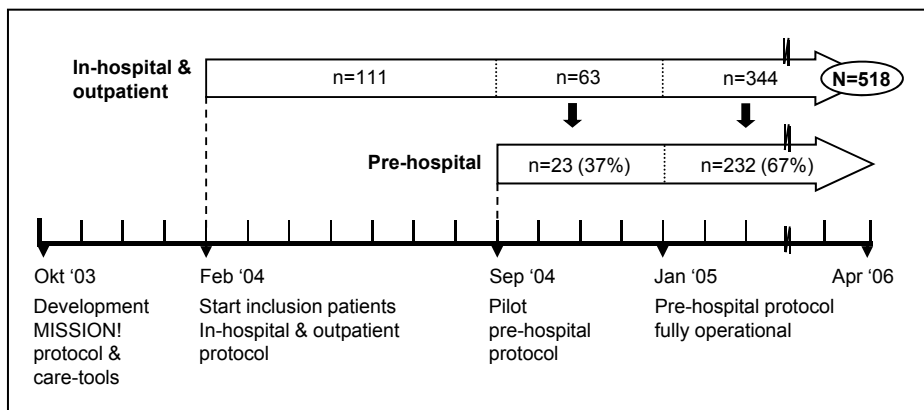


Figure 2.

Timeline of implementation of the MISSION! protocol and inclusion of the MISSION! patients.

Clinical endpoints were all cause mortality and re-infarction, at 30 days, six months and one year. Re-infarction was defined as recurrent ischemic symptoms or electrocardiographic changes, accompanied by recurrent elevation of cardiac enzyme levels.

Continuous data are presented as medians with interquartile ranges. Time values were analyzed using a Man-Whitney test. Other continues data were analyzed by 2-sample t-tests. Categorical data are summarized as proportions and were analyzed using a Fisher exact test or Chi-square test with Yates' correction, as appropriate. To assess the benefit of MISSION! in patient outcome, separate multivariate logistic regression models were used to compare mortality and re-infarction between patients treated according to the MISSION! protocol and the patients in the historical group. Based on univariate analyses and data from the literature following confounders were included: age, sex, index smoking status, diabetes, prior infarction, prior PCI, Killip class ≥ 2 , anterior infarction, and systolic blood pressure. All tests were two-sided, a p-value <0.05 was considered statistically significant. All analyses were performed using SPSS v 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The timeline of implementation of MISSION! and inclusion of patients are shown in Figure 2. A total of 518 consecutive patients were included since the start of the in-hospital and outpatient MISSION! program in 2004. Since 2005 the MISSION! pre-hospital triage protocol became fully operational, and since then 344 patients (66% of the total MISSION! population) were included of whom 232 (67%) were admitted to the hospital following the pre-hospital triage protocol. The remaining patients (n=112, 33%) were either referred to the PCI center by another hospital or were admitted after self referral. As during the study period only a small number of patients (n=18) was transported to a regional hospital to receive thrombolytic therapy they were excluded from analysis.

Baseline characteristics of the historical group (n=84) and the MISSION! group (n=518) are summarized in Table 1. In the MISSION! group fewer patients had a history of prior AMI (13% historical vs. 6% MISSION!; $p=0.02$) or PCI (7% vs. 3%; $p=0.046$). MISSION! patients presented more often with Killip class I (73% vs. 88%; $p<0.001$), and had higher systolic and diastolic blood pressures at the time of admission. More information regarding modifiable cardiovascular risk factors was recorded in MISSION! patients than in historical patients (Table 2).

	Historical group		MISSION!		MISSION! subgroups		
	n=84		n=518	p-value	Without PHT n=112	With PHT n=232	p-value*
Demographics							
Male	65/84 (77)		404/518 (78)	0.9	77/112 (69)	189/232 (82)	0.01
Age (years)	57.3 (49.8-68.7)		60.5 (51.1-69.4)	0.4	59.2 (53.7-69.0)	59.8 (51.1-68.2)	0.9
Range	38-81		22-89		22-89	28-87	
Medical history							
Diabetes	4/82 (5)		47/513 (9)	0.3	11/110 (10)	12/231 (5)	0.1
Hyperlipidemia	18/80 (23)		112/512 (22)	0.9	29/109 (27)	49/231 (21)	0.3
Hypertension	27/82 (33)		159/513 (31)	0.8	29/110 (26)	82/231 (36)	0.1
Current smokers	46/80 (58)		252/512 (49)	0.2	52/110 (47)	115/231 (50)	0.7
Family history	37/79 (47)		218/511 (43)	0.5	55/110 (50)	97/230 (42)	0.2
Previous myocardial infarction	11/83 (13)		29/516 (6)	0.02	8/111 (7)	12/232 (5)	0.5
Previous PCI	6/83 (7)		14/515 (3)	0.046	3/110 (3)	4/232 (2)	0.8
Previous CABG	2/84 (2)		6/515 (1)	0.7	2/111 (2)	2/231 (1)	0.8
Medication use at the time of admission							
Aspirin	15/82 (18)		64/515 (12)	0.2	17/111 (15)	24/231 (10)	0.2
Clopidogrel	1/83 (1)		1/515 (0.2)	0.6	0/111 (0)	0/231 (0)	1
Beta-blocker	16/82 (20)		80/514 (16)	0.4	20/111 (18)	36/230 (16)	0.6
ACE-I/ARB	9/82 (11)		64/514 (13)	0.9	10/111 (9)	33/230 (14)	0.2
Statin	9/82 (11)		74/515 (14)	0.5	20/111 (18)	30/231 (13)	0.3

Clinical							
Anterior myocardial infarction	49/84 (58)	257/518 (50)	0.2	55/112 (49)	104/232 (45)	0.5	
Blood pressure (mm Hg)							
Systolic	130 (110-140)	135 (120-150)	0.004	130 (117-150)	138 (120-150)	0.09	
Diastolic	76 (65-85)	80 (70-90)	0.002	80 (70-89)	80 (70-90)	0.03	
Heart rate (beats/minute)	70 (60-81)	71 (60-84)	0.8	71 (60-81)	73 (60-85)	0.9	
Killip class at admission							
I	60/82 (73)	454/515 (88)		96/111 (87)	214/232 (92)		
II	12/82 (15)	28/515 (5)	0.001	7/111 (6)	6/232 (3)	0.2	
III/IV	10/82 (12)	33/515 (6)		8/111 (7)	12/232 (5)		
Troponine T max (µg/L)	6.5 (2.9-11.4)	4.9 (2.2-9.8)	0.1	4.5 (1.5-8.4)	4.9 (2.4-9.3)	0.9	
Body Mass Index (kg/m ²)	25.7 (23.4-28.3)	25.8 (24.0-28.4)	0.2	25.6 (23.7-28.4)	25.7 (24.0-28.1)	0.9	
<27 Kg/m ²	40/63 (64)	314/506 (62)	0.9	61/105 (58)	149/230 (65)	0.3	
Total cholesterol (mmol/L)	5.1 (4.2-6.0)	5.4 (4.6-6.2)	0.2	5.3 (4.7-6.1)	5.3 (4.6-6.1)	1	
<4.5 mmol/L (175 mg/dL)	15/51 (29)	95/484 (20)	0.1	20/100 (20)	49/231 (21)	0.9	
LDL-cholesterol (mmol/L)	-	3.9 (3.2-4.6)	-	3.9 (3.2-4.6)	3.7 (3.1-4.6)	0.9	
<2.5 mmol/L (100 mg/dL)	-	31/422 (7)	-	8/82 (10)	16/211 (8)	0.6	

Table 1.

Baseline and clinical characteristics of the historical and MISSION! group

Values expressed as n/total (%) or median (25th-75th percentiles)

PHT, pre-hospital triage; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LDL, low-density lipoprotein

*P-value: MISSION! patients without vs. with pre-hospital triage

	In-hospital		p-value	Follow-up				p-value*
	Historical n=84	MISSION! n=518		Historical n=74	1 month n=491	6 months n=487	1 year n=484	
Body Mass Index	63 (75)	506 (98)	<0.001	56 (76)	458 (93)	460 (94)	454 (94)	<0.001
Total cholesterol†	51 (61)	484 (93)	<0.001	60 (81)	464 (95)	415 (85)	400 (83)	0.7
LDLcholesterol†	1 (1)	422 (81)	<0.001	1 (1)	426 (87)	376 (77)	370 (76)	<0.001
Smoking status	80 (95)	512 (99)	0.05	53 (72)	475 (97)	466 (96)	463 (96)	<0.001
Blood pressure	69/70 (99)†	428/444 (96)†	0.6	68 (92)	456 (93)	455 (93)	437 (90)	0.8
Rehabilitation	-	-	-	66 (89)	487 (99)	-	-	<0.001

Table 2.

Available information regarding modifiable cardiovascular risk factors and cardiac rehabilitation program participation in the historical and MISSION! group

Values expressed as n (%)

LDL, low-density lipoprotein

*P-value: Historical follow-up vs. one-year follow-up MISSION!

†Assessment <24 hours of admission

‡Assessment <24 hours before discharge to home

	Historical group 2003	Pre-hospital MISSION! protocol not operational 1/2/4-31/8/4	p-value	Pre-hospital MISSION! protocol fully operational 1/1/5-31/3/6	p-value*	MISSION! 1/1/5-31/3/6		p-value†
						Without PHT n=112 (33%)	With PHT n=232 (67%)	
Patients treated with prim PCI	75/84 (89)	107/111 (96)	0.09	313/344 (91)	0.7	90/112 (80)	223/232 (96)	<0.001
Of whom directly admitted to the PCI center	64/75 (85)	56/107 (52)	<0.001	272/313 (87)	0.7	50/90 (56)	223/223 (100)	<0.001
Symptom onset – Arrival hospital (min)	74 (50-120)	100 (60-132)	0.2	110 (80-186)	<0.001	126 (80-228)	105 (77-180)	0.09
Symptom onset - 1 st AMI ECG	79 (60-123)	106 (64-139)	0.2	89 (51-167)	0.8	138 (86-229)	76 (44-135)	<0.001
<240 minutes	57/59 (97)	94/104 (90)	0.2	247/284 (87)	0.06	54/69 (78)	193/215 (90)	0.02
<360 minutes	57/59 (97)	101/104 (97)	0.9	272/284 (96)	0.8	62/69 (90)	210/215 (98)	0.01
Door-to-Cath lab (min)	52 (40-65)	64 (50-90)	<0.001	27 (15-53)	<0.001	75 (52-100)	20 (14-30)	<0.001
Door-to-Balloon (min)	81 (65-100)	88 (72-120)	0.02	55 (41-82)	<0.001	105 (80-130)	48 (38-60)	<0.001
Door-to-Balloon <90 min	44/67 (66)	51/99 (52)	0.08	238/303 (79)	0.04	29/83 (35)	209/220 (95)	<0.001
Symptom onset-balloon (min)	160 (135-212)	194 (152-243)	0.02	180 (130-262)	0.1	255 (197-345)	162 (123-232)	<0.001

Table 3.

Pre-hospital and in-hospital time delays in patients treated with primary PCI

Values are expressed as n/total (%) and median (25th-75th percentiles)

PHT, pre-hospital triage; PCI, percutaneous coronary intervention; min, minutes; ECG, electrocardiogram

*p-value: Historical group vs. MISSION! patients treated from 1/1/5-31/3/6

†p-value: MISSION! patients without vs. with pre-hospital triage

Pre-hospital performance and time intervals

Table 3 lists the pre-hospital and in-hospital time delays of patients treated with primary PCI, according to the timeline of implementation of MISSION! (Figure 2). Due to the larger geographic area and because more patients (48% vs. 15%, $p<0.001$) were referred for PCI than before MISSION! (due to the participation of the community hospitals), pre- and in-hospital time-intervals increased after the implementation of the in-hospital and outpatient MISSION! protocol (between 1/2/2004 and 31/8/2004). Moreover, patients treated with primary PCI in MISSION! tended to present later after onset of symptoms at the hospital (74 min vs. 100 min; $p=0.2$). This resulted in a prolonged total ischemic time (i.e. symptom onset-balloon time). However, after implementation of the pre-hospital triage protocol, door-to-balloon time decreased with 26 min (81 min vs. 55 min; $p<0.001$), and 79% of the patients benefited a PCI within the guideline-recommended 90 minutes door-to-balloon time compared to 66% before implementation of the pre-hospital triage protocol ($p=0.04$). In the 67% of patients admitted directly to the PCI center after pre-hospital triage, AMI diagnosis was confirmed substantial earlier (i.e. symptom onset - 1st AMI ECG 138 min vs. 76 min; $p<0.001$). Furthermore, nearly all patients admitted after pre-hospital triage benefited primary PCI within 90 minutes door-to-balloon time (35% vs. 95%; $p<0.001$), and total ischemic time was 93 minutes shorter (255 min vs. 162 min; $p<0.001$) compared to the one third of patients not treated according to pre-hospital protocol during the same period.

In-hospital performance

In-hospital performance is presented in Table 4. No difference was seen in the proportion of patients receiving acute reperfusion therapy (95% historical vs. 92% MISSION!; $p=0.4$); though, in MISSION! PCI was more often the reperfusion strategy of choice instead of thrombolytic therapy (94% vs. 99%; $p<0.001$). MISSION! patients received more frequently beta-blockers (64% vs. 84%; $p<0.001$) and ACE-inhibitor therapy <24 hours after admission (40% vs. 87%; $p<0.001$), and more patients were discharged with ACE-inhibitors (70% vs. 98%; $p<0.001$). Furthermore, 73% of MISSION! patients were discharged within three days compared to only 23% of the historical patients ($p<0.001$).

Outpatient phase

At one-year follow-up more MISSION! patients used clopidogrel (72% historical vs. 94% MISSION!; $p<0.001$), beta-blockers (81% vs. 90%; $p<0.05$), and ACE-inhibitors (66% vs. 98%; $p<0.001$) (Table 5). The proportion of patients achieving a target blood

pressure <140/90 mmHg tended to be higher in the MISSION! group (63% vs. 70%; $p=0.3$). Despite the fact that in both groups statin use was >95%, more MISSION! patients achieved target total cholesterol levels of <4.5 mmol/L (58% vs. 80%; $p<0.001$). Before MISSION!, LDL levels were not assessed (table 2); in the MISSION! program the proportion of patients achieving target LDL levels <2.5 mmol/L increased from 7% at the time of index event up to 71% at one-year follow-up. In both groups, a similar proportion of smokers stopped smoking during follow-up

	Historical group n=84	MISSION! n=518	p-value
Primary reperfusion therapy	80/84 (95)	477/518 (92)	0.4
PCI	75/80 (94)	474/477 (99)	<0.001
Abciximab before PCI	70/75 (93)	460/474 (97)	0.2
Medication <24hrs			
Aspirin	78/78 (100)	480/508 (95)	0.07
Clopidogrel	77/78 (99)	492/508 (97)	0.6
Beta-blocker	50/78 (64)	428/508 (84)	<0.001
ACE-I/ABR	31/78 (40)	443/508 (87)	<0.001
Statin	72/78 (92)	479/508 (94)	0.3
Medication discharge*			
Aspirin	64/70 (91)	426/444 (96)	0.1
Clopidogrel	69/70 (99)	442/444 (99)	0.9
Beta-blocker	62/70 (89)	415/444 (94)	0.1
ACE-I/ABR	49/70 (70)	434/444 (98)	<0.001
Statin	70/70 (100)	442/444 (99)	1
Blood pressure at discharge*			
<140/90 mmHg	62/69 (90)	395/428 (92)	0.5
Length of stay* (days)	5 (4-7)	3 (2-4)	<0.001
Discharge ≤ 3 days	16/70 (23)	326/444 (73)	<0.001

Table 4. Performance in-hospital

Values expressed as n/total (%) or median (25th-75th percentiles)

ACE-I, angiotensin-converting enzyme inhibitor; ABR, angiotensin II receptor blocker

*In patients discharge to home

	Historical group Follow-up*	MISSION!			p-value†
		1-mth FU	6-mth FU	1-year FU	
Median follow-up (days)	377 (309-445)	42 (36-48)	201 (192-207)	398 (376-410)	0.2
Patients alive, n (actual visits, n(%))	74 (74(100))	491 (477(97))	487 (468(96))	484 (478(99))	-
Medication					
Aspirin	61/73 (84)	444/477 (93)	435/466 (93)	433/475 (91)	0.06
Clopidogrel	48/67 (72)	470/477 (99)	459/466 (98)	446/475 (94)	<0.001
Beta-blocker	60/74 (81)	454/477 (95)	423/466 (91)	427/475 (90)	0.046
ACE-I/ARB	49/74 (66)	466/477 (98)	457/466 (98)	465/475 (98)	<0.001
Statin	72/74 (97)	470/477 (99)	460/466 (99)	462/475 (97)	1
Blood pressure <140/90 mmHg	43/68 (63)	309/456 (68)	303/455 (67)	307/437 (70)	0.3
Body Mass Index <27 Kg/m ²	29/56 (52)	297/458 (65)	310/460 (67)	295/454 (65)	0.06
Total cholesterol <4.5 mmol/L	35/60 (58)	375/464 (81)	330/415 (80)	318/400 (80)	<0.001
LDL-cholesterol <2.5 mmol/L	-	286/426 (67)	249/376 (66)	262/370 (71)	-
Smokers stopped	24/37 (65)	166/233 (71)	152/234 (65)	146/228 (64)	1
Rehabilitation	62/66 (94)	422/487 (87)	-	-	0.1

Table 5. Performance in the outpatient phase

Values expressed as n/total (%) or median (25th-75th percentiles)

mth, month; FU, follow-up; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LDL, low-density protein

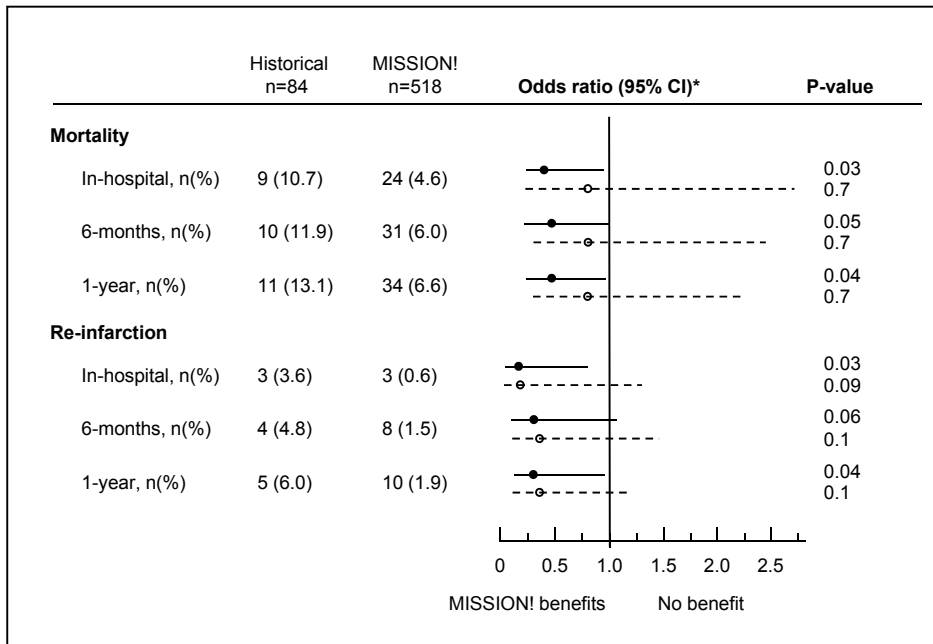
*Follow-up derived from the available historical data closest to 1-year

†P-value assessed out of the historical follow-up data and the 1-year follow-up of MISSION!

(65% vs. 64%; $p=1$); however of the index smokers smoking status during follow-up was unknown in 18% of the historical group compared to only 2% in the MISSION! group ($p<0.001$).

Clinical outcome

In-hospital mortality was 10.7% in the historical versus 4.6% in the MISSION! group ($p=0.03$), 6-month mortality was 11.9% in the historical versus 6.0% in the MISSION! group ($p=0.05$), and at one-year follow-up 13.1% in the historical and 6.6% in

**Figure 3.**

Clinical outcomes in-hospital, at 6 months and one-year.

CI = Confidence interval *Solid lines: unadjusted odds ratio (95% CI); dashed lines: adjusted odds ratio (95% CI), Mortality adjusted for sex, age, diabetes, index smoking status, prior AMI, prior PCI, Killip class ≥ 2 , systolic blood pressure, anterior infarction; Re-infarction adjusted for: sex, age, diabetes, index smoking status, prior AMI, prior PCI, Killip class ≥ 2

the MISSION! group ($p=0.04$) (Figure 3). Moreover, re-infarction occurred less often in the MISSION! group during the in-hospital phase (3.6% historical vs. 0.6% MISSION!; $p=0.03$) and at one-year follow-up (6.0% vs. 1.9%; $p=0.04$). After multivariate adjustment a clear trend remained, with an odds ratio of 0.82 for one-year mortality and 0.35 for one-year re-infarction in favor of MISSION!.

DISCUSSION

Implementation of an all-phases comprising AMI care program resulted in: 1) shortening of treatment delays in the acute phase, 2) increased and improved long-term utilization of evidence-based medication, 3) improved control of cholesterol and blood pressure levels.

Pre-hospital

In line with previous studies, implementation of the pre-hospital MISSION! triage protocol resulted in a significant reduction of treatment delay compared to those not following the pre-hospital triage protocol.(13) The median door-to-balloon time of 55 minutes is shorter than the 70 minutes reported by the second European Heart Survey, and also considerable shorter than 108 minutes reported in the large NRM (National Registry of Myocardial Infarction) study.(5,6) In the last study 37% were treated <90 minutes door-to-balloon window (6); whereas for the total MISSION! population this was 79%, and among those referred by pre-hospital triage even 95%, stressing the importance of a pre-hospital triage protocol. As a larger geographic area was incorporated in MISSION! and due to increased patient delay (reflected by symptom onset-balloon time) total ischemic time (i.e. symptom onset-balloon) was not shortened. Of importance, McNamara et al. showed that not symptom onset-balloon time, but door-to-balloon time is strongly associated with mortality regardless of time from symptom onset to presentation.(16) Of the six pre- and in-hospital strategies to fasten door-to-balloon time defined by Bradley et al., four were applied in MISSION!: 1) the catheterization laboratory is activated while the patient is still en route, 2) a maximum of two calls are needed to activate the catheterization team (i.e. one to the interventional cardiologist and one to the laboratory staff), 3) the interval between page and arrival of catheterization staff is less than 20 minutes, 4) real time feedback.(17) The door-to-balloon time of 55 minutes achieved in MISSION! was shorter than the 79 minutes reported by Bradley.(17) The effectiveness of the pre-hospital MISSION! program is explained by the following factors: 1) the development and use of a clear and simple-to-use pre-hospital flowchart, uniform for the whole region, and for all health care providers involved in acute AMI care(14); 2) the training of all ambulance employees and CCU nurses of the PCI center involved; and 3) performance reviews on a regular basis. Further improvement can be achieved by referring the patient directly to the catheterization laboratory which may shorten the door-to-balloon time with another 20 minutes. The time delay caused by the patient self (i.e. not seeking prompt medical help after onset symptoms), and the 33% of MISSION! patients not "caught" by pre-hospital triage (especially women), warrants that all efforts are addressed to increase public awareness.

In-hospital

The proportion of patients receiving primary PCI was similar in both groups. In patients presenting with ST-elevation the rate of primary PCI was 96%, which is higher compared to routine care worldwide (i.e. reperfusion rates vary between 64% to

71%).(5,6) In a recent study reporting AMI care in Vienna Austria, it was shown that by establishing a cooperative network between ambulance services and cardiology departments, the use of reperfusion therapy in the acute phase increased to 87%. (12)

Although the historical performance in the prescription of evidence-based drugs was reasonable compared to other studies, implementation of the MISSION! program increased the use of beta-blockers and ACE inhibitors. The use of these drugs at the time of discharge was higher compared to prior observations and quality improvement programs.(4,5,7,18) MISSION! resulted in a decreased length of stay in low-risk AMI patient, important in an era of increasing economic pressure. Moreover, in selected patients early discharge appeared to be safe and effective.

Outpatient

MISSION! succeeded to increase the use of medication during follow-up. The use and continuation of a combination of evidence-based drugs is associated with marked survival advantage.(18,19) Discontinuation of medical therapy occurs mainly in the first month after hospital discharge.(18) Hence, short term medical contact followed by systematic outpatient visits after discharge, as in the MISSION! program, seems to play an important role in increasing compliance by monitoring and emphasizing the need for using the prescribed drugs.(18) Statin use was already high in the historical group, yet 80% of the MISSION! patients achieved target lipid compared to only 58% in the historical group. The atherosclerosis management program CHAMP succeeded to increase the proportion of patients achieving the LDL target level from 6% to 58%.(8) Therefore therapy adjustment during follow-up is essential to achieve medical goals.

The proportion of patients achieving a target blood pressure level of <140/90 mmHg increased and blood pressure control at one-year (70%) was better than observed in EuroAspire II (54%).(20) We didn't achieve an increase in the proportion of stopped smokers in the outpatient phase (64%), though performance is better than described in EuroAspire II (52%).(21) Moreover, 87% of MISSION! patients followed a cardiac rehabilitation programs fostering the possibility for maximal psychosocial reintegration of the AMI patient.(1,2)

Clinical outcome

Although not primarily designed to show differences in clinical outcome, mortality and re-infarction rates declined during the first year following the index infarct compared to the results obtained in the historical group. Although baseline characteristics were

different in the historical and MISSION! group after adjustment for several possible confounders a clear trend of clinical improvement remained which is consistent with prior quality improvement initiatives and studies.(8,10,11,19)

LIMITATIONS

Some limitations of the study have to be addressed. MISSION! is a non-randomized cohort study reflecting daily clinical practice, as randomization between evidence-based guideline medicine and standard clinical care was considered unethical.(8-11) Second, MISSION! is limited to the region "Hollands-Midden" in the Netherlands. Healthcare systems differ between countries and even between regions in one country. However MISSION! may serve as a template of an all-phases integrated AMI care program.

CONCLUSION

An all-phases integrated AMI care program is a strong tool to enhance adherence to evidence based medicine and is likely to improve clinical outcome in AMI patients.

REFERENCES

1. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2004;44(3):E1-E211.
2. Van de Werf F, Ardissino D, Betriu A, et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J*. 2003;24:28-66.
3. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J*. 2003;24:1601-10.
4. Carruthers KF, Dabbous OH, Flather MD, et al. Contemporary management of acute coronary syndromes: does the practice match the evidence? The global registry of acute coronary events (GRACE). *Heart*. 2005;91:290-8.
5. Mandelzweig L, Battler A, Boyko V, et al. The second Euro Heart Survey on acute coronary syndromes: Characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. *Eur Heart J*. 2006;27:2285-93.
6. McNamara RL, Herrin J, Bradley EH, et al. Hospital improvement in time to reperfusion in patients with acute myocardial infarction, 1999 to 2002. *J Am Coll Cardiol*. 2006;47:45-51.
7. Roe MT, Parsons LS, Pollack CV, et al. Quality of care by classification of myocardial infarction: treatment patterns for ST-segment elevation vs non-ST-segment elevation myocardial infarction. *Arch Intern Med*. 2005;165:1630-6.
8. Fonarow GC, Gawlinski A, Moughrabi S, Tillisch JH. Improved treatment of coronary heart disease by implementation of a Cardiac Hospitalization Atherosclerosis Management Program (CHAMP). *Am J Cardiol*. 2001;87:819-22.
9. LaBresh KA, Ellrodt AG, Gliklich R, Liljestrand J, Peto R. Get with the guidelines for cardiovascular secondary prevention: pilot results. *Arch Intern Med*. 2004;164:203-9.
10. Marciniak TA, Ellerbeck EF, Radford MJ, et al. Improving the quality of care for Medicare patients with acute myocardial infarction: results from the Cooperative Cardiovascular Project. *JAMA*. 1998;279:1351-7.
11. Eagle KA, Montoye CK, Riba AL, et al. Guideline-based standardized care is associated with substantially lower mortality in medicare patients with acute myocardial infarction: the

American College of Cardiology's Guidelines Applied in Practice (GAP) Projects in Michigan. *J Am Coll Cardiol.* 2005;46:1242-8.

12. Kalla K, Christ G, Karnik R, et al. Implementation of guidelines improves the standard of care: the Viennese registry on reperfusion strategies in ST-elevation myocardial infarction (Vienna STEMI registry). *Circulation.* 2006;113:2398-2405.
13. Ortolani P, Marzocchi A, Marrozzini C, et al. Clinical impact of direct referral to primary percutaneous coronary intervention following pre-hospital diagnosis of ST-elevation myocardial infarction. *Eur Heart J.* 2006;27:1550-7.
14. Liem SS, van der Hoeven BL, Oemrawsingh PV, et al. MISSION!: optimization of acute and chronic care for patients with acute myocardial infarction. *Am Heart J.* 2007;153:14.e1-11.
15. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol.* 2000;36:959-69.
16. McNamara RL, Wang Y, Herrin J, et al. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol.* 2006;47:2180-6.
17. Bradley EH, Herrin J, Wang Y, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. *N Engl J Med.* 2006;355:2308-20.
18. Ho PM, Spertus JA, Masoudi FA, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. *Arch Intern Med.* 2006;166:1842-7.
19. Mukherjee D, Fang J, Chetcuti S, Moscucci M, Kline-Rogers E, Eagle KA. Impact of combination evidence-based medical therapy on mortality in patients with acute coronary syndromes. *Circulation.* 2004;109:745-9.
20. EUROASPIRE II study group. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries; principal results from EUROASPIRE II Euro Heart Survey Programme. *Eur Heart J.* 2001;22:554-72.
21. Scholte op Reimer W, de Swart E, De Bacquer D, Pyorala K, Keil U, Heidrich J, Deckers JW, Kotseva K, Wood D, Boersma E. Smoking behaviour in European patients with established coronary heart disease. *Eur Heart J.* 2006;27:35-41.

CHAPTER 4

Does left ventricular dyssynchrony
immediately after acute myocardial infarction
result in left ventricular dilatation?

Sjoerd A. Mollema
Gabe B. Bleeker
Su San Liem
Eric Boersma
Bas L. van der Hoeven
Eduard R. Holman
Ernst E. van der Wall
Martin J. Schalij
Jeroen J. Bax

ABSTRACT

Background

Reverse remodeling of the left ventricle (LV) is one of the advantageous mechanisms of cardiac resynchronization therapy (CRT). Substantial LV dyssynchrony seems mandatory for echocardiographic response to CRT. Conversely, LV dyssynchrony early after acute myocardial infarction may result in LV dilatation during follow-up.

Objective

The purpose of this study was to evaluate the relation between LV dyssynchrony early after acute myocardial infarction and the occurrence of long-term LV dilatation.

Methods

A total of 124 consecutive patients presenting with acute myocardial infarction who underwent primary percutaneous coronary intervention were included. Within 48 hours of intervention, 2D echocardiography was performed to assess LV volumes, LV ejection fraction (LVEF) and wall motion score index (WMSI). LV dyssynchrony was quantified using color-coded tissue Doppler imaging (TDI). At 6 months follow-up, LV volumes and LVEF were reassessed.

Results

Patients with substantial LV dyssynchrony (≥ 65 ms) at baseline (18%) had comparable baseline characteristics to patients without substantial LV dyssynchrony (82%), except for a higher prevalence of multi-vessel coronary artery disease ($p = .019$), higher WMSI ($p = .042$), and higher peak levels of creatine phosphokinase ($p = .021$). During 6 months follow-up, 91% of the patients with substantial LV dyssynchrony at baseline developed LV remodeling, compared to 2% in the patients without substantial LV dyssynchrony. LV dyssynchrony at baseline was strongly related to the extent of long-term LV dilatation at 6 months follow-up.

Conclusion

Most patients with substantial LV dyssynchrony immediately after acute myocardial infarction develop LV dilatation during 6 months follow-up.

INTRODUCTION

Nowadays, a substantial proportion of patients with moderate to severe ischemic heart failure, despite optimal medical therapy, is treated with cardiac resynchronization therapy (CRT).(1-5) The presence of left ventricular (LV) dyssynchrony seems to be of considerable importance for response and prognosis after CRT.(6-8) Importantly, reverse remodeling of the left ventricle more frequently occurs in those patients with substantial LV dyssynchrony at baseline. In addition, patients with LV reverse remodeling after CRT have a better prognosis than those without LV reverse remodeling.(6-8)

Presumably, LV dyssynchrony after acute myocardial infarction results in LV dilatation. However, no study thus far has systematically examined this potential relationship. Tissue Doppler imaging (TDI) is established for the assessment of myocardial velocities and the detection of LV dyssynchrony, and has been used in patients who had a myocardial infarction.(9) This study evaluates the relation between LV dyssynchrony at baseline, assessed with TDI, and the occurrence of long-term LV dilatation in patients following acute myocardial infarction.

METHODS

Patients

A total of 135 consecutive patients, admitted with an acute myocardial infarction, were screened. Patients who were treated conservatively ($n = 4$) or who underwent thrombolysis ($n = 3$) or coronary artery bypass grafting ($n = 1$) in the acute setting were excluded from the study in order to obtain a homogenous study group. Three patients died during follow-up and therefore did not have the follow-up assessment. These patients were excluded from the study. The final study population comprised 124 patients who all underwent primary percutaneous coronary intervention.

Protocol

Two-dimensional echocardiography was performed within 48 hours of admission (baseline) and at 6 months follow-up. At baseline, conventional echocardiography was used to assess LV volumes, LV ejection fraction (LVEF) and wall motion score index (WMSI). LV dyssynchrony was quantified using color-coded tissue Doppler imaging (TDI). LV volumes and LVEF were reassessed at 6 months follow-up.(10)

The study was approved by the institutional ethics committee, and informed consent was obtained from all patients.

Echocardiography

Patients were imaged in the left lateral decubitus position using a commercially available system (Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin, USA). Standard images were obtained using a 3.5-MHz transducer, at a depth of 16 cm in the parasternal (long- and short-axis) and apical (2- and 4-chamber) views. Standard 2-dimensional and color Doppler data, triggered to the QRS complex, were saved in cine-loop format. LV volumes (end-systolic and end-diastolic) and LVEF were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique.⁽¹¹⁾ LV remodeling at 6 months follow-up was defined as an increase in LV end-systolic volume (LVESV) $\geq 15\%$.^(6,12,13)

The LV was divided into 16 segments. A semiquantitative scoring system (1, normal; 2, hypokinesia; 3, akinesia; 4, dyskinesia) was used to analyze each study. Global WMSI was calculated by the standard formula: sum of the segment scores divided by the number of segments scored.^(14,15)

All echocardiographic measurements were obtained by two independent observers without knowledge of the clinical status of the patient. Inter- and intra-observer agreement for assessment of LV volumes were 90% and 93% for LVESV, and 92% and 93% for LVEDV, respectively.

Tissue Doppler imaging

Color Doppler frame rates were >80 and pulse repetition frequencies were between 500 Hz and 1 KHz, resulting in aliasing velocities between 16 and 32 cm/s. TDI parameters were measured from color images of three consecutive heart beats by offline analysis. Data were analyzed using commercial software (Echopac 6.01, General Electric-Vingmed). To determine LV dyssynchrony, the sample volume (6 x 6 mm) was placed in the LV basal portions of the anterior, inferior, septal and lateral walls (using the two- and four-chamber views) and, per region, the time interval between the onset of the QRS complex and the peak systolic velocity was obtained. LV dyssynchrony was defined as the maximum delay between peak systolic velocities among these four LV regions.⁽⁶⁾ Substantial LV dyssynchrony was defined as LV dyssynchrony ≥ 65 ms.⁽⁶⁾ Inter- and intra-observer agreement for assessment of LV dyssynchrony were reported previously (90% and 96%, respectively).⁽¹⁶⁾

Statistical analysis

Most continuous variables were not normally distributed (as evaluated by Kolmogorov-Smirnov tests). For reasons of uniformity, summary statistics for all continuous variables are therefore presented as medians together with the 25th and 75th percentiles. Categorical data are summarized as frequencies and percentages.

Differences in baseline characteristics between patients who demonstrated substantial LV dyssynchrony versus those who did not were analyzed using Wilcoxon-Mann-Whitney tests, Chi-square tests with Yates' correction or Fisher's exact tests, as appropriate. Linear regression analysis was used to evaluate the relations between baseline variables and the change in LVESV during follow-up. All statistical tests were two-sided. Unless otherwise specified, a p value $< .05$ was considered statistically significant.

RESULTS

Baseline data of the study population

In the present study 124 patients were included (99 men and 25 women, median age 61 (53, 71) years). During primary percutaneous coronary intervention TIMI-III flow was achieved in all but 6 (5%) patients. Multi-vessel disease was observed in 67 (54%) patients. Median creatine phosphokinase (CPK) levels were 2469 (1023, 3702) U/L. Median WMSI was 1.50 (1.31, 1.63). Seven (6%) patients had a previous myocardial infarction. At baseline, median LVESV and LVEDV were 65 (54, 83) ml and 129 (106, 151) ml, respectively, whereas the median LVEF was 48% (42%, 53%). Median LV dyssynchrony as measured by TDI was 10 (0, 40) ms.

Six months follow-up

In the entire patient population, the mean LVESV remained unchanged at 6 months follow-up (64 (51, 84) ml versus 65 (54, 83) ml at baseline, $p = .11$). LVEDV increased significantly during follow-up (130 (110, 155) ml versus 129 (106, 151) ml at baseline, $p = .007$). LVEF remained unchanged (49% (43%, 56%) versus 48 (42, 53) % at baseline, $p = .31$).

LV dilatation in patients with baseline LV dyssynchrony

Patients were subsequently divided into patients with substantial LV dyssynchrony ($n = 22$, 18%) and without LV dyssynchrony ($n = 102$, 82%) at baseline. Patients in the group with substantial LV dyssynchrony had a median dyssynchrony of 85 (80,

100) ms, whereas median dyssynchrony among those without substantial LV dyssynchrony was 10 (0, 20) ms ($p < .0001$, by definition). Clinical and echocardiographic patient characteristics of the 2 groups are summarized in Table 1 and 2, respectively. Various baseline variables differed significantly between patients with and without substantial LV dyssynchrony at baseline. Patients with LV dyssynchrony more often had multi-vessel coronary artery disease. WMSI (as a reflector for infarct size) was higher among those patients with LV dyssynchrony. In addition, peak levels of CPK (reflecting enzymatic infarct size) were higher in the patients with LV dyssynchrony.

Baseline LV volumes and LVEF were similar between patients with and without LV dyssynchrony at baseline. However, at 6 months follow-up LVESV and LVEDV were

	All patients (n = 124)	No LV Dyssynchrony (n = 102)	LV Dyssynchrony (n = 22)	p Value*
Age (yrs)	61 (53, 71)	61 (53, 71)	64 (56, 71)	0.50
Gender (M/F, %)	99/25 (80/20)	81/21 (79/21)	18/4 (82/18)	1.00
Previous MI (%)	7 (6)	7 (7)	0	0.35
QRS duration baseline (ms)	94 (88, 104)	94 (90, 104)	95 (82, 106)	0.78
Wide QRS (≥ 120 ms, %)	6 (5)	5 (5)	1 (5)	1.00
Risk factors for CAD				
Diabetes (%)	11 (9)	10 (10)	1 (5)	0.69
Hypertension (%)	37 (30)	29 (28)	8 (36)	0.54
Hyperlipidemia (%)	25 (20)	22 (22)	3 (14)	0.56
Smoking (%)	59 (48)	50 (49)	9 (41)	0.48
Peak CPK (U/L)	2469 (1063, 3681)	2167 (946, 3395)	3703 (1584, 5616)	0.021
Multi-vessel disease (%)	67 (54)	50 (49)	17 (77)	0.019
Medication at 6 months follow-up				
Beta-blockers (%)	112 (90)	92 (90)	20 (91)	0.52
ACE-inhibitors/ ARBs (%)	122 (98)	100 (98)	22 (100)	0.11
Anti-coagulants (%)	124 (100)	102 (100)	22 (100)	1.00
Statins (%)	122 (98)	100 (98)	22 (100)	0.73

Table 1.

Baseline clinical characteristics of patients without versus with left ventricular dyssynchrony. ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CAD: coronary artery disease; CPK: creatine phosphokinase; MI: myocardial infarction.

* Patients with versus without LV dyssynchrony

	All patients (n = 124)	No LV Dyssynchrony (n = 102)	LV Dyssynchrony (n = 22)	p Value*
Baseline				
LV dyssynchrony (ms)	10 (0, 40)	10 (0, 20)	85 (80, 100)	< 0.0001
WMSI	1.50 (1.31, 1.63)	1.50 (1.25, 1.63)	1.56 (1.38, 1.69)	0.042
LVESV (ml)	65 (54, 82)	65 (52, 79)	70 (54, 88)	0.55
LVEDV (ml)	129 (106, 151)	129 (108, 149)	131 (101, 158)	0.82
LVEF (%)	48 (42, 53)	48 (42, 53)	47 (43, 51)	0.88
6-Months follow-up				
LVESV (ml)	64 (51, 83)	62 (50, 78)	96 (64, 122)	< 0.001
LVEDV (ml)	130 (110, 155)	129 (109, 148)	147 (115, 184)	0.048
LVEF (%)	49 (43, 56)	50 (44, 56)	41 (35, 44)	< 0.0001

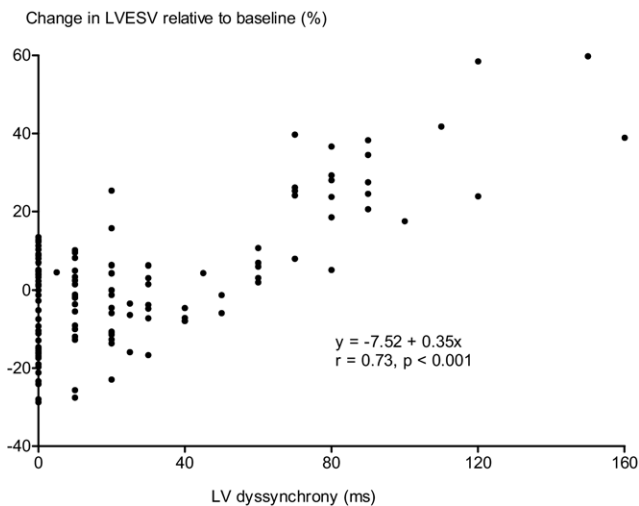
Table 2.

Echocardiographic data of patients without versus with left ventricular dyssynchrony.

Data in parentheses are 25th and 75th percentiles.

LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; WMSI: wall motion score index.

* Patients with versus without LV dyssynchrony

**Figure 1.**

LV dyssynchrony acutely after MI was demonstrated to be strongly related to change in LVESV during 6 months follow-up.

significantly larger in the patients with LV dyssynchrony. Moreover, the LVEF was significantly lower in the patients with LV dyssynchrony. Importantly, LV remodeling at 6 months follow-up was demonstrated in 91% of patients with substantial LV dyssynchrony, whereas only 2% of patients without substantial LV dyssynchrony had LV remodeling.

Baseline variables and relation with LV dilatation

No significant relation was found between WMSI and the extent of LV dilatation at 6 months follow-up. A modest relation was noted between the peak plasma levels of CPK ($y = -5.25 + 0.003x$, $n = 124$, $r = 0.34$, $p < .001$) and the extent of LV dilatation at 6 months follow-up. A strong relation was observed between the severity of LV dyssynchrony and the extent of LV dilatation ($y = -7.52 + 0.35x$, $n = 124$, $r = 0.73$, $p < .0001$; Figure 1).

DISCUSSION

The main findings of the present study can be summarized as follows: 1) substantial LV dyssynchrony was present in 18% of patients early after acute myocardial infarction treated with primary percutaneous coronary intervention; 2) patients with substantial LV dyssynchrony more often had multi-vessel coronary artery disease, higher WMSI and higher peak levels of CPK at baseline; 3) 91% of patients with substantial LV dyssynchrony developed long-term LV remodeling; and 4) LV dyssynchrony at baseline was strongly related to the extent of long-term LV dilatation.

In the present study, 18% of the patients demonstrated substantial LV dyssynchrony early after myocardial infarction followed by successful primary percutaneous coronary intervention (TIMI-III flow was achieved in all but 6 patients during the procedure). Zhang et al. investigated 47 patients after first acute myocardial infarction.⁽¹⁷⁾ The majority of patients were treated with thrombolytic therapy. The authors observed that almost 70% of patients had LV dyssynchrony. This large difference in prevalence can (partially) be explained by differences in mean infarct size between both studies, as infarct size correlates with LV dyssynchrony.⁽¹⁷⁾ However, no adequate comparison regarding infarct size can be made due to differences in assessment of infarct size (contrast-enhanced magnetic resonance imaging versus echocardiographic wall motion score index in the current study). Fahmy et al. demonstrated LV dyssynchrony in 77.5% of 155 patients.⁽¹⁸⁾ Mean WMSI, as a reflector

of infarct size, was higher in their study population compared to the population in the current study (1.78 versus 1.47, respectively).

In addition to differences in infarct size, the definition of LV dyssynchrony may be of importance to explain the difference in prevalence of LV dyssynchrony after myocardial infarction. Both Zhang et al. and Fahmy et al. used the assessment of the standard deviation of time to peak systolic velocity (Ts-SD) as expression for LV dyssynchrony, though different cut-off values based on measurements in control patients were used (Ts-SD >32 ms versus >22.14 ms, respectively).(17,18) In the present study, LV dyssynchrony was defined as the maximum delay between peak systolic velocities among the anterior, inferior, septal and lateral walls and a predefined cutoff of ≥ 65 ms was used.(6) Of note, assessment of LV dyssynchrony using TDI may become jeopardized when basal segments are akinetic, although assessment of LV dyssynchrony was feasible in all patients in the present study.

Both Zhang et al. and Fahmy et al. described the significant impact of infarct size on LV dyssynchrony.(17,18) They demonstrated that the degree of LV dyssynchrony is mainly determined by the infarct size. In the present study, patients with substantial LV dyssynchrony more often had multi-vessel coronary artery disease, higher WMSI (reflector for infarct size) and higher peak levels of CPK (reflector for enzymatic infarct size) at baseline. These observations seem in concordance with the theory that infarct size strongly influences the extent of LV dyssynchrony.

The relation between LV dyssynchrony early after myocardial infarction and the occurrence of LV dilatation still remains unclear. No study thus far has systematically examined this presumed relationship. The clinical importance of LV dilatation was emphasized by White et al., who demonstrated that patients who died during follow-up after myocardial infarction had significantly higher LV volumes and lower LV ejection fractions than survivors.(12) Furthermore, the authors indicated LVESV as the primary predictor of survival after myocardial infarction. As a consequence, early identification of patients with substantial LV dilatation after acute myocardial infarction is of vital importance.

Observations from patients treated with CRT have demonstrated that patients with substantial LV dyssynchrony before implantation more often respond to CRT than patients without substantial LV dyssynchrony.(6-8) Patients who did respond to CRT demonstrated an increase in LV ejection fraction and a decrease in LV volumes, a process referred to as reverse remodeling. Therefore, a relation between LV dyssynchrony and LV dilatation after myocardial infarction is presumed.

In the present study, LV dyssynchrony at baseline was strongly related to the extent of long-term LV dilatation. More than 90% of the patients with substantial LV dyssyn-

chrony at baseline developed long-term LV remodeling during 6 months follow-up. In contrast, no significant relation was found between WMSI, which reflects infarct size, and LV dilatation. Only a modest relation was noted between peak CPK level, which reflects enzymatic infarct size, and LV dilatation.

Still, at this stage it remains uncertain what mainly determines / predicts LV dilatation; the current data suggest that LV dyssynchrony plays a role, but a causal relation cannot be concluded yet and further studies are needed.

CONCLUSION

LV dyssynchrony after acute myocardial infarction is strongly related to LV dilatation and most patients with substantial LV dyssynchrony immediately after acute myocardial infarction develop LV dilatation during 6 months follow-up. Further large studies are needed to confirm these findings.

REFERENCES

1. Abraham WT, Hayes DL: Cardiac resynchronization therapy for heart failure. *Circulation*. 2003;108:2596-603.
2. Auricchio A, Abraham WT: Cardiac resynchronization therapy: current state of the art: cost versus benefit. *Circulation*. 2004;109:300-7.
3. Jarcho JA: Resynchronizing ventricular contraction in heart failure. *N Engl J Med*. 2005;352:1594-7.
4. Leclercq C, Kass DA: Retiming the failing heart: principles and current clinical status of cardiac resynchronization. *J Am Coll Cardiol*. 2002;39:194-201.
5. Leclercq C, Hare JM: Ventricular resynchronization: current state of the art. *Circulation*. 2004;109:296-9.
6. Bax JJ, Bleeker GB, Marwick TH, Molhoek SG, Boersma E, Steendijk P, van der Wall EE, Schalij MJ: Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol*. 2004;44:1834-40.
7. Penicka M, Bartunek J, De Bruyne B, Vanderheyden M, Goethals M, De Zutter M, Brugada P, Geelen P: Improvement of left ventricular function after cardiac resynchronization therapy is predicted by tissue Doppler imaging echocardiography. *Circulation*. 2004;109:978-83.
8. Sogaard P, Egeblad H, Kim WY, Jensen HK, Pedersen AK, Kristensen BO, Mortensen PT: Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. *J Am Coll Cardiol*. 2002;40:723-30.
9. Fukuda K, Oki T, Tabata T, Iuchi A, Ito S: Regional left ventricular wall motion abnormalities in myocardial infarction and mitral annular descent velocities studied with pulsed tissue Doppler imaging. *J Am Soc Echocardiogr*. 1998;11:841-8.
10. Liem SS, van der Hoeven BL, Oemrawsingh PV, Bax JJ, van der Bom JG, Bosch J, Viergever EP, van Rees C, Padmos I, Sedney MI, van Exel HJ, Verwey HF, Atsma DE, van der Velde ET, Jukema JW, van der Wall EE, Schalij MJ: MISSION!: optimization of acute and chronic care for patients with acute myocardial infarction. *Am Heart J*. 2007;153:14-1.
11. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I, .: Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr*. 1989;2:358-67.

12. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ: Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation*. 1987;76:44-51.
13. Yu CM, Fung JW, Chan CK, Chan YS, Zhang Q, Lin H, Yip GW, Kum LC, Kong SL, Zhang Y, Sanderson JE: Comparison of efficacy of reverse remodeling and clinical improvement for relatively narrow and wide QRS complexes after cardiac resynchronization therapy for heart failure. *J Cardiovasc Electrophysiol*. 2004;15:1058-65.
14. Broderick TM, Bourdillon PD, Ryan T, Feigenbaum H, Dillon JC, Armstrong WF: Comparison of regional and global left ventricular function by serial echocardiograms after reperfusion in acute myocardial infarction. *J Am Soc Echocardiogr*. 1989;2:315-23.
15. Sawada SG, Segar DS, Ryan T, Brown SE, Dohan AM, Williams R, Fineberg NS, Armstrong WF, Feigenbaum H: Echocardiographic detection of coronary artery disease during dobutamine infusion. *Circulation*. 1991;83:1605-14.
16. Bleeker GB, Schalij MJ, Molhoek SG, Verwey HF, Holman ER, Boersma E, Steendijk P, van der Wall EE, Bax JJ: Relationship between QRS duration and left ventricular dyssynchrony in patients with end-stage heart failure. *J Cardiovasc Electrophysiol*. 2004;15:544-9.
17. Zhang Y, Chan AK, Yu CM, Lam WW, Yip GW, Fung WH, So NM, Wang M, Sanderson JE: Left ventricular systolic asynchrony after acute myocardial infarction in patients with narrow QRS complexes. *Am Heart J*. 2005;149:497-503.
18. Fahmy EM, Mahfouz BH, Helmy Abo ET, Shawky AE: Asynchrony of left ventricular systolic performance after the first acute myocardial infarction in patients with narrow QRS complexes: Doppler tissue imaging study. *J Am Soc Echocardiogr*. 2006;19:1449-57.

CHAPTER 5

Left ventricular dyssynchrony acutely after myocardial infarction predicts left ventricular remodeling

Sjoerd A. Mollema
Su San Liem
Matthew S. Suffoletto
Gabe B. Bleeker
Bas L. van der Hoeven
Nico R. van de Veire
Eric Boersma
Eduard R. Holman
Ernst E. van der Wall
Martin J. Schalij
John Gorcsan 3rd
Jeroen J. Bax

ABSTRACT

Objectives

We sought to identify predictors of left ventricular (LV) remodeling after acute myocardial infarction.

Background

LV remodeling after myocardial infarction is associated with adverse long-term prognosis. Early identification of patients prone to LV remodeling is needed to optimize therapeutic management.

Methods

A total of 178 consecutive patients presenting with acute myocardial infarction who underwent primary percutaneous coronary intervention were included. Within 48 hours of intervention, two-dimensional echocardiography was performed to assess LV volumes, LV ejection fraction (LVEF), wall motion score index (WMSI), left atrial (LA) dimension, E/E' ratio and severity of mitral regurgitation. LV dyssynchrony was determined using speckle-tracking radial strain analysis. At 6 months follow-up, LV volumes, LVEF and severity of mitral regurgitation were reassessed.

Results

Patients showing LV remodeling at 6 months follow-up (20%) had comparable baseline characteristics to patients without LV remodeling (80%), except for higher peak troponin T levels ($p < 0.001$), peak creatine phosphokinase levels ($p < 0.001$), WMSI ($p < 0.05$), E/E' ratio ($p < 0.05$) and a larger extent of LV dyssynchrony ($p < 0.001$). Multivariable analysis demonstrated that LV dyssynchrony was superior in predicting LV remodeling. Receiver-operating characteristic (ROC) curve analysis demonstrated that a cutoff value of 130 ms for LV dyssynchrony yields a sensitivity of 82% and a specificity of 95% to predict LV remodeling at 6 months follow-up.

Conclusions

LV dyssynchrony immediately after acute myocardial infarction predicts LV remodeling at 6 months follow-up.

INTRODUCTION

The occurrence of left ventricular (LV) dilatation after acute myocardial infarction is not uncommon. Giannuzzi et al. noted severe LV remodeling 6 months after infarction in 16% of the patients.(1) The clinical importance of LV remodeling was emphasized by White et al., who demonstrated that patients who died during follow-up after myocardial infarction had significantly higher LV volumes and lower LV ejection fractions (LVEF) than survivors.(2) Furthermore, they indicated LV end-systolic volume (LVESV) as the primary predictor of survival after myocardial infarction. As a consequence, early identification of patients with LV remodeling after acute myocardial infarction is of vital importance.

Previous studies demonstrated relations between preexisting hypertension, infarct size and anterior location of the infarct, and the occurrence of LV remodeling after myocardial infarction.(3-6) Recently, Zhang et al. demonstrated that myocardial infarction has a significant impact on LV synchronicity and that the degree of LV dyssynchrony is mainly determined by the infarct size.(7)

In this work, we hypothesize that LV dyssynchrony occurring early after myocardial infarction may predict LV remodeling at 6 months follow-up. In the current study, the relation between LV dyssynchrony, as assessed by speckle-tracking radial strain analysis, occurring early after myocardial infarction and LV remodeling at 6 months follow-up was evaluated.

METHODS

Patients

A total of 194 consecutive patients, admitted with an acute myocardial infarction, were evaluated. To acquire a homogenous study population, patients who were treated conservatively (n = 6) or who underwent thrombolysis (n = 4) or coronary artery bypass grafting (n = 2) in the acute setting were excluded from the study. Four patients died during follow-up and therefore did not have the follow-up assessment. These patients were excluded from the study. The final study population comprised 178 patients who all underwent primary percutaneous coronary intervention.

Study protocol

Two-dimensional (2D) echocardiography was performed within 48 hours of admission (baseline) and at 6 months follow-up. At baseline, 2D echocardiography was used to

assess LV volumes, LVEF, wall motion score index (WMSI), left atrial (LA) dimension, the mitral inflow peak early velocity (E)/mitral annular peak early velocity (E'), or E/E' ratio, and severity of mitral regurgitation. LV dyssynchrony was quantified using speckle-tracking radial strain analysis. At 6 months follow-up, LV volumes, LVEF and severity of mitral regurgitation were reassessed.(8) The study was approved by the institutional ethics committee, and informed consent was obtained from all patients.

Echocardiography

Patients were imaged in the left lateral decubitus position using a commercially available system (Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin, USA). Standard images were obtained using a 3.5-MHz transducer, at a depth of 16 cm in the parasternal (long- and short-axis images) and apical (2- and 4-chamber images) views. Standard 2D and color Doppler data, triggered to the QRS complex, were saved in cine-loop format. LV volumes (end-systolic and end-diastolic) and LVEF were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique.(9) LA dimension was measured at end-systole using M-mode.(10)

Pulsed-wave mitral inflow Doppler was obtained by placing the Doppler sample volume between the tips of the mitral leaflets. The E/E' ratio was obtained by dividing E by E' at the basal septal segment.(11)

Severity of mitral regurgitation was graded semiquantitatively from color-flow Doppler data in the conventional parasternal long-axis and apical views. Mitral regurgitation was characterized as: mild = 1+ (jet area/left atrial area < 10%), moderate = 2+ (jet area/left atrial area 10% to 20%), moderately severe = 3+ (jet area/left atrial area 20% to 45%), and severe = 4+ (jet area/left atrial area > 45%).(12)

The LV was divided into 16 segments. A semiquantitative scoring system (1, normal; 2, hypokinesia; 3, akinesia; 4, dyskinesia) was used to analyze each study. Global WMSI was calculated by the standard formula: sum of the segment scores divided by the number of segments scored.(13,14)

All echocardiographic measurements were obtained by 2 independent observers without knowledge of the clinical status of the patient. Inter- and intra-observer agreement for assessment of LV volumes were 90% and 93% for LVESV, and 92% and 93% for left ventricular end-diastolic volume (LVEDV), respectively.

Speckle-tracking radial strain analysis

Radial strain was assessed on LV short-axis images at the papillary muscle level, using speckle-tracking analysis.(15,16) This novel technique tracks frame-to-frame movement of natural acoustic markers on standard gray scale images of the myocardium. Off-line analysis of radial strain was performed on digitally stored images.

The speckle-tracking software makes use of natural acoustic markers, or speckles, that are present on standard ultrasound tissue images. The software automatically subdivides the short-axis images of the LV into blocks of approximately 20 to 40 pixels containing stable patterns of speckles. These speckles move together with the myocardium, and can be followed accurately from frame-to-frame (frame rate varied from 40 to 80 frames/s). A dedicated algorithm tracks the location of the speckles throughout the cardiac cycle, using correlation criteria and sum of absolute differences.(15) Local 2D tissue velocity vectors are then derived from the spatial and temporal data of each speckle. Myocardial strain can then be assessed from temporal differences in the mutual distance of neighboring speckles. The change in length / initial length of the speckle pattern over the cardiac cycle can be used to calculate radial strain, with myocardial thickening represented as positive strain, and myocardial thinning as negative strain.

To assess regional LV strain, a region of interest was manually drawn at the endocardial-cavity boundary on a single frame at end-systole. The speckle-tracking software then automatically created a second larger circle at the epicardial level, such that the region of interest spans the LV myocardium. The automatically created circle width could be adjusted manually by the operator, depending on the LV wall thickness. Starting at the selected frame at end-systole, the speckle-tracking algorithm automatically tracked the region of interest and calculated radial strain throughout the cardiac cycle. Ultimately, the user-defined region of interest covered the entire myocardial wall during the entire cardiac cycle.

Finally, the traced endocardium was automatically divided into 6 standard segments: septal, anteroseptal, anterior, lateral, posterior, and inferior, respectively. The software provided a score for all 6 segments marked in green for good quality and in red for poor quality. Signals from all 6 segments had to be of good quality in order to be able to adequately determine radial strain. Time-strain curves for all 6 segments were then constructed and time from QRS onset to peak radial strain was obtained. Consequently, the location of the earliest and latest activated segments was determined. Inter- and intra-observer agreement for assessment of the absolute difference in time-to-peak radial strain for the earliest versus the latest activated segments was 87% both.

Statistical analysis

Most continuous variables were not normally distributed (as evaluated by Kolmogorov-Smirnov tests). For reasons of uniformity, summary statistics for all continuous variables are therefore presented as medians together with the 25th and 75th percentiles. Categorical data are summarized as frequencies and percentages. LV remodeling at 6 months follow-up was defined as an absolute increase in LVESV of at least 15%.^(2,17,18) Differences in baseline characteristics between patients who developed LV remodeling versus those who did not were analyzed using Wilcoxon-Mann-Whitney tests, Chi-square tests with Yates' correction or Fisher's exact tests, as appropriate. Echocardiographic changes that occurred over time (LVESV, LVEDV and LVEF) were studied by subtracting the baseline values from the values at 6 months follow-up for each individual patient. These changes were then summarized as median values together with 25th and 75th percentiles. Differences in changes between patients with and without LV remodeling were studied by applying the Wilcoxon-Mann-Whitney test.

LV dyssynchrony was defined as the absolute difference in time-to-peak radial strain for the earliest versus the latest activated segments. Univariable and multivariable linear regression analyses were performed to evaluate the relation between LV dyssynchrony at baseline and LVESV at 6 months follow-up, as well as the change in LVESV (indicating the magnitude of LV remodeling) after 6 months follow-up compared to the baseline value. The number of covariates in the final multivariable regression models was limited via a backward selection procedure, and all variables with a p value < 0.15 were maintained.

Additionally, univariable and multivariable logistic regression analyses were applied (with a similar model-building process), relating LV dyssynchrony (continuous variable) to LV remodeling (dichotomous outcome). We realize that dichotomization of a continuous variable (LVESV) will result in loss of statistical power to reveal relevant relations. Still, these analyses are useful from clinical point of view, as patients with a change in LVESV $\geq 15\%$ constitute a cohort at increased risk of adverse events.^(17,18) Crude and adjusted odds ratios with their corresponding 95% confidence intervals are reported.

LV dyssynchrony was associated with LV remodeling. To determine the 'optimal' threshold of LV dyssynchrony for the prediction of LV remodeling, receiver operating characteristic (ROC) curve analysis was applied. This optimum was defined as the value for which the sum of sensitivity and specificity was maximized. As a result of the cut off p value (< 0.15) based on which covariates were included in the final multivariable regression model, the absoluteness of the obtained cut off value for LV

dyssynchrony can be discussed. All statistical tests were 2-sided. For all tests, a p value < 0.05 was considered statistically significant.

RESULTS

Baseline data of the study population

The study sample consisted of 178 patients (140 men, median age 61 (25th, 75th percentiles: 53, 70) years). During primary percutaneous coronary intervention, Thrombolysis In Myocardial Infarction flow grade III flow was obtained in all but 7 (4%) patients. The infarct-related artery was the left anterior descending coronary artery (LAD) in 92 (52%) patients, the left circumflex coronary artery (LCX) in 40 (22%) and the right coronary artery (RCA) in 44 (25%) patients. Multi-vessel disease was present in 95 (53%) patients.

At baseline, median WMSI was 1.50 (1.31, 1.63). Median peak cardiac troponin T and creatine phosphokinase levels were 6.5 µg/L (2.3, 10.3 µg/L) and 2133 U/L (1006, 3570 U/L), respectively. Eight (4%) patients had a previous myocardial infarction.

Median LVESV and LVEDV were 66 ml (54, 83 ml) and 128 ml (106, 150 ml), respectively, whereas median LVEF was 47% (42%, 52%). Median LA dimension was 38 mm (35, 42 mm). The median E/E' ratio at baseline was 12.4 (9.8, 16.2). In 8 (4%) patients moderate to severe mitral regurgitation (≥ grade 2+) was observed.

Median LV dyssynchrony, as measured by speckle-tracking radial strain analysis, was 47 ms (13, 106 ms). In 14 (8%) of patients assessment of LV dyssynchrony using speckle-tracking radial strain analysis was not feasible due to poor quality of the 2D echocardiographic images.

LV remodeling at 6 months follow-up

In the entire patient population, median LVESV at 6 months follow-up was 63 ml (48, 80 ml), median LVEDV was 128 ml (104, 152 ml), whereas median LVEF was 49% (43%, 56%). The number of patients with moderate to severe mitral regurgitation (≥ grade 2+) was 13 (7%) at 6 months follow-up.

Patients were then divided into patients with LV remodeling (n = 36, 20%) and without LV remodeling (n = 142, 80 %) at 6 months follow-up. Baseline patient characteristics of these 2 groups are summarized in Table 1. At baseline, no significant differences were observed between the patients with and without LV remodeling except for the fact that peak levels of cardiac enzymes (reflecting enzymatic infarct size) were higher in the patients with LV remodeling.

	No LV Remodeling (n = 142)	LV Remodeling (n = 36)	p Value
Age (yrs)*	61 (53, 69)	67 (56, 72)	NS
Gender (M/F, %)	110/32 (77/23)	30/6 (83/17)	NS
Previous MI (%)	6 (4)	2 (6)	NS
QRS duration baseline (ms)	94 ± 13	96 ± 15	NS
Wide QRS (≥120 ms, %)	6 (4)	2 (6)	NS
Risk factors for CAD			
Diabetes (%)	13 (9)	4 (11)	NS
Hypertension (%)	43 (30)	12 (33)	NS
Hyperlipidemia (%)	27 (19)	6 (17)	NS
Smoking (%)	76 (54)	16 (44)	NS
Family history of CAD (%)	64 (45)	11 (31)	NS
Peak cTnT level (µg/L)*	5.2 (1.9, 9.8)	10.1 (6.3, 15.3)	< 0.001
Peak CPK level (U/L)*	1893 (868, 3236)	3877 (1816, 5597)	< 0.001
Infarct-related artery			
LAD (%)	70 (49)	22 (61)	NS
RCA (%)	38 (27)	6 (17)	NS
LCX (%)	33 (23)	7 (19)	NS
Multi-vessel disease (%)	73 (51)	22 (61)	NS
Medication at 6 months follow-up			
Beta-blocker (%)	126 (89)	34 (94)	NS
ACE-inhibitor/ARB (%)	139 (98)	35 (97)	NS
Anti-coagulants (%)	142 (100)	36 (100)	NS
Statin (%)	137 (96)	36 (100)	NS

Table 1. Baseline characteristics of patients without versus with left ventricular remodeling (n = 178). 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; LCX: left circumflex coronary artery; MI: myocardial infarction; RCA: right coronary artery. * Values are expressed as n (25th, 75th percentiles).

The echocardiographic data of the patients with and without LV remodeling are shown in Table 2. At baseline, no significant differences in LV volumes and LVEF were observed. At 6 months follow-up however, the LVESV (according to the definition of LV remodeling) and LVEDV were significantly larger in the patients with LV remodeling. Moreover, the LVEF was significantly lower in the patients with LV remodeling.

	No LV Remodeling (n = 142)	LV Remodeling (n = 36)	p Value
Baseline			
LVESV (ml)	64 (54, 70)	76 (54, 91)	NS
LVEDV (ml)	128 (106, 148)	139 (108, 160)	NS
LVEF (%)	47 (42, 52)	47 (42, 51)	NS
WMSI	1.50 (1.25, 1.63)	1.56 (1.38, 1.69)	< 0.05
LA dimension (mm)	38 (34, 42)	41 (37, 43)	NS
E/E' ratio	11.7 (9.7, 15.7)	14.8 (12.3, 18.4)	< 0.05
MR (moderate-severe, %)	6 (4)	2 (6)	NS
LV dyssynchrony (ms)	31 (12, 77)	148 (134, 180)	< 0.001
6 Months follow-up			
LVESV (ml)	58 (46, 74)	112 (70, 130)	< 0.001*
LVEDV (ml)	121 (103, 144)	170 (127, 202)	< 0.001
LVEF (%)	52 (46, 57)	39 (34, 44)	< 0.001
MR (moderate-severe, %)	7 (5)	6 (17)	< 0.05

Table 2. Echocardiographic parameters of patients without versus with left ventricular remodeling. Values are expressed as n (25th, 75th percentiles) unless otherwise indicated. *Per definition E/E': mitral inflow peak early velocity (E) / mitral annular peak early velocity (E'); LA: left atrial; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MR: mitral regurgitation; WMSI: wall motion score index.

Moderate to severe mitral regurgitation ($\geq$ grade 2+) was more often present in the patients with LV remodeling.

At baseline, WMSI, E/E' ratio and LV dyssynchrony (Figure 1) were the only baseline echocardiographic variables that were significantly different between patients with and without LV remodeling. In the patients with LV remodeling median WMSI was 1.56 (1.38, 1.69), whereas median WMSI in patients without LV remodeling was 1.50 (1.25, 1.63; $p < 0.05$). The median value for E/E' ratio in patients with LV remodeling measured 14.8 (12.3, 18.4) and the patients without LV remodeling had a median E/E' ratio of 11.7 (9.7, 15.7; $p < 0.05$).

Median LV dyssynchrony was 148 ms (134, 180 ms) in the patients with LV remodeling, compared with 31 ms (12, 77 ms) in the patients without LV remodeling ($p < 0.001$). The individual data are demonstrated in Figure 2.

Figure 3 shows the prevalence for each LV segment as being the latest activated segment in the patients with LV remodeling after 6 months of follow-up. According to the high prevalence of the LAD as infarct-related artery, the anteroseptal and

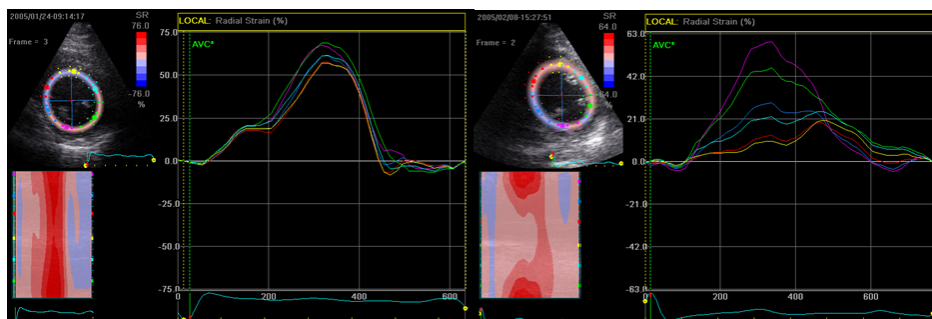


Figure 1.

Extent of LV dyssynchrony was significantly larger in patients with LV remodeling during follow-up versus those without LV remodeling

Left panel demonstrates time-strain curves of a patient without dyssynchrony at baseline. This patient did not show left ventricular (LV) remodeling during follow-up (left ventricular end-systolic volume (LVESV) was 84 vs. 73 ml, baseline vs. 6-month follow-up). **Right panel** demonstrates time-strain curves of a patient with LV dyssynchrony at baseline (earliest activated segments: purple, green, and dark-blue, latest activated segments: light-blue, yellow, and red). This patient showed LV remodeling during follow-up (LVESV was 77 vs. 122 ml, baseline vs. 6-month follow-up).

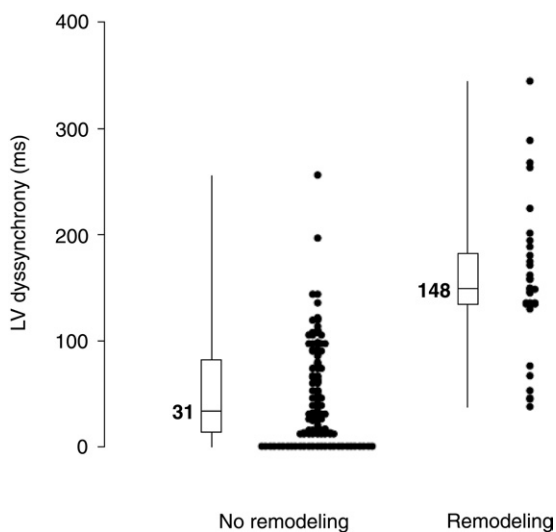


Figure 2.

LV dyssynchrony in patients without versus with LV remodeling at 6-Month follow-up
Box-whisker plot indicates median, first quartile, third quartile, and range. Median left ventricular (LV) dyssynchrony was significantly higher ($p < 0.001$) in the patients with LV remodeling versus without LV remodeling (148 ms (134, 180 ms) vs. 31 ms (12, 77 ms), respectively).

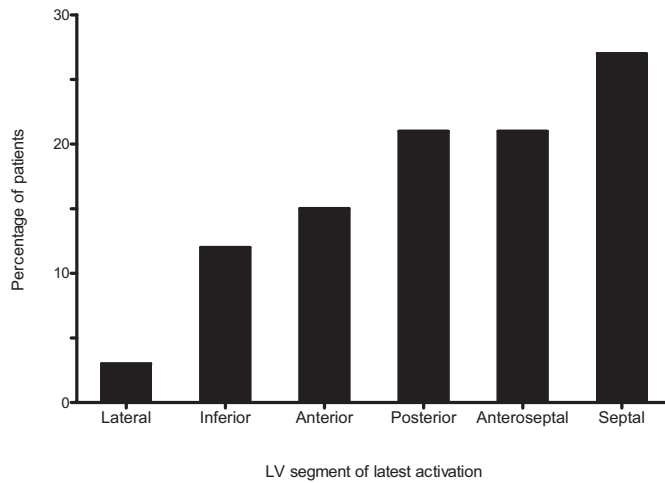


Figure 3.

Distribution of latest activated LV segments in patients with LV remodeling

According to the high prevalence of the left anterior descending coronary artery (LAD) as infarct-related artery, the anteroseptal and septal left ventricular (LV) segments are activated late in a considerable proportion of the patients with LV remodeling.

septal LV segments are activated late in a considerable proportion of the patients with LV remodeling.

Determinants of LV remodeling

Patients with more extensive LV dyssynchrony at baseline had a higher LVESV at 6 months follow-up (Figure 4, left panel). This relation remained after adjustment for the baseline LVESV, peak level of cardiac troponin T and history of hypertension (these variables had a p value < 0.15 in the final model; the R^2 value of the final model was 0.73). Each 10 ms increase in LV dyssynchrony is associated with a 1.2 ml (95% confidence interval (CI) 0.8 to 1.6 ml; $p < 0.001$) larger LVESV at 6 months.

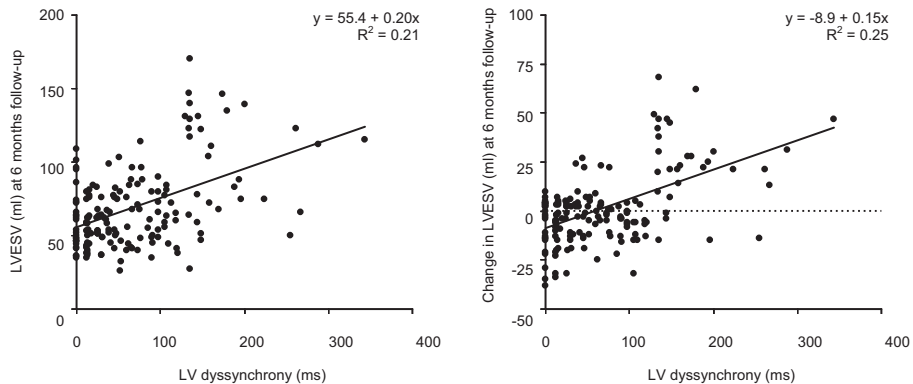
Patients with more extensive LV dyssynchrony at baseline also had a higher change in LVESV in the 6 months period of follow-up (Figure 4, right panel). Of note, the extent of LV dyssynchrony was largest in patients with significant LV remodeling (increase in LVESV $\geq 15\%$) (Figure 5). After adjustment for the baseline LVESV, peak level of cardiac troponin T and history of hypertension, each 10 ms increase in LV dyssynchrony is associated with an 1.2 ml (95% CI 0.8 to 1.6 ml) higher change in

LVESV (note that the 'change model' had similar covariables as the 'absolute value' model; the R^2 value of the final 'change model' was 0.41).

LV dyssynchrony at baseline was also associated with an increased risk of LV remodeling at 6 months follow-up. Table 3 presents the univariable relations between a range of clinical and echocardiographic variables, and the incidence of LV remodeling at 6 months follow-up. Among the variables studied, LV dyssynchrony showed the strongest relation. This relation remained after adjustment for the peak level of cardiac troponin T ($p = 0.015$ in the final model), hypertension ($p = 0.10$), baseline LVESV ($p = 0.14$), and baseline LVEDV ($p = 0.14$). Each millisecond increase in LV

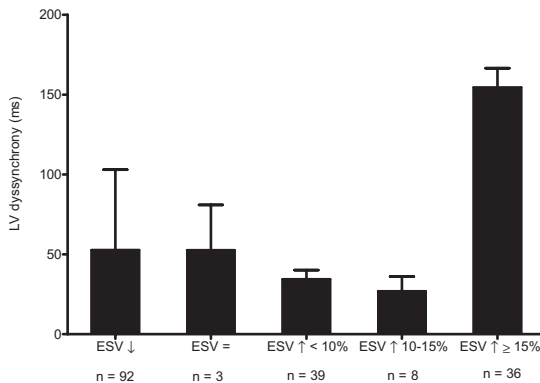
Baseline Variable	Odds ratio	95% Confidence interval	p Value
LV dyssynchrony (per ms)	1.03	1.02 – 1.05	< 0.001
Peak cTnT level (per $\mu\text{g/L}$)	1.14	1.07 – 1.22	< 0.001
Peak CPK level (per U/L)	1.44	1.20 – 1.72	< 0.001
E/E' ratio	1.09	1.01 – 1.17	0.019
WMSI	8.11	1.39 – 47.0	0.020
Age (per year)	1.03	1.00 – 1.07	0.073
LA dimension (per mm)	1.07	0.99 – 1.15	0.081
LVESV (per ml)	1.02	1.00 – 1.03	0.090
LVEDV (per ml)	1.01	1.00 – 1.02	0.094
Positive family history	0.54	0.25 – 1.17	0.12
Culprit vessel LAD	1.96	0.73 – 5.26	0.18
QRS duration (per ms)	1.01	0.99 – 1.04	0.39
Gender	1.45	0.56 – 3.80	0.45
Number of diseased vessels	1.20	0.78 – 1.97	0.46
MR	1.19	0.66 – 2.15	0.57
Culprit vessel LCX	1.34	0.41 – 4.40	0.63
LVEF (per %)	0.99	0.94 – 1.04	0.72
Diabetes	1.24	0.38 – 4.06	0.72
Hypertension	1.15	0.53 – 2.51	0.72
Previous MI	1.33	0.26 – 6.90	0.73
Hyperlipidemia	0.85	0.32 – 2.25	0.75
Smoking	0.94	0.44 – 1.98	0.86

Table 3. Relation between clinical and echocardiographic parameters and LV remodeling. Abbreviations as in Tables 1 and 2.

**Figure 4.**

Correlation between LV dyssynchrony at baseline and LVESV and change in LVESV at 6-Month follow-up

A significant relation existed between baseline left ventricular (LV) dyssynchrony and absolute value for left ventricular end-systolic volume (LVESV) (**left panel**) and change in LVESV (**right panel**) at follow-up.

**Figure 5.**

The extent of LV dyssynchrony according to changes in LVESV during follow-up

Of note, the extent of left ventricular (LV) dyssynchrony was largest in patients with significant LV remodeling (increase in left ventricular end-systolic volume (LVESV) $\geq 15\%$). ES = end-systolic volume.

dyssynchrony was associated with a 3% increased risk of LV remodeling (adjusted odds ratio 1.03 per ms; 95% CI 1.02 to 1.05; $p < 0.001$).

To identify the optimal extent of LV dyssynchrony that was predictive for LV remodeling at 6 months follow-up, ROC curve analysis was performed (Figure 6). At a cutoff value of 130 ms for LV dyssynchrony, ROC curve analysis revealed a sensitivity of 82% with a specificity of 95% to predict LV remodeling at 6 months follow-up.

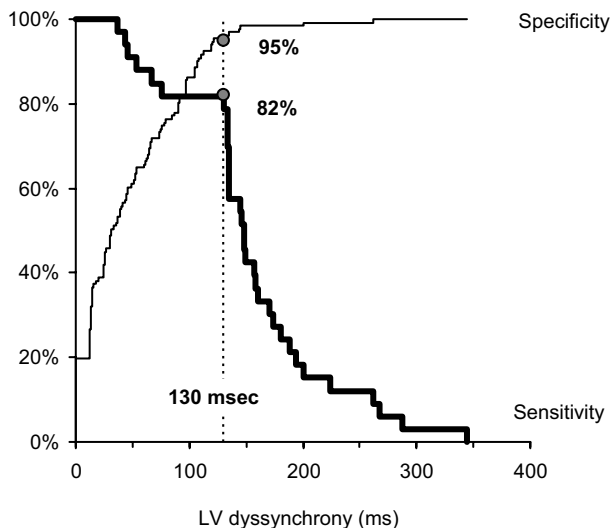


Figure 6.

ROC curve analysis to determine the optimal cutoff value for LV dyssynchrony to predict LV remodeling. Using a cutoff value of 130 ms, a sensitivity of 82% and a specificity of 95% were obtained to predict left ventricular (LV) remodeling. ROC = receiver-operating characteristic.

DISCUSSION

The main findings of the present study can be summarized as follows: 1) 20% of the patients exhibited LV remodeling at 6 months after acute myocardial infarction, 2) patients in which LV remodeling occurred had higher baseline peak levels of cardiac enzymes, WMSI, E/E' ratio and a larger extent of LV dyssynchrony, 3) baseline LV dyssynchrony of 130 ms or more, as assessed by speckle-tracking radial strain analysis, had a sensitivity of 82% and a specificity of 95% to predict LV remodeling at 6 months after acute infarction.

Prediction of LV remodeling

During follow-up, 20% of the study group showed remodeling of the left ventricle. Accordingly, in these patients LVESV and LVEDV increased, while LVEF declined. In the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)-3 Echo Substudy, Giannuzzi et al. showed comparable results. Using the end-diastolic volume index as a marker of remodeling, the authors noted severe LV remodeling at 6 months after infarction in 16% of the patients.(1)

Cardiac remodeling is recognized as an important trigger for the progression of cardiovascular disease. Increasing LVESV (index) and declining LVEF post-infarction are important predictors of mortality.(2,19,20) White et al. measured LV volumes, LV ejection fractions, and severity of coronary occlusions and stenoses in 605 male patients under 60 years of age at 1 to 2 months after a first (n = 443) or recurrent (n = 162) myocardial infarction. During a follow-up period of 78 months there were 101 cardiac deaths. Multivariable analysis showed that LVESV had greater predictive value for survival than LVEDV or LVEF. LVESV was significantly higher in patients who died from a cardiac cause (122 ± 65 ml) than in survivors (72 ± 36 ml).(2) Therefore, early identification of patients with LV remodeling after acute myocardial infarction is of vital importance. In order to identify patients at high risk, parameters with adequate predictive values are needed.

In the current study, it was shown that patients with LV remodeling had significantly higher peak levels of cardiac enzymes, WMSI, E/E' ratio and a significantly larger extent of LV dyssynchrony, compared with the patients without LV remodeling.

Significant relations have been described between cardiac troponin T levels after myocardial infarction and scintigraphic estimate of myocardial infarct size.(21,22) The importance of the infarct size as determinant of LV remodeling was previously noted by McKay et al.(3) The authors demonstrated that infarct size, as assessed by the extent of wall motion abnormalities, was directly proportional to the magnitude of LV remodeling during the acute phase of infarction. The predictive value of infarct size was further confirmed by Popović et al, who described initial infarct size after anterior wall acute myocardial infarction as a major determinant of infarct expansion and ventricular remodeling. Furthermore, the importance of the infarct-related artery patency as predictor for infarct expansion after anterior wall myocardial infarction was emphasized.(5) Unfortunately, systematic information on vessel patency was not available in the current study.

The variables LA dimension and E/E' ratio were evaluated for their relation with long-term LV remodeling. In previous studies, both variables demonstrated to be of clinical importance.(10,11) In the present study, the influence of these variables on LV remodeling was limited, and LV dyssynchrony at baseline appeared superior for prediction of LV remodeling.

Recently, Zhang et al. emphasized the significant impact of acute myocardial infarction on regional myocardial contractility and systolic LV synchronicity early in the course, even in the absence of QRS widening or bundle-branch block. The authors concluded that the degree of LV systolic dyssynchrony was mainly determined by the infarct size. The infarct size was assessed by contrast-enhanced magnetic reso-

nance imaging and was significantly larger in patients with anterior infarction ($n = 24$) compared to inferior infarction ($21.3 \pm 12.1\%$ vs. $13.3 \pm 6.1\%$, respectively). Of note, a greater extent of LV dyssynchrony was demonstrated in patients with anterior than inferior myocardial infarction (46.8 ± 13.9 vs. 34.6 ± 8.5 ms, $p = 0.002$).⁽⁷⁾

LV dyssynchrony predicts long-term LV remodeling

A novel finding in the current study is that the extent of LV dyssynchrony was demonstrated to be an independent predictor of LV remodeling at 6 months follow-up. Moreover, multivariable analysis showed that LV dyssynchrony, measured at baseline after myocardial infarction, was superior to other variables in the prediction of LV remodeling. To identify a cutoff value to predict LV remodeling, we performed an ROC curve analysis and identified an optimal cutoff value of 130 ms. This cutoff value yielded a sensitivity and specificity of 82% and 95% to predict LV remodeling at 6 months follow-up. These findings suggest that assessment of LV dyssynchrony immediately after acute myocardial infarction may provide incremental predictive value for the identification of patients prone to the development of LV remodeling.

Speckle-tracking radial strain analysis to assess LV dyssynchrony

In the present study, the location of the earliest and latest activated segments was determined using speckle-tracking software applied to standard short-axis images. The definition of LV dyssynchrony was based on the absolute difference in time-to-peak radial strain for the earliest versus the latest activated segments. Speckle-tracking radial strain analysis is a novel technique that allows angle-independent measurement of regional strain and time-to-peak radial strain of different LV segments.^(15,16) Recently, this technique has been validated against magnetic resonance imaging.⁽²³⁾ Furthermore, Suffoletto et al. demonstrated that speckle-tracking radial strain analysis can quantify LV dyssynchrony, and can accurately predict response to cardiac resynchronization therapy.⁽²⁴⁾ In contrast to tissue velocity imaging-derived strain, speckle-tracking radial strain is angle-independent and not limited by tethering.⁽²⁵⁾ Therefore, speckle-tracking radial strain analysis permits an accurate quantification of regional wall strain, with a high reproducibility.^(23,25)

Clinical implications

Recently, numerous reports have been published on LV dyssynchrony, mainly in relation to prediction of response to cardiac resynchronization therapy.⁽¹⁷⁾ In these studies, the presence of LV dyssynchrony in severely dilated left ventricles is predictive for response to cardiac resynchronization therapy.

According to the present study, a significant degree of dyssynchrony is highly predictive for the long-term development of LV remodeling after acute myocardial infarction. This finding offers a unique possibility to identify patients at risk for LV remodeling early after infarction and to subsequently intensify treatment of these patients.

There is an important role for medical therapy in the prevention of LV remodeling after myocardial infarction, especially for angiotensin-converting enzyme inhibitors and beta-blockers.(26-33) The SOLVD (Studies of Left Ventricular Dysfunction) prevention trial for instance demonstrated that enalapril (partially) reversed LV dilatation in patients with LV dysfunction.(27) Moreover, beta-blocker therapy has been shown to reduce LVEDV and LVESV indexes in patients with LV dysfunction.(32,33)

In addition to further optimization of medical therapy, early cardiac resynchronization therapy could be considered in patients with severe LV dyssynchrony early after acute myocardial infarction. However, it is currently unclear whether large infarction results in LV dilatation, or whether LV dyssynchrony is most important for LV dilatation. Only when LV dyssynchrony is the main determinant of LV dilatation, cardiac resynchronization may be beneficial. Further studies are needed to explore these issues.

CONCLUSIONS

Patients with LV remodeling after acute myocardial infarction show significant LV dyssynchrony at baseline, as compared to patients without LV remodeling. Using a cutoff value of 130 ms, a sensitivity of 82% and a specificity of 95% were obtained to predict the LV remodeling at 6 months follow-up. LV dyssynchrony may be used to identify patients at high risk for development of LV remodeling after infarction.

REFERENCES

1. Giannuzzi P, Temporelli PL, Bosimini E et al. Heterogeneity of left ventricular remodeling after acute myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-3 Echo Substudy. *Am Heart J* 2001;141:131-8.
2. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 1987;76:44-51.
3. McKay RG, Pfeffer MA, Pasternak RC et al. Left ventricular remodeling after myocardial infarction: a corollary to infarct expansion. *Circulation* 1986;74:693-702.
4. Pirolo JS, Hutchins GM, Moore GW. Infarct expansion: pathologic analysis of 204 patients with a single myocardial infarct. *J Am Coll Cardiol* 1986;7:349-54.
5. Popovic AD, Neskovic AN, Marinkovic J, Thomas JD. Acute and long-term effects of thrombolysis after anterior wall acute myocardial infarction with serial assessment of infarct expansion and late ventricular remodeling. *Am J Cardiol* 1996;77:446-50.
6. Richards AM, Nicholls MG, Troughton RW et al. Antecedent hypertension and heart failure after myocardial infarction. *J Am Coll Cardiol* 2002;39:1182-8.
7. Zhang Y, Chan AK, Yu CM et al. Left ventricular systolic asynchrony after acute myocardial infarction in patients with narrow QRS complexes. *Am Heart J* 2005;149:497-503.
8. Liem SS, van der Hoeven BL, Oemrawsingh PV et al. MISSION!: optimization of acute and chronic care for patients with acute myocardial infarction. *Am Heart J* 2007;153:14-1.
9. Schiller NB, Shah PM, Crawford M et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2:358-67.
10. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart Study. *Circulation* 1995;92:835-41.
11. Naqvi TZ, Padmanabhan S, Rafii F, Hyuhn HK, Mirocha J. Comparison of usefulness of left ventricular diastolic versus systolic function as a predictor of outcome following primary percutaneous coronary angioplasty for acute myocardial infarction. *Am J Cardiol* 2006;97:160-6.
12. Thomas JD. How leaky is that mitral valve? Simplified Doppler methods to measure regurgitant orifice area. *Circulation* 1997;95:548-50.

13. Broderick TM, Bourdillon PD, Ryan T, Feigenbaum H, Dillon JC, Armstrong WF. Comparison of regional and global left ventricular function by serial echocardiograms after reperfusion in acute myocardial infarction. *J Am Soc Echocardiogr* 1989;2:315-23.
14. Sawada SG, Segar DS, Ryan T et al. Echocardiographic detection of coronary artery disease during dobutamine infusion. *Circulation* 1991;83:1605-14.
15. Leitman M, Lysyansky P, Sidenko S et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 2004;17:1021-9.
16. Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. *J Am Soc Echocardiogr* 2004;17:630-3.
17. Bax JJ, Bleeker GB, Marwick TH et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol* 2004;44:1834-40.
18. Yu CM, Fung JW, Chan CK et al. Comparison of efficacy of reverse remodeling and clinical improvement for relatively narrow and wide QRS complexes after cardiac resynchronization therapy for heart failure. *J Cardiovasc Electrophysiol* 2004;15:1058-65.
19. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol* 2000;35:569-82.
20. Gaudron P, Eilles C, Kugler I, Ertl G. Progressive left ventricular dysfunction and remodeling after myocardial infarction. Potential mechanisms and early predictors. *Circulation* 1993;87:755-63.
21. Licka M, Zimmermann R, Zehelein J, Dengler TJ, Katus HA, Kubler W. Troponin T concentrations 72 hours after myocardial infarction as a serological estimate of infarct size. *Heart* 2002;87:520-4.
22. Panteghini M, Cuccia C, Bonetti G, Giubbini R, Pagani F, Bonini E. Single-point cardiac troponin T at coronary care unit discharge after myocardial infarction correlates with infarct size and ejection fraction. *Clin Chem* 2002;48:1432-6.
23. Amundsen BH, Helle-Valle T, Edvardsen T et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. *J Am Coll Cardiol* 2006;47:789-93.
24. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J, III. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. *Circulation* 2006;113:960-8.

25. Cho GY, Chan J, Leano R, Strudwick M, Marwick TH. Comparison of two-dimensional speckle and tissue velocity based strain and validation with harmonic phase magnetic resonance imaging. *Am J Cardiol* 2006;97:1661-6.
26. Konstam MA, Rousseau MF, Kronenberg MW et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD Investigators. *Circulation* 1992;86:431-8.
27. Konstam MA, Kronenberg MW, Rousseau MF et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. SOLVD (Studies of Left Ventricular Dysfunction) Investigators. *Circulation* 1993;88:2277-83.
28. Greenberg B, Quinones MA, Koilpillai C et al. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction. Results of the SOLVD echocardiography substudy. *Circulation* 1995;91:2573-81.
29. Groenning BA, Nilsson JC, Sondergaard L, Fritz-Hansen T, Larsson HB, Hildebrandt PR. Antiremodeling effects on the left ventricle during beta-blockade with metoprolol in the treatment of chronic heart failure. *J Am Coll Cardiol* 2000;36:2072-80.
30. Pfeffer MA, Braunwald E, Moya LA et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;327:669-77.
31. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. *N Engl J Med* 1992;327:685-91.
32. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Australia/New Zealand Heart Failure Research Collaborative Group. *Lancet* 1997;349:375-80.
33. Doughty RN, Whalley GA, Walsh HA, Gamble GD, Lopez-Sendon J, Sharpe N. Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN Echo Substudy. *Circulation* 2004;109:201-6.

CHAPTER 6

Sirolimus-eluting stents versus bare-metal stents in patients with ST-Segment elevation myocardial infarction: 9-month angiographic and intravascular ultrasound results and 12-month clinical outcome Results from the MISSION! Intervention Study

Bas L. van der Hoeven
Su-San Liem
J. Wouter Jukema
Navin Suraphakdee
Hein Putter
Jouke Dijkstra
Douwe E. Atsma
Marianne Bootsma
Katja Zeppenfeld
Pranobe V. Oemrawsingh
Ernst E. van der Wall
Martin J. Schalij

ABSTRACT

Objectives

Our purpose was to evaluate the efficacy and safety of drug-eluting stents in the setting of primary percutaneous coronary intervention for ST-segment elevation myocardial infarction (STEMI).

Background

There is inconsistent and limited evidence about the efficacy and safety of drug-eluting stents in STEMI patients.

Methods

A single-blind, single-center, randomized study was performed to compare bare-metal stents (BMS) with sirolimus-eluting stents (SES) in 310 STEMI patients. The primary end point was in-segment late luminal loss (LLL) at 9 months. Secondary end points included late stent malapposition (LSM) at 9 months as determined by intravascular ultrasound imaging and clinical events at 12 months.

Results

In-segment LLL was 0.68 ± 0.57 mm in the BMS group and 0.12 ± 0.43 mm in the SES group with a mean difference of 0.56 mm, 95% confidence interval 0.43 to 0.68 mm ($p < 0.001$). Late stent malapposition at 9 months was present in 12.5% BMS patients and in 37.5% SES patients ($p < 0.001$). Event-free survival at 12 months was 73.6% in BMS patients and 86.0% in SES patients ($p = 0.01$). The target-vessel-failure-free survival was 84.7% in the BMS group and 93.0% in the SES group ($p = 0.02$), mainly because of a higher target lesion revascularization rate in BMS patients (11.3% vs. 3.2%; $p = 0.006$). Rates of death, myocardial infarction, and stent thrombosis were not different.

Conclusions

Sirolimus-eluting stent implantation in STEMI patients is associated with a favorable midterm clinical and angiographic outcome compared with treatment with BMS. However, LSM raises concern about the long-term safety of SES in STEMI patients (MISSION!; ISRCTN62825862).

INTRODUCTION

Percutaneous coronary intervention (PCI) is the preferred revascularization strategy in patients presenting with ST-segment elevation myocardial infarction (STEMI).(1) Percutaneous coronary intervention is directed at restoring coronary flow, stabilizing the ruptured plaque, and reducing infarct size, thereby improving short- and long-term clinical outcome. Implantation of a bare-metal coronary artery stent (BMS) during primary PCI further improves outcome compared with balloon angioplasty alone by reducing the number of acute complications and the restenosis rate.(2,3) Drug-eluting stents have been proven effective in reducing restenosis in patients with stable and unstable angina.(4–7) Inconsistent and limited results have been presented about the efficacy and safety of drug-eluting stents in STEMI patients.(8,9) In particular, stent thrombosis occurring late after implantation of drug-eluting stents, possibly related to late malapposition of the stent struts, has raised safety concerns.(10,11) Therefore, this randomized prospective study was designed to evaluate midterm angiographic outcome and clinical efficacy of third-generation BMS compared with that seen in sirolimus-eluting stents (SES) in STEMI patients. To address the issue of late stent malapposition (LSM), intravascular ultrasound (IVUS) imaging was performed in both groups at 9-month follow-up.

METHODS

Study design

This is a single-center, single-blind, randomized prospective noninferiority study to evaluate clinical, angiographic, and IVUS 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 angiography were blinded to the treatment assignment. The study was conducted from February 2004 to October 2006. During the study period, all patients were treated according to the institutional STEMI protocol, which included standardized outpatient follow-up.(12)

Patient selection

Patients were eligible if STEMI symptoms started <9 h before the procedure and the electrocardiogram (ECG) demonstrated STEMI (ST-segment elevation ≥ 0.2 mV in

≥ 2 contiguous leads in V1 through V3 or ≥ 0.1 mV in other leads, or [presumed] new left bundle branch block). Furthermore, the target lesion length should be ≤ 24 mm. Exclusion criteria were: 1) age < 18 years or > 80 years; 2) left main stenosis of $\geq 50\%$; 3) triple-vessel disease, defined as $\geq 50\%$ stenosis in ≥ 3 major epicardial branches; 4) previous PCI or coronary artery bypass grafting of the infarct-related artery; 5) thrombolytic therapy for the index infarction; 5) target vessel reference diameter < 2.25 mm or > 3.75 mm; 6) need for mechanical ventilation; 7) contraindication to the use of aspirin, clopidogrel, heparin, or abciximab; 8) known renal failure; or 9) a life expectancy < 12 months.

After crossing the target lesion with a guidewire and after visual estimation of the target vessel reference diameter, 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.

Study procedure

Before the procedure all patients received 300 mg of aspirin, 300 to 600 mg of clopidogrel, and an intravenous bolus of abciximab (25 $\mu\text{g/kg}$), followed by a continuous infusion of 10 $\mu\text{g/kg/min}$ for 12 h. At start of the procedure, 5,000 IU of heparin was given. Lesions were treated according to current interventional practice. Direct stenting was allowed. If more than 1 stent was required, additional assigned study stents were used. Stent size and length selection was based on visual estimation. Before and immediately after the intervention, 2 angiograms in orthogonal projections were obtained. Intravascular ultrasound imaging was performed after stent implantation (motorized pull-back [0.5 mm/s]), starting > 10 mm distal to the stent and ending at the coronary ostium, using a 2.9-F 20-MHz catheter and a dedicated IVUS console (Eagle Eye, Volcano Corp., Rancho Cordova, California) (13) Intravascular-ultrasound-guided stenting was not performed to reflect routine angiographic stent implantation. Each angiogram and ultrasound sequence was preceded by 200 to 300 μg of intracoronary nitroglycerin.

Follow-up and data collection

Patients were seen at the outpatient clinic at 30 days, 3, 6, and 12 months. (12) Aspirin (80 to 100 mg/day) was prescribed indefinitely and clopidogrel (75 mg/day) for 12 months. Patients were treated with betablocking agents, statins, and angiotensin-converting enzyme inhibitors or angiotensin II blockers. Follow-up angiography and IVUS imaging was performed at 9 months.

Quantitative coronary angiography (QCA) and IVUS analysis

Angiograms were analyzed off-line by analysts blinded for the assigned treatment using validated QCA systems (CMS version 6.1, Medis, Leiden, the Netherlands). Measurements were made in a single projection showing the most severe stenosis following standardized operating procedures.(14) The minimal lumen diameter (MLD) was measured, and the percentage diameter stenosis was calculated using the interpolated reference diameter approach. Late luminal loss (LLL) was defined as the difference between the post-procedural MLD and follow-up MLD. Angiographic restenosis was defined as $\geq 50\%$ diameter stenosis at 9-months, follow-up.

Intravascular ultrasound images were analyzed off-line, using quantitative IVUS analysis software (QCU-CMS version 4.14, Medis). The stented segment (+5 mm proximally and distally to the stent) was analyzed. The stent and lumen boundaries were determined in all individual frames. In case of malapposition, the stent boundaries were used as lumen boundaries. The volume within the stent and the luminal volume were calculated applying Simpson's rule.(15) Stent malapposition was defined as a separation of at least 1 stent strut, not overlapping a side branch, from the intimal surface with IVUS evidence of blood speckles behind the strut. (16,17) The site of malapposition was classified as: 1) the body of the stent; 2) the proximal stent edge; or 3) the distal stent edge. Malapposition was persistent if it was present immediately after stent implantation and at follow-up, and acquired if it was present at follow-up only.

Study end points

The primary end point of the study was in-segment LLL at 9-month follow-up angiography. Secondary end points were angiographic restenosis and LSM at 9 months. Additional secondary end points were death, myocardial infarction (MI), target vessel revascularization, target lesion revascularization, target vessel failure, stent thrombosis, procedural success, and clinical success. All deaths were defined as cardiac, unless it was unequivocally proven noncardiac. Myocardial infarction during follow-up was defined as a troponin-T rise $>0.03 \mu\text{g/l}$ with symptoms or PCI, a rise of troponin-T $>0.15 \mu\text{g/l}$ after coronary artery bypass grafting, or a rise of troponin-T $>25\%$ after recent MI in the presence of symptoms or re-PCI, or the development of new Q waves on ECG.(18,19) All infarctions were categorized as spontaneous or procedure related (nonindex procedure).(18,19) Procedural success was defined as the achievement of $<50\%$ diameter stenosis by QCA with achievement of Thrombolysis In Myocardial Infarction flow grade 3. Clinical success was defined as procedural success without death or reinfarction during the index hospitalization. Target vessel

and target lesion 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. Clinically driven target lesion revascularization was defined as repeated revascularization procedure of the target lesion (showing $\geq 50\%$ diameter stenosis) driven by clinical symptoms at rest in conjunction with electrocardiographic evidence of ischemia or a positive stress test (in the presence or absence of clinical symptoms). Target vessel failure was defined as the composite of cardiac death or recurrent 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 angiographically documented thrombus within the stent and/or typical chest pain with recurrent ST-segment elevation in the territory of the infarct-related vessel in combination with a significant rise of troponin levels and/or the presence of new Q waves in the territory of the infarct related vessel. Stent thrombosis was classified as acute if it occurred <24 h after the index procedure, as subacute if it occurred between 1 to 30 days, and as late if it occurred >30 days.⁽⁹⁾ All clinical events were adjudicated by a clinical events committee whose members were blinded for the assigned stent type.

Statistical design and analysis

The study objective was to assess whether the outcome of treatment with BMS was noninferior to the outcome of treatment with SES. To prove noninferiority, a difference of ≤ 0.35 mm angiographic in-segment LLL at 9 months was considered clinically insignificant. The sample size to demonstrate noninferiority of BMS was 244 patients (1-sided) based on the following assumptions: 1) angiographic in-segment LLL at 9 months is 0.40 mm in the SES group and 0.60 mm in the BMS group, with a common within-group standard deviation of 0.40 mm (power 0.90, alpha error of 0.05). To compensate for unsuccessful interventions, crossovers, and losses to follow-up, the sample size was increased to a total of 316 patients. All analyses were conducted according to the intention-to-treat principle. Analysis of post-procedural and follow-up angiographic and IVUS data was conducted according to the number of patients for which complete data were available. All continuous variables were compared between the treatment groups with a *t* test or, in case of non-normality as tested by Shapiro-Wilk's statistics, with an equivalent nonparametric test. Categorical variables were compared with Pearson's chi-square test or Fisher exact test in case of 1 or more cells in the contingency table with expectation <5 . Event-free and target-vessel-failure-free survival were computed using Kaplan-Meier estimates and

compared between treatment groups with the log-rank test. The hazard ratio (HR) was calculated by Cox regression with treatment group as sole covariate. To correct for differences in baseline characteristics, the appropriate multivariate analysis was performed. All p values were 2-sided, and a p value of less than 0.05 was considered statistically significant. All analyses were conducted with SPSS version 12.0.1 statistical analysis software (SPSS Inc., Chicago, Illinois).

RESULTS

Patients

A total of 316 STEMI patients were enrolled in the study (Table 1, Fig. 1). 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. With exception of a 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 the lesion with the SES. Procedural characteristics are summarized in Table 2.

Angiographic results

Post-procedural and follow-up angiographic data were available for 124 BMS patients (81.6%) and 131 SES patients (82.9%). Patients with and without follow-up angiography had similar baseline characteristics. Six patients without follow-up angiography died during follow-up (4 BMS and 2 SES patients). The median time to angiographic follow-up was 272 days (10th to 90th percentiles: 268 to 295 days) in the BMS group and 272 days (10th to 90th percentiles: 270 to 290 days) in the SES group ($p = 0.66$). Post-procedural and follow-up QCA results are summarized in Table 3. The mean difference between BMS and SES patients in in-segment LLL was 0.56 mm (95% confidence interval [CI] 0.43 to 0.68, $p < 0.001$) at 9 months. This difference remained significant after adjustment for baseline characteristics as listed in Table 1 (mean difference 0.60 mm, 95% CI 0.48 to 0.72, $p < 0.001$). The in-segment angiographic restenosis rate was 22.6% in the BMS group and 3.8% in the SES group (relative risk 5.92, 95% CI 2.36 to 14.84). The cumulative percentage diameter stenosis distribution after the procedure and at follow-up angiography is shown in Figure 2.

Characteristic	SES (n = 158)	BMS (n = 152)	p Value
Age (yrs)	59.2 ± 11.2	59.1 ± 11.6	0.99
Male sex	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 CAD	73 (46.2)	60 (39.5)	0.23
Prior myocardial infarction	7 (4.4)	5 (3.3)	0.60
Prior PCI	4 (2.5)	1 (0.7)	0.37*
Prior CABG	1 (0.6)	1 (0.7)	1.00*
Times minutes: median (inter-quartile range)			
Symptoms onset to first ECG	88 (47–153)	106 (71–151)	0.11*
Symptoms onset to balloon inflation	183 (133–258)	195 (153–257)	0.19*
Target vessel			
LAD	87 (55.1)	83 (54.6)	
RCA	40 (25.3)	51 (33.6)	0.09
RCX	31 (19.6)	18 (11.8)	
Multivessel disease	56 (35.4)	50 (32.9)	0.64
TIMI flow 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	1844	2079	0.25*
Interquartile range	863–3413	1012–3792	
QCA before procedure			
Lesion length, mm	13.9 ± 5.6	15.0 ± 8.6	0.47
Reference diameter, mm	2.76 ± 0.54	2.92 ± 0.56	0.02
Minimal luminal diameter, mm	0.21 ± 0.35	0.27 ± 0.41	0.19*
Stenosis, % of luminal diameter	91.0 ± 13.6	92.5 ± 12.4	0.35*

Table 1. Baseline clinical and angiographic characteristics

Data are expressed as number (%) or mean ± standard deviation. All comparisons between groups were performed with *t* test (continuous variables) or Pearson's chi-square test (categorical variables) except as indicated (*).

BMS = bare-metal stent; CABG = coronary artery bypass grafting; CAD = coronary artery disease; ECG = electrocardiogram; LAD = left anterior descending coronary artery; LCX = left circumflex artery; PCI = percutaneous coronary intervention; QCA = quantitative coronary angiography; RCA = right coronary artery; SES = sirolimus-eluting stent; TIMI = Thrombolysis In Myocardial Infarction.

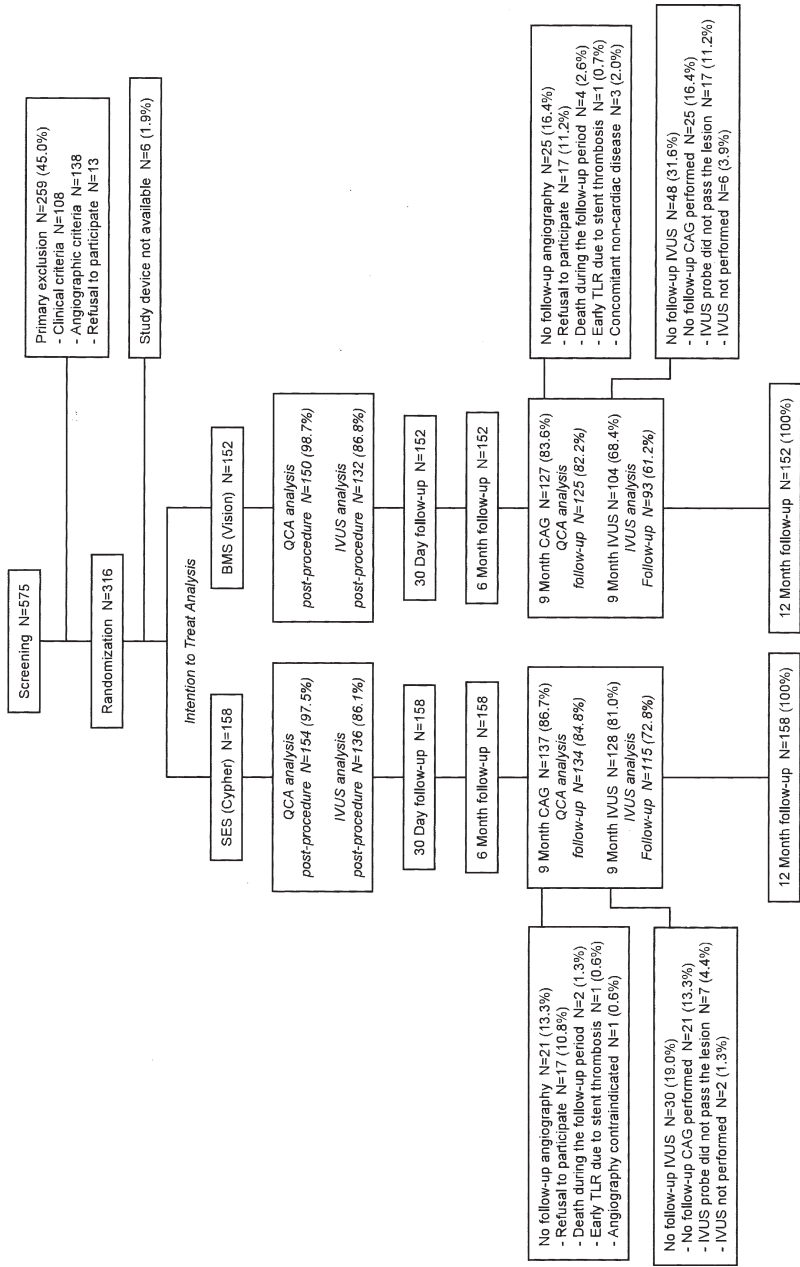


Figure 1. Patient flow chart, enrollment, and outcomes BMS = bare metal stent; CAG = coronary angiography; IVUS = intravascular ultrasound; QCA = quantitative coronary angiography; SES = sirolimus-eluting stent; TLR = target lesion revascularization.

Characteristic	SES (n = 158)	BMS (n = 152)	p Value
Direct stenting	57 (36.1)	59 (38.8)	0.62
Number of stents in the culprit lesion	1.34 ± 0.61	1.38 ± 0.63	0.57*
Implanted stent length, mm	26.5 ± 12.8	26.4 ± 11.1	0.95*
Maximum stent diameter, mm	3.31 ± 0.26	3.37 ± 0.35	0.05
Maximum balloon diameter, mm	3.37 ± 0.31	3.40 ± 0.30	0.30
Maximal balloon pressure, bar	12.3 ± 2.5	12.2 ± 3.0	0.70
Maximal balloon to artery ratio	1.17 ± 0.17	1.15 ± 0.19	0.26
TIMI flow after			
0	1 (0.6)	0 (0.0)	1.00*
1	1 (0.6)	1 (0.7)	
2	10 (6.4)	10 (6.6)	
3	146 (92.4)	141 (92.7)	
Abciximab therapy	158 (100.0)	151 (99.3)	0.49*
Multivessel intervention during the index procedure	10 (6.3)	8 (5.3)	0.69
Procedural success	146 (92.4)	141 (92.8)	0.90
Clinical success	146 (92.4)	140 (92.1)	0.92

Table 2. Procedural characteristics

Data are expressed as number (%) or mean ± standard deviation. All comparisons between groups were performed with *t* test (continuous variables) or Pearson's chi-square test (categorical variables) except as indicated (*). Abbreviations as in Table 1.

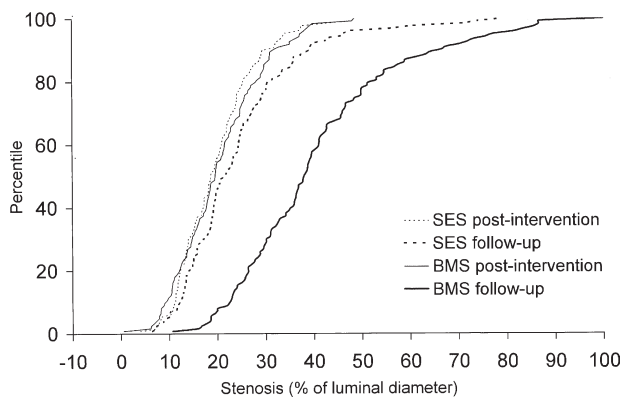


Figure 2. Cumulative rate of in-segment percentage diameter stenosis
Abbreviations as in Figure 1.

Characteristic	SES (n=131)	BMS (n=124)	P-value
Post-procedure			
Stented segment length – mm	22.3±10.0	22.6±8.4	0.77*
Reference diameter – mm	2.94±0.49	3.02±0.53	0.20
Minimal luminal diameter – mm			
In-segment	2.36±0.50	2.41±0.52	0.44
In-stent	2.67±0.38	2.71±0.37	0.33
Proximal margin	2.84±0.52	2.95±0.58	0.15
Distal margin	2.35±0.53	2.40±0.56	0.49
Stenosis – % of luminal diameter			
In-segment	20.0±8.2	20.4±9.1	0.67
In-stent	11.1±6.9	12.4±7.2	0.14
Proximal margin	11.4±9.4	10.8±9.7	0.64
Distal margin	15.1±10.9	14.9±10.8	0.91
Follow-up			
Reference diameter – mm	2.96±0.47	2.92±0.50	0.59
Minimal luminal diameter – mm			
In-segment	2.24±0.55	1.74±0.59	<0.001
In-stent	2.48±0.52	1.77±0.59	<0.001
Proximal margin	2.64±0.58	2.60±0.62	0.67
Distal margin	2.33±0.57	2.24±0.60	0.26
Late luminal loss – mm			
In-segment	0.12±0.43	0.68±0.57	<0.001
In-stent	0.19±0.39	0.95±0.55	<0.001
Proximal margin	0.20±0.33	0.34±0.48	0.01
Distal margin	0.03±0.31	0.16±0.45	0.007
Stenosis – % of luminal diameter			
In-segment	24.3±12.7	40.8±17.5	<0.001
In-stent	16.2±13.0	39.7±18.0	<0.001
Proximal margin	16.0±11.8	16.6±12.7	0.71
Distal margin	15.0±11.4	17.4±14.5	0.16
Angiographic restenosis			
In-segment	5 (3.8)	28 (22.6)	<0.001
In-stent	3 (2.3)	28 (22.6)	<0.001
Proximal margin	1 (0.9)	2 (1.9)	0.61
Distal margin	1 (0.8)	2 (1.7)	0.61

Table 3. Results of quantitative coronary angiography post-procedure and at follow-up
Data are expressed as number (%) or mean ± standard deviation. All comparisons between groups were performed with a *t* test except as indicated(*). Abbreviations as in Table 1.

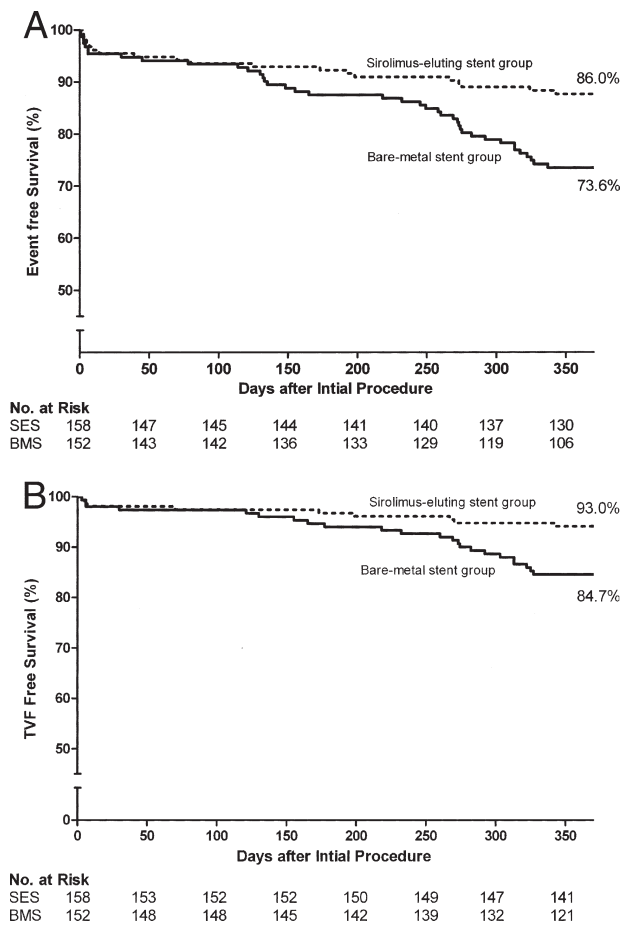


Figure 3. Event free and TVF free survival
(A) Kaplan-Meier estimates of survival free from any events among patients treated with BMS and those treated with SES. The event-free survival was significantly higher in the SES group than the BMS group ($p = 0.01$). (B) Kaplan-Meier estimates of survival free from target vessel failure (TVF) among patients treated with BMS and those treated with SES. The TVF free survival was significantly higher in the SES group than the BMS group ($p = 0.02$). Abbreviations as in Figure 1.

IVUS results

Follow-up IVUS results were available for 93 (61.2%) BMS patients and 115 (72.8%) SES patients ($p = 0.03$). Inability to cross the stented segment with the IVUS catheter in patients with significant restenosis was an important reason for the lower number of IVUS studies in BMS patients. Quantitative IVUS data are summarized in Table 4.

At follow-up, the minimal luminal area was $4.01 \pm 1.38 \text{ mm}^2$ in the BMS group and $5.67 \pm 1.59 \text{ mm}^2$ in the SES group ($p < 0.001$). The percentage neointimal volume was $27.0 \pm 11\%$ in the BMS group and $3.3 \pm 5.0\%$ in the SES group ($p < 0.001$). Late stent malapposition was present in 12.5% BMS patients and 37.5% SES patients. Late stent malapposition was persistent in 11.3% BMS patients and 18.3% SES patients ($p = 0.19$). Late stent malapposition was acquired in 5.0% BMS patients and

Characteristic	SES (n = 115)	BMS (n = 93)	p Value
Area, mm^2			
Minimal stent area	6.05 ± 1.56	6.54 ± 1.41	0.02
In-stent MLA	5.67 ± 1.59	4.01 ± 1.38	<0.001
Proximal margin MLA	6.81 ± 2.15	6.57 ± 2.53	0.55
Distal margin MLA	5.77 ± 2.09	5.52 ± 2.10	0.45
Volume, mm^3			
Stent volume	188 ± 86	199 ± 77	0.32
Lumen volume	181 ± 81	145 ± 60	<0.001
Neointimal volume	7 ± 12	54 ± 31	<0.001*
Percentage neointimal volume	3.3 ± 5.0	27.0 ± 11.0	<0.001*
Late stent malapposition†			
Number evaluated	104	80	
Any site‡	39 (37.5)	10 (12.5)	<0.001
Persistent	19 (18.3)	9 (11.3)	0.19
Acquired	26 (25.0)	4 (5.0)	<0.001*
Proximal stent edge	17 (16.3)	7 (8.8)	0.13
Persistent	14 (13.5)	7 (8.8)	0.32
Acquired	3 (2.9)	0 (0.0)	0.26*
Stent body	27 (26.0)	2 (2.5)	<0.001*
Persistent	6 (5.8)	1 (1.3)	0.14*
Acquired	21 (20.2)	1 (1.3)	<0.001*
Distal stent edge	13 (12.5)	4 (5.0)	0.08*
Persistent	6 (5.8)	2 (2.5)	0.47*
Acquired	7 (6.7)	2 (2.5)	0.30*

Table 4. Results of coronary ultrasound analysis at follow-up

Data are expressed as number (%) or mean $\pm$ standard deviation. All comparisons between groups were performed with *t* test (continuous variables) or Pearson's chi-square test (categorical variables) except indicated (); †Data are presented for patients with paired (post-procedural and follow-up) intravascular ultrasound results; ‡Some patients had both persistent and acquired late stent malapposition (6 SES, 3 BMS). MLA = minimal luminal area; other abbreviations as in Table 1.

in 25% SES patients ($p < 0.001$). Acquired LSM within the body of the stent occurred almost exclusively in SES patients (20.2% vs. 1.3% in BMS patients, $p < 0.001$).

Event	SES (n=158)	BMS (n=152)	P-value
Death	2 (1.3)	4 (2.6)	0.44*
Non-cardiac	-	2 (1.3)	0.24*
Cardiac	2 (1.3)	2 (1.3)	1.00*
Target vessel related	2 (1.3)	2 (1.3)	1.00*
Recurrent myocardial infarction	9 (5.7)	14 (9.2)	0.24
Spontaneous	2 (1.3)	3 (2.0)	0.68*
Target vessel related	2 (1.3)	3 (2.0)	0.68*
Procedure related	7 (4.4)	11 (7.2)	0.29
Target vessel related	2 (1.3)	6 (3.9)	0.17*
Revascularization procedure [†]	19 (12.0)	35 (23.0)	0.01
PCI	17 (10.8)	30 (19.7)	0.03
CABG	2 (1.3)	5 (3.3)	0.28*
Target vessel revascularization [†]	8 (5.1)	20 (13.2)	0.01
PCI	6 (3.8)	17 (11.2)	0.01
CABG	2 (1.3)	3 (2.0)	0.68*
Target lesion revascularization [†]	5 (3.2)	17 (11.2)	0.006
PCI	3 (1.9)	14 (9.2)	0.005
CABG	2 (1.3)	3 (2.0)	0.68*
Clinically driven revascularization	4 (2.5)	12 (7.9)	0.03
Any event	22 (13.9)	40 (26.3)	0.01‡
Target vessel failure	11 (7.0)	23 (15.1)	0.02‡
Stent thrombosis	2 (1.3)	3 (2.0)	0.68*
Acute (<24 hours)	-	-	-
Subacute (1 day – 30 days)	2 (1.3)	2 (1.3)	1.00*
Late (>30 days)	-	1 (0.7)	0.49*
Angiographically documented	1 (0.6)	1 (0.7)	1.00*

Table 5. Clinical events during 12-Months follow-up

Data are expressed as number (%). All comparisons between groups were performed with Pearson's chi-square test (categorical variables), except as indicated (Fisher exact test*; log-rank test‡); †If the patient underwent more than 1 procedure, for every type of revascularization procedure (revascularization, target vessel revascularization, or target lesion revascularization) the first event per patient was counted. Abbreviations as in Table 1.

Clinical outcome

No patients were lost to follow-up. Adverse events during follow-up are listed in Table 5. The event-free survival was 73.6% in BMS patients and 86.0% in SES patients (HR 1.96, 95% CI 1.17 to 3.30) (Fig. 3A). During follow-up 6 patients died (1.9%), 4 BMS patients and 2 SES patients ($p = 0.44$). Recurrent MI occurred in 9.2% of BMS patients and 5.7% of SES patients ($p = 0.24$); in 7.2% and in 4.4% of the patients this was related to a re-PCI procedure, respectively ($p = 0.29$). Spontaneous MI, all related to stent thrombosis, occurred in 2.0% of BMS patients and in 1.3% of SES patients ($p = 0.68$). Target lesion revascularization rate was 11.2% in BMS patients and 3.2% in SES patients ($p = 0.006$). The clinically driven target lesion revascularization rate was 7.9% in BMS patients and 2.5% in SES patients ($p = 0.03$). Target-vessel-failure-free survival was 84.7% in the BMS group and 93.0% in the SES group (HR 2.24, 95% CI 1.09 to 4.60) (Fig. 3B). Clinical event rates were not significantly different between patients who underwent follow-up angiography and patients who did not.

DISCUSSION

Compared with treatment with BMS, both in-segment LLL and target vessel failure rates were significantly lower after treatment with SES in patients with acute MI. However, after SES implantation LSM was seen more often than after implantation of BMS.

Angiographic results

Angiographic in-segment LLL at 9-months' follow-up was chosen as the primary end point, since it reflects the luminal response of the treated segment, including the segments just outside the stent. Late luminal loss is a surrogate but powerful end point to compare the efficacy of stents for the prevention of restenosis.(20) In-segment LLL in the SES group was comparable to the LLL found in the angiographic subgroup of the recently published TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Angioplasty).(9) The SES LLL was in fact comparable to the LLL in stable angina patients and superior to LLL achieved with BMS in other STEMI studies.(2,5,6) The rate of LLL in the BMS group was slightly higher than in the TYPHOON study, which may be explained by the longer implanted stent length in our study.

IVUS results

As in patients with stable angina, SES treatment in STEMI patients is associated with negligible neointimal hyperplasia, whereas BMS treatment is associated with significant hyperplasia at follow-up.(21) This finding explains the low angiographic in-stent restenosis rate in the SES group. However, despite excellent angiographic results, a significant rate of LSM (37.5%) was observed in the SES group. The majority of these malappositions was not present immediately after implantation but developed during follow-up, predominantly along the body of the stent (20.2%). The rate of LSM after SES in STEMI patients is even higher than observed in the SIRIUS (Sirolimus-Eluting Stent in Coronary Lesions) (16.3%) and RAVEL (A Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization) (21%) studies, both comparing SES with BMS in patients with stable and unstable angina. (5,22) In line with our findings, acquired LSM in the SIRIUS study was also mainly located alongside the body of stent.(22) There are only limited data about LSM after stenting in STEMI patients. Hong et al.(23) reported an LSM rate of 11.5% after BMS implantation. In contrast, LSM after drug-eluting stent implantation was present in 31.8% in an observational study of the same group.(24)

Late stent malapposition may be caused by 3 different factors: 1) insufficient stent deployment during implantation; 2) resolution of thrombus and/or plaque behind the stent; or 3) positive remodeling of the vessel wall. Persistent LSM, mainly involving the proximal or distal edges of the stents, may be caused by insufficient stent deployment and is thought to be of minor clinical importance.(23) In contrast, acquired LSM, especially when located along the body of the stent, may be due to an adverse effect of the drug on the vessel wall resulting in positive remodeling. This type of LSM cannot be avoided during stent implantation and raises concern about long-term safety, as LSM has been related to very late (>1 year) stent thrombosis.(11,25)

Clinical outcome

The reduction of target vessel failure rate after SES implantation in STEMI patients was in line with the results of the TYPHOON study.(9) In contrast, the PASSION (Paclitaxel Eluting Stent Versus Conventional Stent in ST-Segment Elevation Myocardial Infarction) study, comparing paclitaxel-eluting stents and BMS in STEMI patients, failed to demonstrate a reduction in the target vessel failure rate in the paclitaxel-eluting stent group.(8) This difference may be explained by differences in baseline characteristics such as a larger reference diameter and shorter implanted stent length, differences in stent design and drug efficacy, or the lack of angiographic follow-up in the PASSION study.(26)

Mortality and MI rates were low in both groups. The MI rate was slightly higher than in the TYPHOON study, possibly because of the strict definitions used in our study. Of interest, the stent thrombosis rate at 12 months was lower and comparable to the results of the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent vs. Abciximab and Bare-Metal Stent in Myocardial Infarction) study (comparing SES with tirofiban and BMS with abciximab in STEMI patients). (27) There were no cases of acute stent thrombosis (<24 h), possibly because of the intensive antithrombotic regimen applied, including the administration of abciximab in all patients. Late stent thrombosis (>30 days) occurred in 1 BMS patient (0.7%).

Study limitations

With regard to the outcome, the noninferiority design of the study is a relative limitation. (28) At the time of conception of the study, only limited information about the efficacy of SES and third-generation BMS in STEMI patients was available. It was assumed that, despite limited differences in late loss, third-generation BMS were not inferior to drug-eluting stents with regard to efficacy, whereas adverse effects of drug-eluting stents such as LSM and delayed re-endothelialization could be avoided by using BMS. (11) Another limitation is that the angiographic and clinical results of this study cannot be translated into general daily clinical practice, as this was a single-center study in selected patients, and patients were followed using a strict guideline-based follow-up protocol, which is not common practice yet. Moreover, this study was underpowered to detect differences in safety events such as death, recurrent MI, or stent thrombosis. Since IVUS follow-up was not possible in some BMS patients because of restenosis, we cannot exclude that LSM was underestimated in the BMS group, although this is unlikely since these patients had more neointimal growth. Finally, we cannot exclude that the routine angiographic follow-up did result in additional revascularization procedures, magnifying the difference in clinical outcome between BMS and SES.

CONCLUSIONS

The SES implantation in STEMI patients is associated with superior midterm clinical and angiographic results compared with BMS implantation. However, LSM is frequently observed in STEMI patients treated with SES, raising concern about long-term safety warranting long-term clinical follow-up. Therefore, based on this study, we cannot recommend or discourage SES use in STEMI patients.

ACKNOWLEDGEMENT

Clinical Events Committee: A.V.G. Bruschke, MD, PhD, Leiden, The Netherlands and S.A.I.P. Trines, MD, PhD, Leiden University Medical Center, Leiden, The Netherlands.

REFERENCES

1. Zijlstra F, Hoorntje JC, de Boer MJ, et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1999;341:1413-9.
2. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* 1999;341:1949-56.
3. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002;346:957-66.
4. Fajadet JF, Wijns WF, Laarman GJ, et al. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation* 2006;114:798-806.
5. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;346:1773-80.
6. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315-23.
7. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;350:221-31.
8. Laarman GJ, Suttorp MJ, Dirksen MT, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. *N Engl J Med* 2006;355:1105-13.
9. Spaulding C, Henry P, Teiger E, et al. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. *N Engl J Med* 2006;355:1093-1104.
10. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004;364:1519-21.
11. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006;48:193-202.
12. Liem SS, van der Hoeven BL, Oemrawsingh PV, et al. MISSION!: Optimization of acute and chronic care for patients with acute myocardial infarction. *Am Heart J*. 2007 Jan;153:14.e1-11
13. Oemrawsingh PV, Mintz G, Schalij M, et al. Intravascular ultrasound guidance improves angiographic and clinical outcome of stent implantation for long coronary artery stenoses:

final results of a randomized comparison with angiographic guidance (TULIP Study). *Circulation* 2003;107:62-7.

14. Doucet S, SchaliJ MJ, Vrolix MC, et al. Stent placement to prevent restenosis after angioplasty in small coronary arteries. *Circulation* 2001;104:2029-33.
15. Koning GF, Dijkstra JF, von Birgelen CF, et al. Advanced contour detection for three-dimensional intracoronary ultrasound: a validation - in vitro and in vivo. *Int J Cardiovasc Imaging* 2002;18:235-48.
16. Mintz GS, Nissen SE, Anderson WD, et al. American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2001;37:1478-92.
17. Mintz GS, Shah VM, Weissman NJ. Regional remodeling as the cause of late stent malapposition. *Circulation* 2003;107:2660-3.
18. Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;36:959-69.
19. Apple FS, Wu AH, Jaffe AS. European Society of Cardiology and American College of Cardiology guidelines for redefinition of myocardial infarction: how to use existing assays clinically and for clinical trials. *Am Heart J* 2002;144:981-6.
20. Mauri LF, Orav EJ, Kuntz RE. Late loss in lumen diameter and binary restenosis for drug-eluting stent comparison. *Circulation* 2005;111:3435-42.
21. Serruys PW, Degertekin M, Tanabe K, et al. Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (RAnomized study with the sirolimus-eluting VELOCITY balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial. *Circulation* 2002;106:798-803.
22. Ako J, Morino Y, Honda Y, et al. Late incomplete stent apposition after sirolimus-eluting stent implantation: a serial intravascular ultrasound analysis. *J Am Coll Cardiol* 2005;46:1002-5.
23. Hong MK, Mintz GS, Lee CW, et al. Incidence, mechanism, predictors, and long-term prognosis of late stent malapposition after bare-metal stent implantation. *Circulation* 2004;109:881-6.
24. Hong MK, Mintz GS, Lee CW, et al. Late stent malapposition after drug-eluting stent implantation: an intravascular ultrasound analysis with long-term follow-up. *Circulation* 2006;113:414-9.
25. Cook S, Wenaweser P, Togni M, et al. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation* 2007;115:2426-36.

26. Kastrati A, Dibra A, Eberle S, et al. Sirolimus-eluting stents vs paclitaxel-eluting stents in patients with coronary artery disease: meta-analysis of randomized trials. *JAMA* 2005;294:819-25.
27. Valgimigli MF, Percoco GF, Malagutti PF, et al. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. *JAMA* 2005;293:2109-17.
28. Piaggio G, Elbourne DR, Altman DG, et al. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* 2006;295:1152-60.

CHAPTER 7

Cardiovascular risk in young
apparently healthy descendents
from Asian Indian migrants in the
Netherlands: the SHIVA study

Su San Liem
Pranobe V. Oemrawsingh
Suzanne C. Cannegieter
Saskia Le Cessie
Joop Schreur
Frits R. Rosendaal
Martin J. Schalij

ABSTRACT

Background

Asian Indian migrants in the Western world are highly susceptible for ischaemic heart disease (IHD). Until now, most IHD risk studies were performed in first and second generation Asian Indian expatriates. For optimal prevention, knowledge of the cardiovascular risk profile of younger generations is crucial.

Method

In a cross-sectional study we assessed the prevalence of conventional IHD risk factors and Framingham risk score in asymptomatic third to seventh generation Asian Indian descendants, compared with Europeans. Subjects were classified as asymptomatic if they did not have documented IHD, diabetes, hypertension or high cholesterol.

Results

A total of 1790 Asian Indians (45% men, age 35.9 ± 10.7 years) and 370 native Dutch hospital employees (23% men, age 40.8 ± 10.1 years) were recruited. Asian Indians had higher levels of total cholesterol, low-density lipoprotein, triglycerides, and lower high-density lipoprotein levels than the Dutch. Glucose intolerance was present in 7.1 vs. 0.5% men, and in 6.1 vs. 1.4% women (both $p < 0.001$). Asian Indian women were more frequently obese (12 vs. 5%; $p < 0.001$), and centrally obese (44 vs. 25%; $p < 0.001$) as compared with the Dutch women. Prevalence of most of the conventional and modifiable cardiovascular risk factors in each ten-year age group was higher in Asian Indians compared with controls, which reflected in higher Framingham risk scores.

Conclusion

This study demonstrates the persistence of an unfavourable cardiovascular risk profile in young, third to seventh generation migrated Asian Indians and supports an aggressive screening and intervention strategy.

INTRODUCTION

Asian Indian people exhibit a high risk for the development of ischaemic heart disease (IHD).(1,2) This increased risk has been reported in emigrated Asian Indians as well as in Asian Indians living in urban areas of their native countries.(1-3) In addition, IHD becomes manifest at a younger age and is more often fatal, especially in young Asian Indian men, as compared with other ethnic groups.(1,2,4)

The underlying mechanism of the higher risk of IHD in Asian Indians compared with other ethnic groups is unclear. Conventional risk factors alone cannot explain this excess risk, and other biological and environmental factors seem to play an important role.(5) For example, although generally the degree of sub-clinical atherosclerosis is related to clinical cardiovascular events, Asian Indians appear to have less atherosclerosis, yet they have more events.(5) Furthermore, clinical manifestations of insulin resistance are consistently reported to be more frequent in Asian Indians compared with other ethnic groups, irrespective of their geographical location.(6,7) Insulin resistance is associated with the development of IHD and manifests as a constellation of interrelated risk factors as notably elevated triglycerides levels, reduced high-density lipoprotein (HDL) levels, central obesity, hyperinsulinaemia and an increased prevalence of diabetes type 2.(8) At a genetic level, explanations can be found in adverse gene-environmental interactions and the thrifty gene hypothesis.(9) Furthermore, the rural-urbanization shift in South Asia has the same deteriorating effects on the risk profile and prevalence of IHD as the migration of Asian Indians to Western countries.(3,10)

There is a large Asian Indian community in the Netherlands (approximately 200,000 persons). This community mainly consists of migrants from Surinam, a former South American Dutch colony. Historically, the abolishment of slavery in 1863 was the start of migration of Asian Indians from India to Surinam. These migrants were contract workers on former plantations and were almost exclusively recruited from the Indian state Bihar. The declaration of independence of Surinam in 1975 initiated a second wave of migration of these Asian Indians, this time to the Netherlands. Nowadays, these immigrants and their offspring form a third to seventh generation of Asian Indians. As in other Western countries, these young generation Asian Indian descendants also exhibit higher rates of early onset cardiovascular morbidity and mortality in comparison with the native Dutch population.(11)

Until now, most IHD risk studies in Asian Indians were performed in first and second generation Asian Indian expatriates.(5,6,10,12,13) To optimize preventive strategies in younger generations of this high-risk population, knowledge of the

current cardiovascular risk profile is crucial. Hence, we performed the SHIVA study (Screening of **H**industans for cardio**V**ascular risk factors).

METHODS

Design

SHIVA is a cross-sectional study, designed to assess the prevalence of conventional IHD risk factors and the ten-year Framingham risk scores of asymptomatic third to seventh generation Asian Indian migrants in the Netherlands.⁽¹⁴⁾ All data were compared with a control group comprising healthy native Dutch hospital employees. Every participant provided written informed consent. The institutional ethical committee approved the study protocol.

Study population

Asian Indian subjects (aged 18 to 60 years) were recruited at the Milan cultural festival held in The Hague in the Netherlands, in July 2004. This festival is organised annually and attended by 50,000 to 60,000 Asian Indians. Subjects were classified as Asian Indians if at least one parent's ancestor originated from the Indian subcontinent. Considering the ancestors emigrated from South Asia in the latter part of the 19th century, and based on one generation of 20 years, this group forms a third to seventh generation of Asian Indian migrants. Asian Indians born in the Indian subcontinent were excluded. The control group comprised healthy Dutch hospital employees (Medical Center Haaglanden, The Hague, the Netherlands). Dutch origin was defined as both parents being Dutch from European origin. Subjects were classified as asymptomatic when they did not have documented IHD, diabetes, hypertension or high cholesterol and were not receiving any form of treatment for any of these conditions. All others were excluded.

A total of 2102 study participants and 560 controls were screened. Of them 502 subjects (19%) were excluded; 120 due to unknown or neither Asian Indian nor Dutch origin; 122 Asian Indians because of unknown place of birth or born in the Indian subcontinent; 214 participants for not being asymptomatic; and 46 subjects who did not match the age range of interest (18 to 59 years). This left 1790 Asian Indians and 370 native Dutch subjects who were included in this analysis.

Procedures

Similar procedures were performed in both study and control group. The participants completed a short questionnaire, including age, sex, medical history, family history of cardiovascular disease, the use of medication, smoking habits, alcohol intake and time of last meal. A positive family history was defined as a father, mother, brother or sister who suffered from cardiovascular disease before the age of 60 years. Current smoking was defined as using tobacco in the previous six months before participating in the SHIVA project.

Standardized anthropometric measurements, including height, weight and waist circumference, were performed by trained nurses. The waist circumference was defined as the narrowest circumference above the iliac crest and below the ribs. A waist circumference of ≥ 94 cm (men) and ≥ 80 cm (women) was considered as out-sized, a waist circumference of ≥ 102 cm (men) and ≥ 88 cm (women) was considered as central obesity. Body mass index (BMI) was calculated (kg/m^2), and overweight was defined as a BMI ≥ 25 kg/m^2 and obesity as a BMI ≥ 30 kg/m^2 .

Blood pressure was measured using an appropriately sized cuff in a sitting position. Hypertension was defined as a systolic blood pressure ≥ 160 mmHg and/or a diastolic blood pressure ≥ 90 mmHg. The cut-off value for systolic hypertension was set at 160 mmHg, while due to the setting, blood pressure measurements could be performed only once instead of serially. In addition, we also estimated the prevalence of subjects with the commonly used definition hypertension (systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg).(15)

Laboratory measurements were performed using the Cholestech LDX[®] analyser (Cholestech Corporation, Hayward USA). From 35 μl of blood, drawn from the finger, non-fasting total cholesterol, HDL cholesterol, triglycerides and glucose were measured. Low-density lipoprotein (LDL) cholesterol was estimated using Friedewald formula.(16) Very-low-density lipoprotein (VLDL) was estimated by dividing the triglycerides value by a factor of 2.2. A total cholesterol of ≥ 6.5 mmol/l was considered too high, and an HDL cholesterol ≤ 0.9 mmol/l too low. A non-fasting glucose of ≥ 7.8 mmol/l and ≤ 11 mmol/l was defined as impaired glucose tolerance. A non-fasting glucose of > 11 mmol/l was defined as diabetes mellitus.

Data collection

All data were entered into a customized database, and the ten-year Framingham risk scores were calculated.(14) All participants received a printed copy of their risk assessment and, if necessary, personal lifestyle recommendations.

Data analyses

Prevalence and mean of each risk factor were calculated for both groups. Since the age distribution was different between control group and study group, risk factor data of the control group were standardized for age by using the size of each five-year age group of the study population as weights. Standard errors of these standardized values were obtained by calculation of a weighted average of the variances in the age groups with the squared size of the age groups in the study population as weights. 95% confidence intervals (CI) of the differences between the two groups were calculated using the standard normal distribution.

To identify potentially modifiable risk factors in each age group, we assessed the prevalence of risk factors in each ten-year age group. Moreover, as healthcare workers may be more health conscious, we also mirrored our ten-year age group risk factor data with a Dutch population survey conducted on municipal health services in 2001 ('Regenboog' project).(17) Individual estimated Framingham risk scores of the Asian Indians were categorised as >10%, >15% and >20% for each five-year age group, and for smokers and non-smokers.(14) All data were analysed with SPSS v 12.0.1 (SPSS Inc., Chicago, Ill).

RESULTS

Asian Indians on average were younger than Dutch subjects (men 35.8 years, 95% CI 35.1 to 36.5 vs. 40.7 years, 95% CI 38.4 to 43.0, and women 36.0 years, 95% CI 35.3 to 36.7 vs. 40.8 years, 95% CI 39.7 to 42.0), although the age range was similar (18 to 59 years). The groups were different with respect to sex distribution (men 45.4% in Asian Indians vs. 23.0% in the control group).

Prevalence of risk factors

Cardiovascular risk factors and blood chemistry measurements for both groups are shown in table 1. Asian Indians had a higher prevalence of a positive family history of cardiovascular disease, hypertension and diabetes compared with the control group. Fewer Asian Indian women smoked compared with Dutch women. Both Asian Indian men and women were more overweight compared with the control group. Asian Indian women were more frequently obese and had more central obesity. These differences were not seen in men.

In both Asian Indian men and women elevated cholesterol levels ≥ 6.5 mmol/l were more prevalent compared with the controls. Asian Indians more frequently had a low high-density lipoprotein (HDL). Mean low-density lipoprotein (LDL), triglycerides and very-low-density lipoprotein (VLDL) levels were all higher in Asian Indians. Impaired glucose tolerance was more common in Asian Indians compared with the controls. Among the Asian Indians 0.7% men and 0.9% women were diagnosed as de novo diabetes mellitus versus none in the control group.

Prevalence of risk factors per ten-year age group

To study the distribution of risk factors in each age group, prevalence of risk factors for each decade was determined in Asian Indians and Dutch subjects (table 2). Several risk factors were already present in a considerable proportion of subjects before the age of 30 years. Overweight, elevated cholesterol, low HDL and impaired glucose tolerance were all more prevalent in Asian Indians compared with the Dutch controls for both sexes regardless of age. Above the age of 40 years hypertension was more prevalent in Asian Indians. Asian Indian men smoked more frequently before the age of 50 compared with the control group. Asian Indian women had more (central) obesity as compared with Dutch women in each age category.

Comparing 'Regenboog' data with data of Asian Indians, Asian Indian men had more hypertension and lower HDL regardless of age, and in the youngest age group central obesity was more prevalent. Asian Indian women exhibited more obesity between the age of 40-49 years; more central obesity and low HDL in all age groups; more hypertension between 30-49 years, and more diabetes de novo between 20-29 years and 40-49 years.(17)

Framingham risk scores

In figure 1 the mean ten-year Framingham risk scores for each ten-year age group are shown. Asian Indian men exhibited higher Framingham risk scores in all age groups as compared with the controls. In Asian Indian women the same trend was found.

Figure 2 presents the prevalence of increased ten-year Framingham risk ($>10\%$) in each five-year age group for smoking and non-smoking Asian Indians. As many as 23% of smoking Asian Indian men aged 30-35 years had a risk $>10\%$, whereas non-smokers all had a risk $\leq 10\%$. In the age group 50-54 years all of the smoking men had a ten-year risk $>10\%$, and 77% had a risk $>20\%$. In smoking Asian Indian women between 40 and 44 years 29% had a ten-year risk $>10\%$; this was all above the age of 50 years.

	Men				Women			
	Asian Indian n=813		Dutch ^a n=85		Asian Indian n=977		Dutch ^a n=285	
		95% CI ^b		95% CI ^b		95% CI ^b		95% CI ^b
Family history of								
Cardiovascular disease, n(%)	259 (32)	29-35	19 (19)**	11-27	297 (30)	28-33	58 (19)***	14-24
Hypertension, n(%)	354 (44)	40-47	22 (24)***	13-34	487 (50)	47-53	122 (41)*	35-47
Hyperlipidemia, n(%)	111 (14)	11-16	14 (19)	9-30	183 (19)	16-21	67 (24)	18-29
Diabetes, n(%)	380 (47)	43-50	14 (15)**	7-22	497 (51)	48-54	48 (15)***	11-20
Smokers, n(%)	241 (30)	27-33	19 (28)	18-39	132 (14)	11-16	61 (22)**	16-27
Body Mass Index (Kg/m ²)	25.0	24.8-25.3	24.1*	23.4-24.9	24.9	24.6-25.2	23.2***	22.8-23.6
BMI ≥25 kg/m ² , n(%)	386 (47)	44-51	34 (35)*	25-45	445 (46)	42-49	79 (25)***	20-30
BMI ≥30 kg/m ² , n(%)	59 (7)	5-9	6 (5)	0.4-10	116 (12)	10-14	13 (5)**	2-7
Waist circumference	92.1	91.4-92.9	90.5	87.8-93.1	86.4	85.7-87.1	81.6***	80.3-82.8
≥94 cm for men or	361 (44)	41-48	36 (38)	28-48	-	-	-	-
≥80 cm for women, n(%)	-	-	-	-	705 (72)	69-75	167 (54)***	48-61
≥102 cm for men or	135 (17)	14-19	13 (13)	6-21	-	-	-	-
≥88 cm for women, n(%)	-	-	-	-	429 (44)	41-47	77 (25)***	20-31
Systolic blood pressure (mmHg)	136.8	135.6-138.0	138.0	133.7-142.3	125.3	124.2-126.4	126.0	124.2-127.9
Diastolic blood pressure (mmHg)	79.1	78.3-80.0	79.0	76.1-81.9	78.1	77.4-78.9	77.3	76.1-78.4
SBP ≥160 and/or DBP ≥90 mmHg, n(%)	168 (21)	18-24	17 (16)	9-23	163 (17)	14-19	44 (13)	9-17
SBP ≥140 and/or DBP ≥90 mmHg, n(%)	340 (42)	39-45	38 (47)	34-60	239 (25)	22-27	71 (22)	17-26
Cholesterol (mmol/l)	5.01	4.95-5.08	4.4***	4.2-4.6	4.75	4.69-4.80	4.6*	4.5-4.7
≥6.5 mmol/l, n(%)	42 (5.2)	3.6-6.7	0 (0)***	0.0-4.3	33 (3.4)	2.2-4.5	3 (0.5)***	0.0-1.1
HDL cholesterol (mmol/l)	1.01	0.99-1.03	1.20***	1.13-1.26	1.24	1.23-1.26	1.42***	1.38-1.45
≤0.9 mmol/l, n(%)	291 (36)	33-40	12 (16)***	8-24	102 (10)	9-12	3 (0.8)***	0.0-1.8

LDL cholesterol (mmol/l)	2.9	2.82-2.94	2.6**	2.4-2.7	2.73	2.68-2.78	2.62*	2.53-2.70
Triglycerides (mmol/l)	2.6	2.5-2.7	1.6***	1.3-1.9	1.72	1.66-1.77	1.26***	1.18-1.34
VLDL (mmol/l)	1.0	0.98-1.06	0.66***	0.58-0.75	0.77	0.74-0.79	0.58***	0.54-0.61
Total cholesterol/HDL	5.3	5.2-5.4	3.9***	3.6-4.1	3.98	3.92-4.05	3.3***	3.2-3.4
>5, n(%)	420 (52)	49-56	17 (20)***	13-28	160 (16)	14-19	12 (3)***	1-5
Non-fasting glucose	5.9	5.8-6.0	5.1***	4.8-5.3	5.86	5.77-5.94	5.3***	5.1-5.4
≥7.8 mmol/l, n(%)	58 (7.1)	5.4-8.9	1 (0.5)***	0.03-6.4	59 (6.1)	4.6-7.6	4 (1.4)***	0.0-2.9
>11 mmol/l, n(%)	6 (0.7)	0.1-1.3	0 (0)*	0.0-4.3	9 (0.9)	0.3-1.5	0 (0)**	0.0-1.3

Table 1. Cardiovascular risk factors of the Asian Indians and the Dutch control group by sex

^a In the Dutch control group: Means, % and 95% confidence intervals (CI) are standardised according to the age distribution of the Asian Indians.

^b 95% CI of the mean in continuous variable and 95% CI of the percentage in categorical variable

* P<0.05; ** P<0.01; ***P<0.001; BMI, Body Mass Index; DBP, Diastolic blood pressure; SBP, Systolic blood pressure

	Asian Indian					Dutch control group					"Regenboog" project ^ψ				
	Age group (years)		20-29	30-39	40-49	50-59	20-29	30-39	40-49	50-59	20-29	30-39	40-49	50-59	
MEN			n=217	n=234	n=225	n=94					n=75	n=151	n=176	n=192	
Smokers (%)			34	25	31	29	17	20	23	31	NA	NA	NA	NA	
SBP ≥140 and/or DBP ≥90 mmHg (%)			35	36	47	67	56	45	36	50	13	17	38	48	
Body Mass Index ≥30 Kg/m2 (%)			4	10	8	7	0	10	7	13	6	8	15	15	
Waist circumference ≥102 cm (%)			9	20	22	20	6	21	19	13	4	19	26	33	
Cholesterol ≥6.5 mmol/L (%)			2	6	8	7	0	0	0	0	5	4	11	19	
HDL cholesterol ≤0.9 mmol/l (%)			38	42	37	27	6	30	13	6	17	24	20	18	
Glucose >11 mmol/L (%)			0	1	1	2	0	0	0	0	0*	2*	4*	5*	
WOMEN			n=243	n=251	n=310	n=106	n=53	n=59	n=115	n=56	n=89	n=177	n=159	n=180	
Smokers (%)			19	12	12	9	19	20	24	20	NA	NA	NA	NA	
SBP ≥140 and/or DBP ≥90 mmHg (%)			9	18	39	46	15	22	30	29	7	12	26	46	
Body Mass Index ≥30 Kg/m2 (%)			11	10	15	15	6	7	4	2	9	11	10	14	
Waist circumference ≥88 cm (%)			26	45	55	64	15	25	35	26	17	30	36	48	
Cholesterol ≥6.5 mmol/L (%)			2	2	3	12	0	0	0	5	2	3	9	20	
HDL cholesterol ≤0.9 mmol/l (%)			9	12	14	7	0	2	1	2	2	6	8	2	
Glucose >11 mmol/L (%)			1	0	2	2	0	0	0	0	0*	0*	0*	2*	

Table 2. Modifiable risk factors per 10-year age group by sex^ψ Viet AL, et al. (17) DBP, Diastolic blood pressure; HDL, High Density Lipoprotein; NA, data not available; SBP, Systolic blood pressure.* Prevalence of fasting glucose $\geq$ 7.0 mmol/L in 50% of the men and 54% of the women

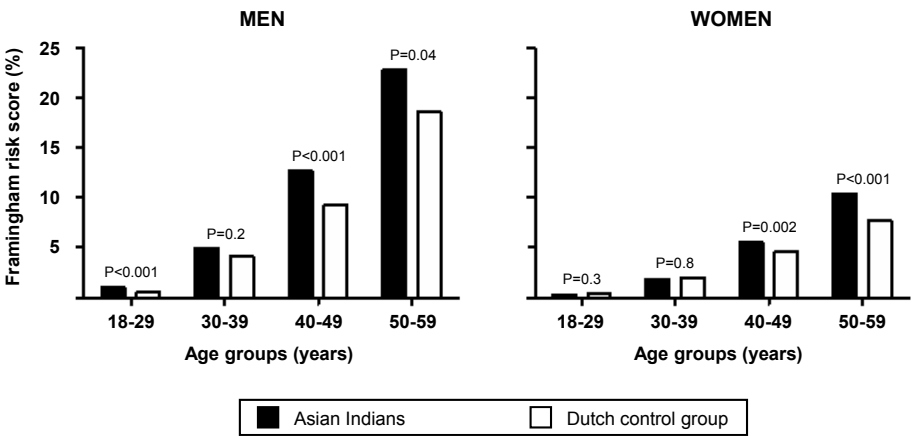


Figure 1.
Framingham risk score in men and women

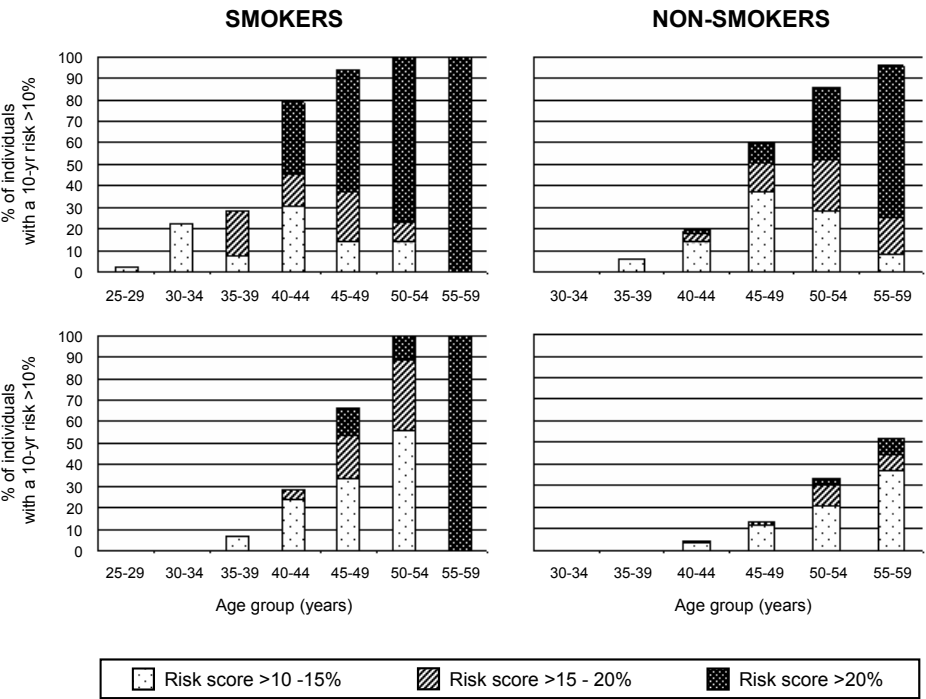


Figure 2.
Prevalence of increased Framingham risk (>10%) in smoking and non-smoking Asian Indians

DISCUSSION

The key finding of this study is the striking unfavourable IHD risk profile present in young, apparently healthy third to seventh generation Asian Indians. Most of the earlier studies of cardiovascular risk in Asian Indians involved first and second generation migrants who were older than the subjects in this study.(5,6,10,12,13) However, knowledge of the IHD risk profile of younger generations is of utmost importance both for the development of prevention strategies and for the insight into the aetiology of IHD disease in this high-risk population.

Prevalence of risk factors

In comparison with the Dutch control group, Asian Indians more often had a positive family history for cardiovascular disease, hypertension, and diabetes. Furthermore, levels of total cholesterol, VLDL and triglycerides were higher, HDL levels were lower, and impaired glucose intolerance was more prevalent. These findings correspond with prior studies reporting a high prevalence of insulin resistance in Asian Indians. (18,19) Glucose intolerance, a predisposition to develop type 2 diabetes mellitus, was diagnosed 14 times more often in Asian Indian men and four times more often in Asian Indian women compared with Dutch controls.

Overweight was more common in both Asian Indian men and women compared with the Dutch controls. With regard to the prevalence of (central) obesity a sex difference was observed. In line with previous studies, Asian Indian women suffered significantly more from obesity and central adiposity as compared with the control group; no differences were found among men.(12,13,19) Furthermore, despite equal proportion of (central) obesity in Asian Indian and Dutch men, Asian Indian men exhibited higher rates of dyslipidaemia and glucose intolerance. This is in agreement with the observation of Chandalia et al.(20) who reported that insulin resistance in Asian Indian men is commonly present even in the absence of excessive body fat content or abdominal obesity. Moreover, using the population specific cut-off points from the International Diabetes Federation, the Asian Indian men had more central obesity compared with the Dutch controls (59 vs. 38%), which suggests that Asian Indians may easily be overlooked for adequate prevention interventions.(21)

Prevalence of risk factors with respect to age

Multiple modifiable risk factors were already present in a large number of Asian Indians before the age of 30 years. Furthermore, prevalence of most risk factors was higher in Asian Indians as compared with Dutch controls in each age group. Despite

the fact that 11 % of the 'Regenboog' participants were known with hypertension and 3% with diabetes, important differences in the prevalence of risk factors remained between our Asian Indians and the 'Regenboog' population.(17) As modification of these cardiovascular risk factors affects long-term outcome, prevention strategies in Asian Indians should focus on the younger age groups. Main targets should be to revert conditions as overweight, dyslipidaemia and glucose intolerance, which can be achieved by effective lifestyle changes and, if necessary, additional drug therapy. (8) Adequate interventions can decrease the high prevalence of hypertension in Asian Indians above the age of 40 years.(8,15) In addition, among Asian Indian men smoking is an important issue to address.

Framingham risk score

The Asian Indians exhibited higher ten-year Framingham risk scores compared with the control groups. Grundy et al.(22) stressed the importance of also focussing on long-term risk (>10 years), which is especially interesting in young and middle-aged adults. A risk score of 10% in a 30-year asymptomatic adult may still be considered of limited clinical importance for the short-term; however, it will inevitably lead to a risk >20% before the age of 50 years.(22) The guidelines of the joint European societies have not defined a specific age threshold for screening.(23) In the Dutch guidelines, an age of 50 years in smoking men and 55 years in smoking women is recommended.(24) This is based on the chance to identify an individual with a ten-year risk of IHD >10%.(24) Our prevalence data of Asian Indian subjects with a Framingham risk >10% indicate that on the same basis, screening may be justified in smoking Asian Indian men at the age of 30 and smoking Asian Indian women at the age of 40. These screening time points can be extended with five years in the non-smoking Asian Indian population. However, further study is necessary to assess the health benefits and cost-effectiveness of this approach.

LIMITATIONS

There are some limitations to be discussed. First, persons with cardiovascular disease in the family might have been keener to participate than those without, hence attracting volunteers with a higher risk profile for IHD than non-volunteers. A sub-analysis in those without a known family history of cardiovascular disease resulted in similar results with slight variations due to the smaller sizes of the groups.

Second, due to the setting, non-fasting blood samples were used for chemistry measurements in most of the study and control subjects. This affected the VLDL, LDL and triglycerides measurements.(25) Slight underestimation or overestimation of the prevalence of glucose intolerance and de novo diabetes can not be excluded. In addition, blood pressure measurements were performed only once instead of serially, and white-coat effect also varies between different ethnicities.(26) Although the cut-off value for systolic hypertension was chosen higher than commonly used, overestimation of hypertension prevalence may have occurred.

Lastly, a recalibrated model for IHD risk prediction specified to Asian Indians does not exist. Small sample size studies revealed that the Framingham model seems to predict IHD outcomes in this group fairly well, whereas the SCORE model does not.(27) Others recommend adjusting the underestimation of risk in Asian Indians by multiplying IHD risk with factor 1.79 or to lower the risk threshold, which seems reasonable regarding the higher prevalence of IHD in Asian Indians.(28,29) Additionally, risk factors such as obesity, a family history of premature cardiovascular disease and elevated triglyceride levels are common in our study population, but not included in the Framingham assessment.(22) Nevertheless, these risk function models are still the best guiding tools for risk reduction management in daily clinical practice. (22,23)

CONCLUSIONS

The results of this study demonstrate that conventional and modifiable risk factors are already present at a young age in a significant number of apparently healthy third to seventh generation Asian Indians. In order to modify this risk profile, and thereby to decrease the chance of subsequent early onset of cardiovascular events, screening followed by adequate treatment should start at a younger age than recommended in the current guidelines.

ACKNOWLEDGEMENT

We thank Mrs A. Mahabier Panday (BBA) and Drs R.D.A. Baboeram for their support in organizing and facilitating this study.

REFERENCES

1. Balarajan R. Ethnic differences in mortality from ischaemic heart disease and cerebrovascular disease in England and Wales. *BMJ* 1991;302:560-4.
2. Enas EA, Yusuf S, Mehta JL. Prevalence of coronary artery disease in Asian Indians. *Am J Cardiol* 1992;70:945-9.
3. Singh RB, Sharma JP, Rastogi V, Raghuvanshi RS, Moshiri M, Verma SP, et al. Prevalence of coronary artery disease and coronary risk factors in rural and urban populations of north India. *Eur Heart J* 1997;18:1728-35.
4. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937-52.
5. Anand SS, Yusuf S, Vuksan V, Devanese S, Teo KK, Montague PA, et al. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE). *Lancet* 2000;356:279-84.
6. McKeigue PM, Ferrie JE, Pierpoint T, Marmot MG. Association of early-onset coronary heart disease in South Asian men with glucose intolerance and hyperinsulinemia. *Circulation* 1993;87:152-61.
7. Misra A, Vikram NK. Insulin resistance syndrome (metabolic syndrome) and obesity in Asian Indians: evidence and implications. *Nutrition* 2004;20:482-91.
8. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112:2735-52.
9. Khunti K, Samani NJ. Coronary heart disease in people of south-Asian origin. *Lancet* 2004;364:2077-8.
10. Bhatnagar D, Anand IS, Durrington PN, Patel DJ, Wander GS, Mackness MI, et al. Coronary risk factors in people from the Indian subcontinent living in west London and their siblings in India. *Lancet* 1995;345:405-9.
11. Bos V, Kunst AE, Keij-Deerenberg IM, Garssen J, Mackenbach JP. Ethnic inequalities in age- and cause-specific mortality in The Netherlands. *Int J Epidemiol* 2004;33:1112-9.
12. Bhopal R, Unwin N, White M, Yallop J, Walker L, Alberti KG, et al. Heterogeneity of coronary heart disease risk factors in Indian, Pakistani, Bangladeshi, and European origin populations: cross sectional study. *BMJ* 1999;319:215-20.

13. Cappuccio FP, Cook DG, Atkinson RW, Strazzullo P. Prevalence, detection, and management of cardiovascular risk factors in different ethnic groups in south London. *Heart* 1997;78:555-63.
14. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837-47.
15. Whitworth JA. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 2003;21:1983-92.
16. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499-502.
17. Viet AL, van den Hof S, Elvers LH, Ocké MC, Vossenaar M, Seidel JC, et al. Risk factors and health in the Netherlands: a survey on municipal health services (REGENBOOG project). 2001 <http://www.rivm.nl/bibliotheek/rapporten/260854004.pdf>
18. Knight TM, Smith Z, Whittles A, Sahota P, Lockton JA, Hogg G, et al. Insulin resistance, diabetes, and risk markers for ischaemic heart disease in Asian men and non-Asian in Bradford. *Br Heart J* 1992;67:343-50.
19. McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet* 1991;337:382-6.
20. Chandalia M, Abate N, Garg A, Stray-Gundersen J, Grundy SM. Relationship between generalized and upper body obesity to insulin resistance in Asian Indian men. *J Clin Endocrinol Metab* 1999;84:2329-35.
21. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. 2005. <http://www.idf.org/home/>
22. Grundy SM, Pasternak R, Greenland P, Smith S Jr, Fuster V. AHA/ACC scientific statement: Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *J Am Coll Cardiol* 1999;34:1348-59.
23. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J* 2003;24:1601-10.
24. Dutch Society of General Practitioners. NHG-standard Cardiovascular Risk Management. Houten, the Netherlands: Bohn Stafleu van Loghum, 2006.
25. Rifai N, Merrill JR, Holly RG. Postprandial effect of a high fat meal on plasma lipid, lipoprotein cholesterol and apolipoprotein measurements. *Ann Clin Biochem* 1990;27:489-93.

26. Agyemang C, Bhopal R, Bruijnzeels M, Redekop WK. Does the white-coat effect in people of African and South Asian descent differ from that in White people of European origin? A systematic review and meta-analysis. *Blood Press Monit* 2005;10:243-8.
27. Bhopal R, Fischbacher C, Vartiainen E, Unwin N, White M, Alberti G. Predicted and observed cardiovascular disease in South Asians: application of FINRISK, Framingham and SCORE models to Newcastle Heart Project data. *J Public Health* 2005;27:93-100.
28. Aarabi M, Jackson PR. Predicting coronary risk in UK South Asians: an adjustment method for Framingham-based tools. *Eur J Cardiovasc Prev Rehabil* 2005;12:46-51.
29. Cappuccio FP, Oakeshott P, Strazzullo P, Kerry SM. Application of Framingham risk estimates to ethnic minorities in United Kingdom and implications for primary prevention of heart disease in general practice: cross sectional population based study. *BMJ* 2002;325:1271.

CHAPTER 8

Role of calcified spots detected by intravascular ultrasound in patients with ST-segment elevation acute myocardial infarction

Barend L. van der Hoeven
Su-San Liem
Pranobe V. Oemrawsingh
Jouke Dijkstra
J.Wouter Jukema
Hein Putter
Douwe E. Atsma
Ernst E. van der Wall
Jeroen J. Bax
Johan C. Reiber
Martin J. Schalij

ABSTRACT

Background

Electron Beam Computed Tomography studies have demonstrated that the extent of intracoronary calcium is related to the risk of coronary events.

Objective and methods

This study was performed to gain further insight in the distribution of focal calcifications and their relation to the site of plaque rupture within the culprit artery of consecutive patients ($n = 60$) with an acute myocardial infarction (AMI) using Intravascular Ultrasound (IVUS) imaging. Calcifications in the culprit lesion and adjacent segments were classified and counted according to their arc ($<45^\circ$, $45-90^\circ$, $90-180^\circ$, $>180^\circ$), length (<1.5 , $1.5-3.0$, $3.0-6.0$, >6.0 mm) and dispersion (number of spots per millimeter). Calcifications at the edge of a visible rupture or ulceration were considered to be related to the AMI.

Results

Compared to adjacent proximal and distal segments, the culprit lesion contained more calcified spots per millimeter (respectively 0.14, 0.10, and 0.21; $p < 0.05$). Small calcified spots (arc $<45^\circ$, length of <1.5 mm) were more common ($p < 0.05$). Plaque rupture or ulceration was manifest in 31 culprit lesions (52%) of which 14 (45%) contained focal calcifications. These calcified spots extended more often to $90-180^\circ$ degrees of the vessel circumference and were more often of moderate length (3-6 mm) when compared culprit lesions without visible plaque rupture ($p < 0.05$).

Conclusions

We conclude that culprit lesions in patients with AMI contain more and smaller calcifications compared to adjacent segments. Calcifications related to plaque rupture appear to be larger and extend over a wider arc compared to these calcified spots. Those larger calcified spots may play a role in plaque instability in a subgroup of lesions.

INTRODUCTION

Electron beam computer tomographic studies have demonstrated that the calcium burden in coronary arteries is related to the incidence of acute coronary syndromes. (1-6) However, several studies have reported that patients with unstable angina or acute myocardial infarction (AMI) generally have less extensive calcification within the culprit lesion compared with patients with stable angina. (7,8) The role of intracoronary calcium in the pathogenesis of AMI is therefore not fully understood. In most patients with acute coronary syndromes, the culprit lesion is characterized by a fibrofatty plaque composition with positive remodeling and focal calcified spots. (9) Moreover, the number of calcifications with an arc of <90 degrees within these lesions was larger compared with the number in patients with stable angina. However, a causal relation between intracoronary calcifications and plaque rupture remains to be demonstrated.

To gain further insight in the distribution of intracoronary calcifications and their relation with the site of plaque rupture, we performed an intravascular ultrasound (IVUS) imaging study of culprit arteries in patients presenting with ST-segment elevation AMI.

METHODS

From February to July 2004, 95 consecutive patients with ST-segment elevation AMI who were referred to our hospital for primary percutaneous coronary intervention (PCI) were considered for this study. Patients with previous PCI or bypass grafting of the infarct-related artery ($n = 8$), refusal to sign informed consent ($n = 2$), or anatomic factors comprising a potential risk from IVUS in the acute phase ($n = 17$) were excluded. The institutional ethical committee approved the protocol. Written informed consent was obtained from all patients before starting the PCI procedure.

Before the procedure all patients received 5,000U of heparin and a loading dose of 300 mg of acetylsalicylic acid and 300 mg of clopidogrel. Intravenous abciximab was administered as a bolus ($0.25 \mu\text{g/kg}$) and infused at $0.125 \mu\text{g/kg/min}$ for 12 hours (maximum $10 \mu\text{g/kg/min}$) in all patients. Abciximab was started before the PCI procedure.

IVUS was performed with 2.9Fr 20-MHz catheters (Eagle Eye, Volcano, Brussels, Belgium). The ultrasound transducer was carefully advanced beyond the culprit lesion under fluoroscopic guidance, immediately after crossing the stenosis with the guidewire. Automated pullback at 0.5mm/s was performed from 15mm distal to the culprit lesion to the coronary ostium after intracoronary nitroglycerin. All images were acquired and stored digitally.

Quantitative analysis was performed with QCU-CMS 4.0 (Medis, Leiden, The Netherlands).(10) From a distal major side branch to a proximal major side branch or the coronary ostium, the vessel and lumen contours were detected semiautomatically. The reference lumen area of the culprit lesion was derived from interpolation between the proximal and distal reference lumen areas. Start of the lesion was defined as the point where the lumen decreased in comparison with the calculated reference area. The end of the lesion was the point where the lumen equalized the interpolated reference area.

Plaque type was determined to be fibrofatty if >70% of the plaque had a gray value lower than the adventitia and fibrous if the gray value was equivalent or exceeded the adventitia in >70% of the plaque.(11) A calcified plaque had an arc >180° of calcium in ≥ 1 frame of the lesion. All other plaques were considered mixed. Plaque eccentricity at the site of plaque rupture was calculated as: (maximal plaque thickness - minimal plaque thickness) / maximal plaque thickness. Plaque burden was calculated from the formula: (vessel area - lumen area) / vessel area $\times$ 100%. Plaque rupture was identified by a tear in a fibrous cap or clear ulceration of a coronary plaque without enlargement of the external elastic membrane within 10mm of the minimal lumen area. Calcifications at the edge of visible plaque rupture or inside an ulceration were considered related to the AMI. The remodeling index was defined as the ratio of the interpolated external elastic membrane cross-sectional area to the observed external elastic membrane cross-sectional area at the site of the minimum lumen area. Calcium was identified as a bright echogenic spot with acoustic shadowing. Calcified spots were described within the lesion and 15mm proximal and distal of the lesion. If a calcified spot crossed the segment border, it was proportionally attributed to the respective segment. Calcified spots were categorized according to their maximum arc (<45°, 45°-90°, 90°-180°, $\geq 180^\circ$) and length (<1.5, 1.5 to 3, 3 to 6, ≥ 6 mm). The number of spots divided by segment length was calculated to evaluate the dispersion of calcified spots. Figure 1 shows different plaque characteristics and Figure 2 an example of the distribution of calcified spots within a culprit lesion and adjacent segments.

Results are expressed as mean $\pm$ SD. Means of paired variables were compared with paired-sample t test if the distribution was normal. Otherwise, Wilcoxon's rank-sum test was used. Categorical variables were evaluated with chi-square test. Correlation of sets of continuous variables was calculated by Pearson's method. If the data were normally distributed, 1-way analysis of variance was used to compare ≥ 3 paired variables. Otherwise, the Kruskal-Wallis test was used. Bonferroni's correction was used if applicable. A p value <0.05 was considered statistically significant.

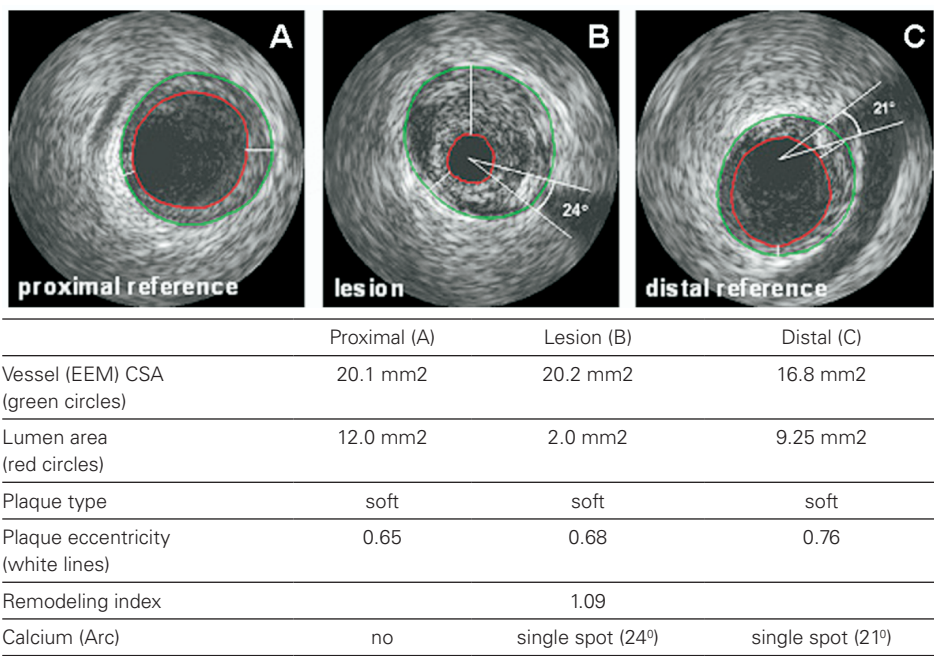


Figure 1.
(A to C) Definition and examples of plaque characteristics and quantitative measurements of the culprit lesion and reference segments. CSA = cross-sectional area; EEM = external elastic membrane.

RESULTS

In 68 patients who were eligible for IVUS, adequate IVUS pullbacks for analysis were obtained in 60; their baseline characteristics are listed in Table 1. In 8 patients it was not possible to advance the IVUS catheter beyond the stenosis (n = 5) or the motorized pullback was of poor quality (n = 3). At the start of the procedure, 35 patients (58%) had Thrombolysis In Myocardial Infarction grade 0 to 1 flow, whereas 25 (42%) had Thrombolysis In Myocardial Infarction grade 2 to 3 flow.

Calcium within the culprit lesion was detected in 53 patients (88%). Within the proximal and distal segments, calcium was identified in 41 (68%) and 32 (53%) segments, respectively. Of all calcified spots within the culprit lesion, 19 (9%) crossed the proximal and 10 (5%) the distal lesion border. Of these 29 spots, the maximum arc was located within the culprit lesion in 21 (72%). Additional plaque characteristics of the culprit lesion in comparison with adjacent segments are presented in Table

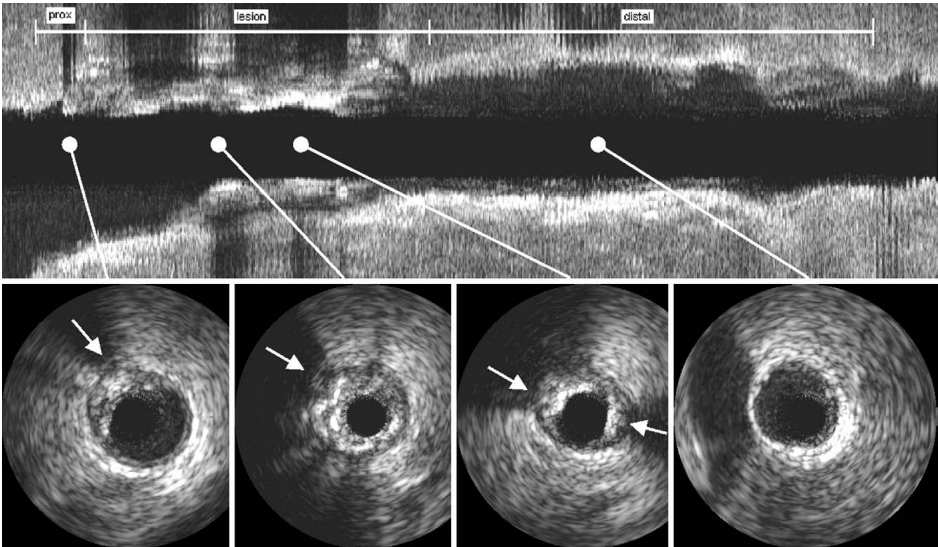


Figure 2. Example of distribution of calcified spots, visible as bright echogenic spots with acoustic shadowing (arrows), within the culprit lesion.

Age	57.5 ± 12.7 yrs
Men	49 (82%)
Diabetes mellitus	5 (8%)
History of hypertension	13 (21%)
History of hyperlipidemia or statin use	9 (15%)
Smoker	36 (59%)
Previous myocardial infarction, PCI or CABG	3 (5%)
Culprit vessel	
Left anterior descending artery	39 (65%)
Right coronary artery	20 (33%)
Left circumflex artery	1 (2%)

Table 1. Baseline characteristics (n = 60)

2. The number of calcified spots and their mean length per millimeter of analyzed segment were increased within the culprit lesion compared with proximal and distal segments. As presented in Table 3, especially calcified spots with a small arc and a short length were more frequent within the culprit lesion.

	Proximal (n=56)	Lesion (n=60)	Distal (n=59)
Segment length (mm)	9.5 ± 5.0	18.8 ± 6.8	14.0 ± 2.7
Plaque type			
Fibrofatty	32 (57%)	26 (43%)	40 (68%)
Fibrous	9 (16%)	7 (12%)	10 (17%)
Mixed	13 (23%)	14 (23%)	9 (15%)
Calcified	2 (4%)	13 (22%)	0 (0.0%)
Plaque eccentricity	0.78 ± 0.17	0.72 ± 0.18	0.71 ± 0.20
Calcified spots (n)	58	219	79
Calcified spots / segment (n)	1.07 ± 1.09	3.62 ± 2.63	1.34 ± 1.80
Length (mm)			
Median	2.30	1.86	2.05
Range	0.26–15.00	0.16–15.85	0.17–14.02
Maximum arc (°)			
Median	50	45	38
Range	7–243	7–360	14–149
Number of spots / mm*	0.14 ± 0.16	0.21 ± 0.16	0.10 ± 0.14
Length of all spots / mm†	0.38 ± 0.40	0.54 ± 0.45	0.27 ± 0.39

Table 2. Plaque characteristics per segment

* p<0.001, lesion versus distal; p=0.001, lesion versus proximal; NS, proximal versus distal.

† p<0.001, lesion versus distal; p<0.001, lesion versus proximal; NS, proximal versus distal.

	Arc *				Length (mm)*			
	<45°	45–<90°	90–<180°	≥180°	<1.5	1.5–<3	3–<6	≥6
Proximal	0.062 [†] (27)	0.051 (21)	0.022 (8)	0.003 [†] (2)	0.036 [†] (19)	0.021 (11)	0.032 (17)	0.019 (10)
Lesion	0.105 (105)	0.056 (63)	0.034 (38)	0.013 (13)	0.078 (88)	0.043 (49)	0.039 (44)	0.027 (31)
Distal	0.053 [†] (44)	0.037 (26)	0.010 [†] (9)	0.000 [†] (0)	0.034 [†] (28)	0.035 (29)	0.019 (16)	0.006 [†] (5)

Table 3. Distribution of calcified spots per segment, sorted by arc and length

* Average number of spots / mm segment (total number of spots); † p<0.05 versus lesion

There was a significant positive correlation between the length and maximum arc of calcified spots ($R^2=0.44$, $p=0.01$). There was no relation between plaque thickness or eccentricity and number of calcified deposits per millimeter or maximum calcium arc within the culprit lesion. Moreover, type of remodeling was not related to maximum arc of calcium or number of calcified spots per millimeter.

Plaque rupture was observed in 31 patients (52%). The rupture was located at the shoulder of the plaque in 22 (69%) of these lesions and at the center of the plaque in 9 (31%). In 14 lesions (45%) with discernible plaque rupture, calcified spots were present at the edge of a rupture or inside an ulceration. Lesions with a noticeable plaque rupture related to a calcified spot had more calcified spots per millimeter compared with lesions without a detectable rupture or lesions with an evident rupture without associated calcified spots (0.29 ± 0.17 vs. 0.17 ± 0.15 vs. 0.18 ± 0.17 , $p < 0.05$). In these lesions, especially spots with an arc of 90° to 180° (0.069 ± 0.077 vs. 0.028 ± 0.046 vs. 0.009 ± 0.018) and a length of 3 to 6 mm (0.068 ± 0.065 vs. 0.029 ± 0.049 vs. 0.022 ± 0.035) were significantly more common ($p < 0.05$ for the 2 comparisons). Figure 3 displays some examples of the relation between plaque rupture and ulcerations in different lesions.

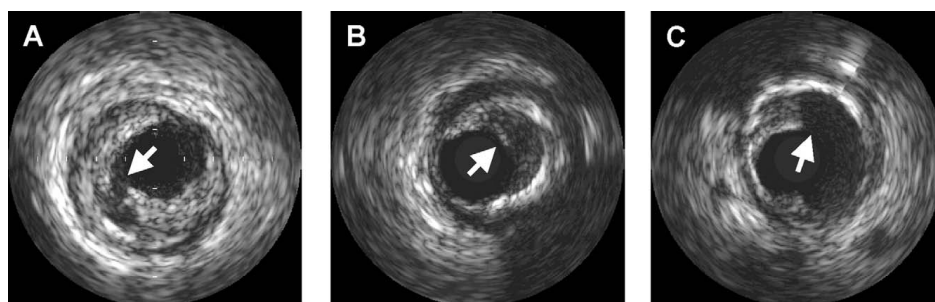


Figure 3. Relation between calcified spots and plaque ruptures or ulcerations.

(A) Site of plaque rupture (arrow) within a fibrofatty plaque without evidence of calcified spots. **(B)** Plaque rupture with calcified spots on the bottom of an ulceration, including a residual fibrous cap (arrow). **(C)** Plaque ulceration (arrow) on top of a large calcium spot.

DISCUSSION

The key finding of this study was that culprit lesions in patients with AMI contain more and smaller calcified spots compared with adjacent segments. Moreover, plaque rupture was evident in 52% of patients and 45% of these ruptures contained associated calcified deposits. The calcified spots, which might be associated with plaque rupture or ulceration, were more often of intermediate arc and length compared with lesions without evident plaque rupture or lesions with plaque rupture without related calcifications.

To our knowledge, no study has been published that has assessed the distribution and characteristics of calcified deposits within a culprit lesion and adjacent segments

in patients who present with AMI.(1-6) Coronary calcium distribution as assessed by electron beam computer tomography has an axial distribution comparable to calcium plaque accumulation as observed in pathologic and angiographic studies. (12) However, until now it was unclear whether the site of accumulation of calcium was related to coronary events. Integrating distribution and size of calcified deposits in electron beam computer tomographic coronary calcium scoring may therefore improve its ability to predict events, although this will depend on the size of the calcified spots, which can be detected by electron beam computer tomography.

A limitation of the present study is that the characteristics and distribution of calcifications in culprit lesions in patients with stable angina were not evaluated. This prohibits the conclusion that the reported distribution of calcium spots is typical for unstable lesions. Further, the prevalence of calcified spots near a ruptured plaque could be underestimated due to the presence of thrombus, because thrombus has an ultrasound appearance similar to that of soft plaque. However, this seems to play a minor role, because the prevalence of the different types of spots near a rupture or ulceration was similar for lesions without calcified spots next to a rupture or ulceration and lesions without a demonstrable plaque rupture.

REFERENCES

1. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827–32.
2. Shaw LJ, Raggi P, Schisterman E, et al. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. *Radiology* 2003;228:826–33.
3. Pohle K, Ropers D, Maffert R, et al. Coronary calcifications in young patients with first, unheralded myocardial infarction: a risk factor matched analysis by electron beam tomography. *Heart* 2003;89:625–8.
4. Raggi P, Callister TQ, Coöl B, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 2000;101:850–5.
5. Arad Y, Spadaro LA, Goodman K, et al. Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol* 2000;36:1253–60.
6. Wayhs R, Zelinger A, Raggi P. High coronary artery calcium scores pose an extremely elevated risk for hard events. *J Am Coll Cardiol* 2002;39:225–30.
7. Beckman JA, Ganz J, Creager MA, et al. Relationship of clinical presentation and calcification of culprit coronary artery stenoses. *Arterioscler Thromb Vasc Biol* 2001;21:1618–22.
8. Shemesh J, Stroh CI, Tenenbaum A, et al. Comparison of coronary calcium in stable angina pectoris and in first acute myocardial infarction utilizing double helical computerized tomography. *Am J Cardiol* 1998;81:271–5.
9. Ehara S, Kobayashi Y, Yoshiyama M, et al. Spotty calcification typifies the culprit plaque in patients with acute myocardial infarction: an intravascular ultrasound study. *Circulation* 2004;110:3424–29.
10. Koning G, Dijkstra J, von Birgelen C, et al. Advanced contour detection for three-dimensional intracoronary ultrasound: a validation—in vitro and in vivo. *Int J Cardiovasc Imaging* 2002;18:235–48.
11. Potkin BN, Bartorelli AL, Gessert JM, et al. Coronary artery imaging with intravascular highfrequency ultrasound. *Circulation* 1990;81:1575–85.
12. Schmermund A, Mohlenkamp S, Baumgart D, et al. Usefulness of topography of coronary calcium by electron-beam computed tomography in predicting the natural history of coronary atherosclerosis. *Am J Cardiol* 2000;86:127–32.

Summary, conclusions
and future perspectives

SUMMARY

The main topic of this thesis was the design, implementation and subsequent evaluation of an all-phases integrated care program for patients with acute myocardial infarction: the MISSION! protocol. The aim of MISSION! was to improve daily care for patients with an acute myocardial infarction by implementation of the most recent guidelines into clinical practice. Although prior surveys did show an improvement of care over the years, still a major gap exists between optimal care and daily clinical practice. Important aspect of MISSION! was the alignment of treatment strategies of the different healthcare professionals involved in the treatment of AMI patients. By doing so, unnecessary and harmful treatment delays were reduced and long-term care for patients with an acute myocardial infarction was improved.

Within the implementation of the MISSION! protocol it became possible to perform clinical evaluation studies. For example, the development of left ventricular remodeling after myocardial infarction was studied. By early identification of patients prone to develop left ventricular dilatation it may become possible to intervene at an early stage by optimizing drug-treatment, surgery or resynchronization therapy. In this thesis, the results of two studies are reported aimed at identifying predictors of left ventricular remodeling after acute myocardial infarction. Moreover, studies were performed to investigate plaque characteristics of the infarct-related coronary artery and to evaluate the use of drug-eluting stents in patients with acute myocardial infarction. In the SHIVA study, conventional cardiovascular risk factors and Framingham-risk scores were assessed in asymptomatic 3rd to 7th generation Asian Indian descendants, compared to Europeans. It appeared that young Asian Indians exhibited frequently an unfavorable cardiovascular risk profile.

In **Chapter 1** an overview is given of the epidemiology and pathophysiology of ischemic heart disease. In this part, the treatment goals as recommended by the guidelines are described. Furthermore, an explanation is given why implementation of guidelines in daily clinical practice is often difficult. Cardiovascular diseases are the number one cause of death worldwide and are projected to remain so for the next decades. Ischemic heart disease is caused by atherosclerosis. Atherosclerosis represents a chronic inflammatory response to the stress imposed by various risk factors, i.e. male sex, tobacco use, psychosocial stress, unhealthy diet, diabetes, hypertension, obesity and physical inactivity. Rupture or erosion of the atherosclerotic lesion causes partial or total occlusion of the coronary artery by forming a luminal thrombus. Irreversible myocardial damage occurs already after 15 to 20 minutes

of occlusion of the coronary artery. The extent of myocardial damage is inversely related to the time of onset of the coronary artery occlusion (start symptoms) and the restoration of blood flow. In the acute phase, it is essential to open the occluded coronary as quickly as possible. This can be achieved by thrombolytic drugs or by mechanical revascularization (Percutaneous Coronary Intervention, PCI). Nowadays, stents are used in more than 90% of the PCI procedures, to scaffold the stenosis and to seal dissections against the vessel wall. Hereby, the chance for restenosis is significantly reduced compared to balloon angioplasty alone.

Since an acute myocardial infarction is the reflection of an acute exacerbation of a chronic process, interventions have to focus not only on the acute event, but also on a reduction of the burden of atherosclerosis and the complications of the myocardial infarction during follow-up. To achieve this, amongst other interventions, drug therapy is of significant importance. Antithrombotic therapy reduces the risk of new thrombotic events. Beta-blockers decrease myocardial oxygen demand and prevent arrhythmias. ACE-inhibitors reduce left ventricular remodeling, and statins are given to improve cholesterol levels and to achieve plaque stabilization. To lower the risk of sudden cardiac death, an Implantable Cardioverter Defibrillator is implanted in patients with a low ventricular ejection fraction after a large myocardial infarction. A healthy lifestyle, like no tobacco use, healthy diet and regular exercise, is essential for optimal secondary prevention. To achieve this, participation in a cardiac rehabilitation program can be very helpful for the patient.

To optimize care and outcome of patients with an acute myocardial infarction many organizations, e.g. the European Society of Cardiology, the American College of Cardiology with the American Heart Association, and The Netherlands Society of Cardiology, have published guidelines for the treatment of patients with myocardial infarction. Guidelines are systematically developed statements to assist practitioners and patients in making evidence-based decisions about appropriate health care for specific clinical conditions. Prior studies and surveys revealed that implementation of guidelines in daily clinical practice will result in a lower number of complications: i.e. fewer patients will develop heart failure related symptoms and re-infarctions, and most important better adherence to guidelines will lower the short- and long-term mortality.

Lack of implementation of guidelines can be explained by several factors: the guidelines themselves, patient- and physician's constraints, and organizational barriers. First, the guidelines themselves: the basis of these guidelines ranges from randomized clinical trials to expert panel opinions. The "generalisability" of trial data is sometimes questionable due to the often highly selected study populations enrolled

in these randomized trials. Moreover, the guidelines are extensive and complex. Second, some physicians judge guidelines as oversimplified, “cookbook” medicine and a threat for the autonomy of the physicians. Third, patients play a central role in the success of therapy. It takes a lot of effort, time and money to adopt and maintain a healthier behavior and to use all prescribed drugs. Fourth, optimal treatment of patients with an acute myocardial infarction should be a continuum-of-care; it should include acute and long-term. Therefore, regional ambulance services, general physicians, regional hospitals, cardiologists, nurses and rehabilitation centers should work all together. Guidelines of the different professionals should be aligned to make smooth transition from one setting to the other possible. Besides optimizing care processes, political, economical and financial issues have to be overcome.

Prior acute myocardial infarction quality improvement projects mainly focused on acute cardiac care and secondary prevention strategies during the index hospitalization phase only. In the last few years, more and more projects installed pre-hospital care systems: networks of collaborating emergency medical services, community hospitals and interventional cardiac centers to foster early reperfusion therapy in patients with acute myocardial infarction. Although, as addressing systematically one phase of myocardial infarction care improves outcome significantly, it can be expected that further improvement of care and outcome can be achieved by maximizing the use of evidence-based therapy during all essential phases of care for patients with an acute myocardial infarction. Therefore, in 2004 we developed and implemented an all-phases integrated quality improvement program: the MISSION! protocol.

Chapter 2 describes the rationale, design and implementation of the MISSION! protocol. The aim of MISSION! is to improve acute and long-term care for patients with acute myocardial infarction by implementation of the most recent guidelines of the European Society of Cardiology and the American Heart Association/American College of Cardiology. To our knowledge the concept of MISSION! is unique as it contains all essential phases of acute myocardial infarction care: i.e. the prehospital, in-hospital, and outpatient phase, up to 1 year after the index event. By the use of care-tools we created a clinical framework for decision making and treatment. MISSION! concentrates on rapid diagnosis and early reperfusion, followed by active lifestyle improvement and structured medical therapy. Because MISSION! covers both acute and chronic phases of myocardial infarction care, this design implies an intensive multidisciplinary collaboration among all regional health care providers.

Chapter 3 presents the results of the MISSION! protocol on acute myocardial infarction care. Using a before (n= 84, treated in 2003) and after implementation cohort of patients with an acute myocardial infarction (n= 518, treated from 2004 to 2006) we assessed the impact of MISSION! by the use of performance indicators. In MISSION!, more patients benefited primary PCI (99% MISSION! vs. 94% historical group), the occluded coronary was opened more rapidly ("door-to-balloon time" decreased from 81 min to 55 min), and more patients were treated within the guideline-recommended 90-minutes door-to-balloon time (79% vs. 66%). In the acute phase, more patients received beta-blockers (84% vs. 64%) and ACE-inhibitors (87% vs. 40%). At one-year follow-up more patients used clopidogrel (94% vs. 72%), beta-blockers (90% vs. 81%), and ACE-inhibitors (98% vs. 66%). Target total cholesterol levels <4.5 mmol/L were achieved more frequently in MISSION! patients (80% vs. 58%). In conclusion, an all-phases integrated care program for patients with an acute myocardial infarction is a strong tool to enhance adherence to evidence based medicine and is likely to improve clinical outcome.

In **Chapter 4** we evaluated the relation between left ventricular dyssynchrony early after acute myocardial infarction and the occurrence of long-term left ventricular dilatation. One out of 6 acute myocardial infarction patients develops left ventricular dilatation (defined as an increase of left ventricle end-systolic volume of $\geq 15\%$). LV dilation is associated with adverse long-term prognosis. Early identification of patients prone to left ventricular remodeling is needed to optimize therapeutic management (i.e. in the form of medication, resynchronization or surgical therapy), which likely improves prognosis. In this study a total of 124 consecutive patients presenting with acute myocardial infarction were included. Within 48 hours of intervention, patients were examined with two-dimensional echocardiography; reassessment took place at 6-months follow-up. Of all patients, 18% exhibited left ventricular dyssynchrony (≥ 65 ms) immediately after acute myocardial infarction. Patients with left ventricular dyssynchrony had comparable baseline characteristics to patients without substantial left ventricular dyssynchrony, except for a higher prevalence of multi-vessel coronary artery disease and a larger size of myocardial infarction. During 6 months follow-up, 91% of the patients with substantial left ventricular dyssynchrony immediately after infarction developed left ventricular remodeling, compared to 2% in the patients without left ventricular dyssynchrony. In conclusion, most patients with substantial left ventricular dyssynchrony immediately after acute myocardial infarction develop left ventricular dilatation during 6 months follow-up.

In the additional study, described in **Chapter 5**, we also sought to identify predictors of left ventricular remodeling after acute myocardial infarction. However, instead of examining left ventricular dyssynchrony using tissue Doppler technique, two-dimensional “speckle-tracking strain” analysis was used. This new technique utilizes the natural acoustic markers, or speckles, that are present on standard gray-scale ultrasound tissue images. By following accurately these speckles from frame to frame, velocities and deformations of the myocardium can be determined.

In total, 178 patients with acute myocardial infarction underwent echocardiographic examination during index hospitalization and at 6 months follow-up. Of these patients 20% exhibited left ventricular dilatation at 6 months. Patients with left ventricular dilatation had comparable baseline characteristics to patients without left ventricular dilatation, except that myocardial infarction size was larger. Multivariable analysis demonstrated that left ventricular dyssynchrony was superior in predicting left ventricular remodeling compared to other parameters. Receiver-operating characteristic (ROC) curve analysis demonstrated that a cutoff value of 130 ms for left ventricular dyssynchrony yields a sensitivity of 82% and a specificity of 95% to predict left ventricular remodeling at 6 months follow-up.

In **Chapter 6** the results of the MISSION! Intervention Study are described. Since the introduction of PCI, recurrent luminal narrowing (restenosis) is a major drawback of PCI both in patients with stable angina and in patients with acute coronary syndrome. With the introduction of the intracoronary stent, restenosis rates could be lowered significantly to 7-15%. With the introduction of the drug-eluting stents restenosis rates could be lowered even more in patients with stable or unstable angina pectoris. However, patients with acute myocardial infarction were excluded in most studies.

The aim of the MISSION! Intervention Study was to evaluate safety and effectiveness of drug-eluting stents compared with stents without any drug (i.e. bare metal stents (BMS)) in patients with acute myocardial infarction. This study was single-blind and performed in one center. In total 310 patients were randomized for a drug-eluting stent (SES: Sirolimus-eluting stent) or BMS. The primary endpoint was in-segment late luminal loss (LLL) at 9 months. Secondary endpoints included late stent malapposition (LSM) at 9 months as determined by intravascular ultrasound imaging and clinical events at 12 months. In-segment LLL was significantly lower after SES implantation (0.12 ± 0.43 mm vs. 0.68 ± 0.57 mm), with a mean difference of 0.56 mm (95% CI 0.43-0.68 mm). Moreover, the event free survival at 12 months was higher in the SES group (86.0% vs. 73.6%) and the target vessel failure free survival

was also higher in the SES group (93.0% vs. 84.7%). However, LSM at 9 months was significantly more often present after SES implantation (37.5% vs. 12.5% in the BMS group). Rates of death, myocardial infarction and stent thrombosis were not different. Thus, SES implantation in patients with acute myocardial infarction is associated with favorable mid-term clinical and angiographic outcome compared to treatment with BMS. However, LSM raises concern about the long-term safety of SES in patients with acute myocardial infarction.

In **Chapter 7** the results of the SHIVA study are described. Prior studies revealed that Asian Indians living in the Western world are more prone to develop cardiovascular diseases and at an earlier age as compared with Europeans. Therefore, knowledge of the cardiovascular risk profile of this high-risk population is of major importance for development of adequate primary and secondary prevention strategies. Until now, most studies are performed in 1st and 2nd generation emigrants. To optimize prevention, knowledge of current risk profile of younger generations is needed.

There is a large Asian Indian community in the Netherlands (approximately 200,000 persons). This community mainly consists of migrants from Surinam, a former South American Dutch colony. Historically, the abolishment of slavery in 1863 was the start of migration of Asian Indians from India to Surinam. These migrants were contract workers on former plantations and were almost exclusively recruited from the Indian state Bihar. The declaration of independence of Surinam in 1975 initiated a second wave of migration of these Asian Indians, this time to the Netherlands. Nowadays, these immigrants and their offspring form a 3rd to 7th generation of Asian Indians.

In the SHIVA study, a cross-sectional study, we assessed the prevalence of conventional ischemic heart disease risk factors and the ten-years risk for ischemic heart disease (Framingham risk score) in these young generation Asian Indian descendants, compared with Europeans. Subjects were included if they were asymptomatic: i.e. if they did not have documented ischemic heart disease, diabetes, hypertension or high cholesterol. A total of 1790 Asian Indians (45% men, age 35.9 ± 10.7 years) and 370 native Dutch hospital employees (23% men, age 40.8 ± 10.1 years) were recruited. Asian Indians had higher levels of total cholesterol, low-density lipoprotein, triglycerides, and lower high-density lipoprotein levels than the Dutch. Glucose intolerance was present in 7.1 vs. 0.5% men, and in 6.1 vs. 1.4% women. Asian Indian women were more frequently obese (12 vs. 5%), and centrally obese (44 vs. 25%) as compared with the Dutch women. Prevalence of most of the conventional and modifiable cardiovascular risk factors in each ten-year age group was higher in Asian Indians compared with controls, which reflected in higher Framingham risk

scores. In conclusion, this study demonstrates the persistence of an unfavorable cardiovascular risk profile in young, 3rd to 7th generation migrated Asian Indians and supports an aggressive screening and intervention strategy.

Chapter 8 describes the results of a study investigating the distribution, arc and location of calcified spots in the infarct-related coronary lesion (culprit lesion) of patients with an acute myocardial infarction. From Electron Beam Computed Tomography studies it is known that the extent of intracoronary calcium is related to the risk of coronary events. This study was performed in 60 patients using Intravascular Ultrasound (IVUS) imaging. Calcifications in the culprit lesion and adjacent segments were classified and counted according to their arc (<45°, 45-90°, 90-180°, >180°), length (<1.5, 1.5-3.0, 3.0-6.0, >6.0 mm), and dispersion (number of spots per millimeter). Calcifications at the edge of a visible rupture or ulceration were considered to be related to the myocardial infarction. Compared to adjacent proximal and distal segments, the culprit lesion contained more calcified spots per millimeter (respectively 0.14, 0.10 and 0.21), which were mainly small calcified spots (arc <45°, length <1.5 mm). Plaque rupture or ulceration was manifest in 31 culprit lesions (52%) of which 14 (45%) contained focal calcifications related to a plaque rupture or ulceration. These calcified spots extended more often to 90-180° of the vessel circumference and were more often of moderate length (3-6 mm) when compared to culprit lesions without visible plaque rupture. It was concluded that culprit lesions of patients with an acute myocardial infarction contain more and smaller calcifications compared to adjacent segments. Moreover, calcifications related to plaque rupture or ulceration appear to be larger and extend over a wider arc. These larger calcifications may play a role in plaque instability.

CONCLUSIONS

MISSION! is a multidisciplinary guideline-based treatment protocol for patients with an acute myocardial infarction, containing all essential phases of care: i.e. the prehospital, in-hospital and outpatient phase, up to 1 year after the index event.

An all-phases integrated care program for patients with an acute myocardial infarction, like MISSION!, results in an increase of guideline adherence and improves clinical outcome.

Most patients with substantial left ventricular dyssynchrony immediately after acute myocardial infarction will develop left ventricular dilatation during 6 months follow-up.

The optimal cutoff value for left ventricular dyssynchrony is 130 ms, which yields a sensitivity of 82% and a specificity of 95% to predict left ventricular remodeling at 6 months follow-up.

Sirolimus-eluting stent implantation in patients with acute myocardial infarction is associated with favorable mid-term clinical and angiographic outcome compared to treatment with bare-metal stents. Late stent malapposition is however more common after sirolimus-eluting stent implantation.

Young 3rd to 7th generation Asian Indians exhibit an unfavourable risk profile for cardiovascular diseases compared to Europeans.

Culprit lesions in patients with acute myocardial infarction contain more and smaller calcified spots (arc <45°, length <1.5 mm) compared to adjacent segments. Calcifications related to plaque rupture or ulceration extend over a wider arc and are longer (arc 90-180°, length 3-6 mm).

FUTURE PERSPECTIVES

Development and implementation of a guideline-based treatment protocol for patients with an acute myocardial infarction.

During the last two decades, treatment of patients with an acute myocardial infarction improved dramatically resulting in a significant decrease of mortality both during the acute and chronic phase. As a result, the quality of daily care for patients with acute myocardial infarction is improving; on the other hand to let the patients benefit from all different options becomes a challenging process. Guidelines are systematically developed statements to assist practitioners and patients in making evidence-based decisions about appropriate care. Implementation of guidelines in the real world remain however difficult. The results of the MISSION! protocol proved the effectiveness of an all-phases integrated protocol to treat patients with an acute myocardial infarction. By doing so, care is not only determined by clinical experience, knowledge and intuition of the individual physician, but is based on a

multidisciplinary framework across the entire system of care. As a result, the inter-physician and inter-patient variations decreased. Quality of care was assessed by the use of performance-indicators, creating the possibility of evaluation, feedback and continuously improvement. Using predefined quality of care performance indicators is importance to allow better evaluation of results. This transparency of care is needed to improve the quality of care and for patients, the government, and the health insurance companies to decide whether a care provider delivers good quality care. Besides these positive effects one should be cautious when relying too much on a guideline-based treatment protocol: it can restrain new insights. The guidelines themselves: not all recommendations are evidence-based and the “generalisability” of trial data is sometimes questionable due to the often highly selected study populations enrolled in these randomized trials. Additionally, it might be possible that individual proven treatment strategies won’t be effective anymore or even harmful for the patient when combined.

Lessons learned from MISSION! and recommendations for the future are: 1) to develop and implement a treatment protocol for patients with an acute myocardial infarction, all efforts should be focused on creating a close inter- and multidisciplinary collaboration across the system of care. 2) Herein, the patient plays a central role. 3) Only application of (inter-) national guidelines in daily care is not effective. Customization is required according to local and regional possibilities, capacity and finance. 4) The use of care-tools in the form of medical orders and IT systems plays a crucial role in the success of implementation 5) Continuous quality assessment is mandatory, not only to verify if the protocol is applied correctly, but also to improve the protocol itself according to new clinical data or scientific insights. 6) A protocol should function as a guide to facilitate and to make appropriate decisions, however it should never replace a carefully considered clinical judgment.

Samenvatting, conclusies
en toekomstperspectief

Het hoofdonderwerp van dit proefschrift is het beschrijven en evalueren van een intensief zorgprogramma voor patiënten met een acuut hartinfarct: het MISSION! protocol. Het doel van MISSION! is de zorg voor patiënten met een acuut hartinfarct te verbeteren middels implementatie van de meest recente richtlijnen in de dagelijkse praktijk. Eerdere prestatieanalyses lieten zien dat ondanks het feit dat de zorg niet slecht was, deze op veel fronten verbeterd kon worden. Belangrijke aspecten van MISSION! zijn het op elkaar afstemmen van de verschillende behandelstrategieën van de verschillende zorgaanbieders én het regionaliseren van de zorg om onder andere onnodige vertraging in behandeling te voorkomen en om de nazorg voor deze groep patiënten te verbeteren.

Binnen het MISSION! project zijn ook een aantal gerelateerde studies uitgevoerd. Zo is gekeken naar linker kamer dilatatie. Als linker kamer dilatatie vroegtijdig kan worden opgespoord kan wellicht door intensievere medicamenteuze of chirurgische therapie verdere verslechtering worden voorkomen en kan de prognose van patiënten worden verbeterd. In dit proefschrift worden de resultaten beschreven van twee studies waarin werd bekeken welke parameters van voorspellende waarde zijn voor linker ventrikel dilatatie onmiddellijk na het hartinfarct. Verder werd er onderzoek gedaan naar de zogenaamde plaquekarakteristieken van de bij het infarct betrokken kransslagader van hartinfarctpatiënten en naar de behandeling van deze patiënten met medicijn-afgevend stents (drug-eluting stents). In de SHIVA-studie werd het risicoprofiel voor hart- en vaatziekten van Hindoestanen vergeleken met een Nederlandse controlegroep. Hieruit kwam naar voren dat jonge Hindoestanen vaak een zeer ongunstig risicoprofiel laten zien.

In de introductie van dit proefschrift (**Hoofdstuk 1**) wordt een overzicht gegeven van de epidemiologie en pathofysiologie van ischemische hartziekten. De behandeldoelen voor patiënten met een acuut hartinfarct worden beschreven zoals ze geadviseerd worden in de internationale richtlijnen. Tevens wordt een verklaring gegeven voor het feit dat de daadwerkelijke implementatie van de richtlijnen in de dagelijkse praktijk zo moeizaam gaat.

Hart- en vaatziekten zijn nog steeds doodsoorzaak nummer één in de wereld. Dit blijft ook zo voor de komende decennia. Ischemische hartziekten ontstaan als gevolg van atherosclerose. Dit is een chronisch ontstekingsproces als respons op allerlei beïnvloedbare stressfactoren, zoals roken, psychosociale stress, ongezond eten, suikerziekte, hoge bloeddruk, overgewicht en fysieke inactiviteit. Ruptuur of erosie van een atherosclerotische plaque in de kransslagader van het hart zorgt voor gedeeltelijke dan wel totale afsluiting van het bloedvat door een bloedstolsel. Na

15 tot 20 minuten volledige afsluiting sterft hartweefsel af ten gevolge van zuurstof tekort. De mate van schade aan het hart is gerelateerd aan de duur van afsluiting. In de acute fase is het dan ook essentieel om de kransslagader zo snel mogelijk te openen, middels bijvoorbeeld een dotterprocedure of met geneesmiddelen. Bij een dotterprocedure wordt in de meeste gevallen een stent geplaatst, dit is een soort pennenvaar die in de acute fase het bloedvat beter openhoudt en ook de kans op een hernieuwde vernauwing verkleint.

Essentieel is dat een hartinfarct een acute verergering is van een chronische ziekte. Na de acute fase is het daarom van groot belang om de kans op complicaties, een herhaling van het hartinfarct en progressie van het vaatlijden zoveel mogelijk te verkleinen. Geneesmiddelen spelen hierbij een belangrijke rol. Plaatjesremmers voorkomen vorming van nieuwe bloedstolsels. Bètablokkers zorgen voor een vermindering van de zuurstofbehoefte van de hartspier en voorkomen het optreden van ritmestoornissen. ACE-remmers gaan het uitzetten van het hart tegen (linkerventrikel dilatatie) en statines zorgen voor een verlaging van het cholesterol en voor plaque stabilisatie. Patiënten met een groot infarct kunnen baat hebben van een implanterbare defibrillator ter bescherming van levensbedreigende hartritmestoornissen. Gezonde levenswijzen, zoals niet roken, gezonde voeding en voldoende bewegen zijn van groot belang bij optimale secundaire preventie. De patiënt kan hierbij worden geholpen door het volgen van een hartrevalidatieprogramma.

Instanties, zoals de European Society of Cardiology, de American Heart Association en de Nederlandse Vereniging voor Cardiologie, hebben richtlijnen opgesteld waarin staat beschreven hoe een patiënt met een hartinfarct het beste kan worden behandeld. Richtlijnen geven handvaten om gepaste en kwalitatief goede zorg te leveren aan de patiënt. Richtlijnen zijn zoveel mogelijk gebaseerd op wetenschappelijk bewezen effectieve en doelmatige strategieën (evidence-based medicine). Studies bevestigen ook dat het beter volgen van de richtlijnen resulteert in minder complicaties zoals hartfalen en een herhaling van een infarct. Nog belangrijker, de sterfte neemt af. Ondanks bewezen effectiviteit worden nog een significant aantal patiënten onderbehandeld.

Redenen voor moeilijke implementatie in de dagelijkse praktijk zijn multifactorieel: 1) de richtlijnen zelf: ze zijn meestal gebaseerd op uitkomsten van grote internationale studies. Deze studies hanteren strenge in- en exclusie criteria. Hierdoor komt de studiepatiënt niet altijd overeenkomst met de patiënt in de dagelijkse praktijk. De richtlijnen zijn erg uitgebreid en complex. 2) De arts heeft aversie tegen “kookboek-geneeskunde” of ziet het als een bedreiging voor zijn autonomie. 3) Voor de patiënt kost het veel inspanning om alle voorgeschreven medicijnen te gebruiken en om

gezonde levenswijzen aan te leren en vol te houden. 4) Verder zijn er organisatorische problemen: optimale hartinfarctzorg begint bij de patiënt met pijn-op-de-borst thuis, gaat door in het ziekenhuis en heeft een intensieve poliklinische follow-up. Dit vereist een intensieve samenwerking tussen alle verantwoordelijke zorgverleners, zoals de huisarts, ambulancepersoneel, cardiologen en revalidatieartsen. Richtlijnen van deze meestal op zichzelf functionerende instanties moeten dan ook op elkaar worden afgestemd. Naast het stroomlijnen van zorgprocessen, moeten financiële, economische en politieke barrières worden overwonnen.

Eerdere kwaliteitsverbeterende zorgprogramma's waren met name gericht op de acute zorg in het ziekenhuis. De laatste jaren worden steeds meer regionale ambulance-ziekenhuis systemen opgezet om onnodige behandelingsvertragingen te voorkomen in de pre-hospitale setting. Verondersteld kan worden dat, als de richtlijnen worden toegepast in één fase en dit de zorg verbeterd, verdere optimalisatie kan worden bewerkstelligd door implementatie van de richtlijnen in alle essentiële zorgfasen (d.w.z. pre-hospitaal, in-hospitaal en poliklinisch). Dit heeft geleid tot het ontwikkelen en implementeren van een intensief zorgprogramma voor patiënten met een hartinfarct in regio "Hollands-Midden": het MISSION! hartinfarctprotocol.

Hoofdstuk 2 beschrijft de ontwikkeling en implementatie van het MISSION! hartinfarctprotocol. MISSION! heeft als doel de zorg voor de hartinfarctpatiënt te verbeteren middels implementatie van de meest recente richtlijnen van de European Society of Cardiology en de American Heart Association/American College of Cardiology. Het invoeren van één doelgericht en handzaam protocol, ondersteund door zogenaamde zorghulpmiddelen ("care-tools"), creëert een raamwerk voor optimale zorg in de dagelijkse praktijk. MISSION! is uniek ten opzichte van eerdere implementatieprogramma's, aangezien het alle essentiële zorgfasen voor de patiënt met een hartinfarct omvat (namelijk de preklinische, klinische en poliklinische fase tot één jaar na het infarct). MISSION! is gericht op het zo snel mogelijk diagnosticeren van het hartinfarct, snelle reperfusie van de afgesloten kransslagader en op gestructureerde medische therapie en verbetering van levensstijl na de acute fase. Het bundelen van zowel de acute als chronische zorg in één programma vraagt om een intensieve multidisciplinaire samenwerking tussen de verschillende hulpverleners in de regio.

Hoofdstuk 3 beschrijft de resultaten van het MISSION! protocol op de zorg. Middels vooraf opgestelde prestatie-indicatoren werd de zorg in een historische groep hartinfarctpatiënten net vóór implementatie van MISSION! (n=84, behandeld in 2003) vergeleken met een groep patiënten na implementatie van MISSION! (n=518,

behandeld in 2004 tot en met 2006). MISSION! heeft ervoor gezorgd dat meer patiënten profiteerden van een dotterbehandeling tijdens de acute fase (99% in de MISSION! groep vs. 94% in de historische groep), de kransslagader sneller geopend werd ("door-to-balloon" tijd 55 min vs. 81 min.) en dat dit vaker gebeurde binnen de door de richtlijnen geadviseerde 90-minuten "door-to-balloon" tijd (79% vs. 66%). In de acute fase kregen meer patiënten bètablokkers (84% vs. 64%) en ACE-remmers (87% vs. 40%). Na één jaar gebruikte meer patiënten clopidogrel (94% vs. 72%), bètablokkers (90% vs. 81%), en ACE-remmers (98% vs. 66%). Meer patiënten behaalde de geadviseerde cholesterol waarde van minder dan 4.5 mmol/L (80% vs. 58%). Geconcludeerd kon dan ook worden dat implementatie van een intensief zorgprogramma voor patiënten met een acuut hartinfarct heeft geresulteerd in een betere naleving van de richtlijnen en een significant betere uitkomst.

In **Hoofdstuk 4** wordt gekeken welke parameters na een hartinfarct van voorspellende waarde zijn voor het ontstaan van linker kamer dilatatie (gedefinieerd als toename van de linker kamer eind-systolische volume met $\geq 15\%$). Eerdere studies toonden aan dat bij één op de zes hartinfarctpatiënten de linkerventrikel dilateert en dat dit sterk geassocieerd is met sterfte. Namelijk, patiënten die sterven na een hartinfarct hebben significant grotere linker kamer volumes en lagere linker kamer ejectiefracties. Door vroegtijdig te voorspellen welke patiënten het risico lopen op linker kamer dilatatie kan wellicht door intensievere therapie (medicamenteus, resynchronisatie therapie en/of door middel van chirurgie) de prognose van de patiënten worden verbeterd. In deze studie werd de relatie tussen linker kamer dyssynchronie onmiddellijk na het hartinfarct en linker kamer dilatatie 6 maanden na het infarct bestudeerd.

In totaal werden 124 hartinfarctpatiënten geïnccludeerd. Zij werden binnen 48 uur na de primaire dotterbehandeling en 6 maanden na het infarct onderzocht middels onder andere echocardiografie. Van alle patiënten vertoonde 18% linker kamer dyssynchronie net na het hartinfarct. De klinische karakteristieken van deze patiënten waren vergelijkbaar met de karakteristieken van patiënten die geen linker kamer dyssynchronie vertoonden, met uitzondering dat deze patiënten vaker afwijkingen hadden in meerdere kransslagaders en een groter infarct hadden. Van de patiënten met linker kamer dyssynchronie onmiddellijk na het infarct ontwikkelde 91% linker kamer dilatatie in de 6 maanden na het hartinfarct ten opzichte van slechts 2% van de patiënten zonder linker kamer dyssynchronie. Geconcludeerd kon dan ook worden dat de meeste patiënten met linker kamer dyssynchronie onmiddellijk na het hartinfarct linker kamer dilatatie ontwikkelden gedurende de 6 maanden na het hartinfarct.

Dit is een belangrijk gegeven waar wellicht middels bijvoorbeeld resynchronisatie therapie wat aan gedaan kan worden.

In **Hoofdstuk 5** wordt tevens bestudeerd welke andere parameters van voorspellende waarde zijn voor linker kamer dilatatie. Echter linker kamer dyssynchronie werd nu niet bepaald middels de tissue doppler techniek, maar met de tweedimensionale "speckle tracking strain" analyse. Bij deze nieuwe techniek wordt gebruik gemaakt van natuurlijke akoestische markers (de zogenaamde "speckles") op standaard gray-scale echo beelden. Door deze speckles frame per frame te vervolgen kunnen snelheden en vervormingen van het hartspierweefsel worden bepaald. In totaal ondergingen 178 acute hartinfarctpatiënten een echocardiografische evaluatie tijdens opname en na 6 maanden. Van deze 178 patiënten vertoonden 20% linker kamer dilatatie na 6 maanden. Baseline karakteristieken waren nagenoeg hetzelfde vergeleken met de patiënten zonder linker kamer dilatatie, echter patiënten met linker kamer dilatatie hadden een significant groter infarct. Tevens was linker kamer dyssynchronie frequenter en in grotere mate aanwezig. Multivariate analyse liet zien dat de aan- of afwezigheid van linker kamer dyssynchronie superior was bij het voorspellen van linker kamer dilatatie ten opzichte van andere parameters. Uit analyse van de receiving-operating curve (ROC) bleek dat het optimale afkappunt voor linker kamer dyssynchronie 130 ms was, waarmee een sensitiviteit van 82% en een specificiteit van 95% werd behaald voor het voorspellen van linker kamer dilatatie na 6 maanden follow-up.

In **Hoofdstuk 6** worden de resultaten beschreven van de MISSION! Interventie studie. Het plaatsen van een stent bij een patiënt met een acuut hartinfarct heeft als doel het opnieuw vernauwen van de kransslagader (restenose) te voorkomen. Een stent verhindert het acuut elastisch terugveren van de atherosclerotische vernauwing en voorkomt vorming van littekenweefsel. Echter door het plaatsen van een stent is er meer groei van gladde spiercellen en extracellulaire matrix in de stent (de vorming van neointima weefsel). Hierdoor is bij 7 tot 15% een tweede dotterbehandeling of bypass operatie noodzakelijk. De meest recente ontwikkeling in de dotterbehandeling van patiënten met ischemische hartziekten is de medicijn-afgeevende stent. Deze stent combineert het mechanische effect van het stutten van de atherosclerotische vernauwing tegen de vaatwand met het afgeven van medicijn om neointima vorming te voorkomen. Eerdere studies bewezen de effectiviteit en veiligheid van deze medicijn-afgeevende stents in patiënten met (in-)stabiele angina pectoris of stille ischemie, echter patiënten met een acuut hartinfarct werden in deze

studies geëxcludeerd. Het doel van de MISSION! Interventie studie was de werking en veiligheid van medicijn-afgevende stents te evalueren in vergelijking met stents zonder medicijn bij patiënten met een acuut hartinfarct. De studie was eenzijdig geblindeerd en uitgevoerd in één centrum.

In totaal werden 310 patiënten met een acuut hartinfarct gerandomiseerd voor een medicijn-afgevende stent (SES: Sirolimus-eluting stent) of een stent zonder medicijn (BMS: Bare metal stent). Het primaire eindpunt was in-segment (gestente vaatsegment $\pm$ 5mm) lumen diameter verlies (het verschil tussen de minimale lumen diameter net na de primaire dotterprocedure en de diameter na 9 maanden). Secundaire eindpunten waren onder andere late stent malappositie na 9 maanden en klinische gebeurtenissen na 12 maanden. Het in-segment lumen diameter verlies was significant lager na SES implantatie (0.12 ± 0.43 mm vs. 0.68 ± 0.57 mm) met een gemiddeld verschil van 0.56 mm (95% CI 0.43-0.68 mm). De overleving na 12 maanden (zonder nieuwe events) was hoger na SES implantatie (86.0% vs. 73.6%). De overleving zonder hernieuwde revascularisatie van de kransslagader waarin de stent was geplaatst, was tevens hoger in de SES groep (93% vs. 84.7%). Echter, late stent malappositie na 9 maanden werd frequenter gezien na SES implantatie (37.5% vs. 12.5%). Er was geen verschil in de kans op overlijden, hartinfarct of stent thrombose na 12 maanden. Geconcludeerd kon worden dat de behandeling met SES bij patiënten met een acuut hartinfarct resulteerde in een betere middellange klinische en angiografische uitkomst vergeleken met de behandeling met BMS. Frequent late stent malappositie geeft bedenkingen over de lange termijn veiligheid van SES bij patiënten met een acuut hartinfarct.

In **Hoofdstuk 7** worden de resultaten beschreven van de SHIVA studie. Eerdere studies hebben laten zien dat mensen afkomstig uit Zuid-Azië en wonend in het Westen frequenter en op vroegere leeftijd hart- en vaatziekten krijgen vergeleken met de blanke westerse bevolking. Het goed in kaart hebben van het cardiovasculair risicoprofiel van deze hoog-risico populatie is van groot belang voor adequate primaire en secundaire interventies. Tot nu toe zijn deze studies voornamelijk verricht bij 1e en 2e generatie emigranten. Echter, voor optimale preventie is kennis van jongere generaties nodig. In Nederland woont een grote Hindoestaanse gemeenschap, bestaande uit zo'n 200.000 mensen. Zij zijn oorspronkelijk afkomstig uit het Indiase subcontinent. Zij emigreerde eind negentiende eeuw naar Suriname om te werken als slavenarbeiders op de plantages. In 1975, na de onafhankelijk van Suriname als Nederlandse kolonie volgde een 2de emigratiegolf naar Nederland. De

huidige populatie van Hindoestanen wonend in Nederland bestaat uit 3de tot 7de generatie Hindoestanen.

Met SHIVA hebben we middels een cross-sectionele studie de prevalentie van conventionele risicofactoren voor hart- en vaatziekten en het 10-jaars risico op ischemisch hartlijden (Framingham-score) in deze groep onderzocht en vergeleken met een Nederlandse controlegroep. Individuen werden geclassificeerd als asymptomatisch als ze niet bekend waren met ischemische hartziekte, suikerziekte, een te hoge bloeddruk of te hoge cholesterolwaarden. In totaal werden 1790 Hindoestanen (45% man, gemiddelde leeftijd 35.9 ± 10.7 jaar) en 370 autochtone Nederlandse ziekenhuismedewerkers (23% man, gemiddelde leeftijd 40.8 ± 10.1 jaar) geïnccludeerd. Hindoestanen hadden hogere totaal cholesterol-, LDL- en triglyceriden-waarden, en lagere HDL-waarden vergeleken met de Nederlandse controlegroep. Glucose intolerantie kwam frequenter voor bij Hindoestanen (mannen 7.1% vs. 0.5%, vrouwen 6.1% vs. 1.4%). Hindoestaanse vrouwen vertoonden vaker overgewicht (12% vs. 5%) en centrale obesitas (toegenomen hoeveelheid buikvet, 44% vs. 25%) vergeleken met de Nederlandse vrouwen. Prevalentie van de meeste conventionele en beïnvloedbare cardiovasculaire risicofactoren in elke 10-jaars leeftijdsgroep was hoger in de Hindoestaanse groep vergeleken met de Nederlandse controlegroep, wat zich ook uitte in hogere Framingham risico scores. Geconcludeerd kon worden dat in deze jonge 3de tot 7de generatie Hindoestanen een ongunstig risicoprofiel voor hart- en vaatziekten aanwezig was. Deze onderzoeksresultaten ondersteunen een agressief en structureel screeningsprogramma voor jonge Hindoestanen om de kans tot ontwikkeling op vroegtijdig symptomatisch hart- en vaatziekte te verkleinen.

Hoofdstuk 8 beschrijft de resultaten van een studie naar de distributie, boog en locatie van verkalkingen (calcificaties) in de infarct-veroorzakende atherosclerotische plaque (culprit laesie) bij patiënten met een acuut hartinfarct. Uit eerdere CT-scan studies is gebleken dat de mate van intracoronaire calcificatie gerelateerd is aan het risico op een acuut coronair syndroom. Deze studie werd uitgevoerd bij 60 patiënten met behulp van een intravasculaire echo (IVUS: intravasculaire ultrasound). Calcificaties in de culprit laesie en aanliggende vaatsegmenten werden geclassificeerd en geteld naar hun boog (<45°, 45-90°, 90-180°, >180°), lengte (<1.5, 1.5-3.0, 3.0-6.0, >6.0 mm) en spreiding (aantal calcificaties per millimeter). Calcificaties op de rand van een zichtbaar ruptuur of ulceratie werden beschouwd als gerelateerd aan het hartinfarct. Vergeleken met de aanliggende proximale en distale vaatsegmenten bevatten de culprit laesies meer calcificaties per millimeter (respectievelijk 0.14, 0.10 en 0.21) die met name klein waren (boog <45°, lengte < 1.5 mm). Plaque ruptuur of ulceratie

was zichtbaar in 31 laesies (52%) waarvan er 14 (45%) calcificaties bevatten die gerelateerd waren aan de ruptuur of ulceratie. Deze calcificaties hadden vaker een boog van 90-180° en een lengte van 3-6 mm vergeleken met culprit laesies zonder zichtbare plaque ruptuur of ulceratie. Concluderend bevatten culprit laesies van patiënten met een acuut hartinfarct meer en kleinere calcificaties vergeleken met aanliggende vaatsegmenten. Daarnaast zijn de calcificaties die gerelateerd zijn aan een plaque ruptuur of ulceratie langer en hebben een grotere boog. Deze grotere calcificaties spelen mogelijk een rol bij plaque instabiliteit.

CONCLUSIES

MISSION! is een multidisciplinair, richtlijn gebaseerd behandelprotocol voor patiënten met een acuut hartinfarct, dat alle essentiële fasen van zorg omvat: namelijk de preklinische, klinische en poliklinische fase tot één jaar na het hartinfarct.

Implementatie van een intensief zorgprogramma zoals MISSION! resulteert in betere naleving van de richtlijnen voor patiënten met een acuut hartinfarct en een betere uitkomst.

De meeste patiënten met linker kamer dyssynchronie onmiddellijk na het hartinfarct ontwikkelen linker kamer dilatatie gedurende de 6 maanden na het hartinfarct.

Het optimale afkappunt voor linker kamer dyssynchronie is 130 ms, waarmee een sensitiviteit van 82% en een specificiteit van 95% wordt behaald voor het voorspellen van linker kamer dilatatie 6 maanden na het hartinfarct.

Sirolimus-eluting stent implantatie bij patiënten met een acuut hartinfarct leidt tot betere klinische en angiografische resultaten op middellange termijn vergeleken met bare-metal stent implantatie. Late stent malappositie wordt frequenter waargenomen na Sirolimus-eluting stent implantatie.

Jonge Hindoestanen -3de tot 7de generatie- vertonen een ongunstig risicoprofiel voor hart- en vaatziekten ten opzichte van autochtone Nederlanders.

Culprit laesies bij patiënten met een acuut hartinfarct bevatten meer en kleinere calcificaties (boog <45°, lengte < 1.5 mm) dan aanliggende vaatsegmenten. Culprit

laesies met een zichtbare plaque ruptuur of ulceratie bevatten calcificaties met een grotere boog en lengte (boog 90-180°, lengte 3-6 mm) vergeleken met culprit laesies waarbij geen ruptuur of ulceratie kan worden waargenomen.

TOEKOMSTPERSPECTIEF

Ontwikkeling en implementatie van een richtlijn gebaseerd behandelprotocol voor patiënten met een acuut hartinfarct

Kennis en mogelijkheden in de behandeling van patiënten met een acuut hartinfarct zijn in de afgelopen decennia enorm toegenomen. Nog steeds is er ontwikkeling gaande in rap tempo. De zorg die hierdoor wordt geboden verbeterd, maar wordt ook steeds complexer. Richtlijnen geven handvaten om gepaste en kwalitatief goede zorg te leveren aan de patiënt. Deze richtlijnen zijn zoveel mogelijk gebaseerd op wetenschappelijk bewezen effectieve en doelmatige strategieën. Hoewel studies laten zien dat implementatie van richtlijnen bij patiënten met een acuut hartinfarct zorgt voor vermindering van sterfte, laat daadwerkelijke implementatie van de richtlijnen in “real world” te wensen over. De resultaten van het MISSION! protocol laat zien dat het invoeren van een handzaam protocol effectief is. Zorg wordt nu niet louter op individuele basis bepaald -op basis van de klinische ervaring, kennis en intuïtie van de dokter- maar wordt bepaald door een multidisciplinair en transmurale gefundeerd systeem. Hierdoor verminderen de inter-dokter en inter-patiënt variaties. Hulpprofessionals leggen verantwoording af aan het systeem en aan elkaar waarom iets wel of niet volgens protocol is gedaan. De zorg kan getoetst worden met zogenaamde prestatie-indicatoren en dit geeft weer de mogelijkheid tot evaluatie, feedback en een continu proces tot verbetering. Transparantie wordt geschept voor externe instanties zoals de overheid of zorgverzekeraars. Naast al deze positieve punten moet men ook beducht zijn op het teveel leunen op een richtlijn gebaseerd behandelprotocol: het kan een remmende werking hebben op nieuwe ontwikkelingen. Richtlijnen zelf hebben beperkingen: niet alle gegeven adviezen zijn evidence-based en de kennis verkregen uit grote klinische trials is gebaseerd op een selecte patiëntenpopulatie, wat frequent niet overeenkomt met de dagelijkse patiënt. Verder bestaat de mogelijkheid dat individueel bewezen strategieën juist gecombineerd niet effectief of zelfs schadelijk zijn.

Geleerde lessen uit MISSION! en adviezen voor de toekomst zijn: 1) er moet gestreefd worden naar een intra-, interdisciplinaire en transmurale samenwerking bij

de ontwikkeling en implementatie van een behandelprotocol voor patiënten met een acuut hartinfarct. 2) De patiënt moet hierin centraal staan. 3) Louter appliceren van (inter-) nationale richtlijnen op de dagelijkse praktijk werkt niet. Aanpassing is vereist naar lokale en regionale mogelijkheden, capaciteit en financiën. 4) “Care-tools” in de vorm van medische orders en informaticasystemen dragen substantieel bij aan het succes van implementatie. 5) Continue kwaliteitscontrole is vereist niet alleen om na te gaan of het protocol goed wordt nageleefd, maar ook ter verbetering van het protocol zelf naargelang nieuwe klinische en/of wetenschappelijke inzichten. 6) Een protocol dient als leidraad om de juiste medische beslissingen te nemen, maar mag nooit een weloverwogen klinisch oordeel vervangen.

Verder onderzoek naar kosteneffectiviteit zou het programma nog doelmatiger kunnen maken. Echter dit wordt bemoeilijkt door de betrokkenheid van de verschillende instanties, en de ethische, maatschappelijke en politieke aspecten met betrekking tot het volgen van richtlijnen. Tevens moet vermeld worden dat de studiepopulatie te klein was om het effect van MISSION! primair te toetsen op harde klinische eindpunten. Deze gegevens hopen we in de nabije toekomst te kunnen leveren, aangezien de inclusie van patiënten in het MISSION! protocol doorgaat.

List of publications

LIST OF PUBLICATIONS

van Looij MA*, Liem SS*, van der Burg H, van der Wees J, De Zeeuw CI, van Zanten BG. Impact of conventional anesthesia on auditory brainstem responses in mice. *Hear Res.* 2004;193(1-2):75-82

van der Wees J, van Looij MA, de Ruiter MM, Elias H, van der Burg H, Liem SS, Kurek D, Engel JD, Karis A, van Zanten BG, de Zeeuw CI, Grosveld FG, van Doorninck JH. Hearing loss following Gata3 haploinsufficiency is caused by cochlear disorder. *Neurobiol Dis.* 2004;16(1):169-178

Van der Velde ET, Liem SS, van der Hoeven BL, Witteman TA, Foeken H, Oemrawsingh PV, Schalij MJ
Multi-vendor solution for reception and review of ECG to shorten treatment delay in AMI patients. *Computers in Cardiology* 2005; 32:61-63

van der Hoeven BL, Liem SS, Oemrawsingh PV, Dijkstra J, Jukema JW, Putter H, Atsma DE, van der Wall EE, Bax JJ, Reiber JC, Schalij MJ.
Role of calcified spots detected by intravascular ultrasound in patients with ST-segment elevation acute myocardial infarction. *Am J Cardiol.* 2006;98(3):309-313

Liem SS, van der Hoeven BL, Oemrawsingh PV, Bax JJ, van der Bom JG, Bosch J, Viergever EP, van Rees C, Padmos I, Sedney MI, van Exel HJ, Verwey HF, Atsma DE, van der Velde ET, Jukema JW, van der Wall EE, Schalij MJ
MISSION!: Optimization of acute and chronic care for patients with acute myocardial infarction. *Am Heart J* 2007;153:14.e1214.e11

Liem SS, Jukema JW, Schalij MJ
Response to the letter to the Editor by van de Werf. *Am Heart J* 2007;153:e35.

Mollema SA, Bleeker GB, Liem SS, Boersma E, van der Hoeven BL, Holman ER, van der Wall EE, Schalij MJ, Bax JJ.
Does left ventricular dyssynchrony immediately after acute myocardial infarction result in left ventricular dilatation? *Heart Rhythm.* 2007;4(9):1144-1148

Mollema SA, Liem SS, Suffoletto MS, Bleeker GB, van der Hoeven BL, van de Veire NR, Boersma E, Holman ER, van der Wall EE, Schalij MJ, Gorcsan J 3rd, Bax JJ.

Left ventricular dyssynchrony acutely after myocardial infarction predicts left ventricular remodeling. *J Am Coll Cardiol.* 2007;50(16):1532-1540

van der Hoeven BL, Liem SS, Jukema JW, Suraphakdee N, Putter H, Dijkstra J, Atsma DE, Bootsma M, Zeppenfeld K, Oemrawsingh PV, van der Wall EE, Schalij MJ. Sirolimus-eluting stents versus bare-metal stents in patients with ST-segment elevation myocardial infarction: 9-month angiographic and intravascular ultrasound results and 12-month clinical outcome results from the MISSION! Intervention Study. *J Am Coll Cardiol.* 2008; 51(6):618-626

de Jager SC, Kraaijeveld AO, Grauss RW, de Jager W, Liem SS, van der Hoeven BL, Prakken BJ, Putter H, van Berkel TJ, Atsma DE, Schalij MJ, Jukema JW, Biessen EA. CCL3 (MIP-1 alpha) levels are elevated during acute coronary syndromes and show strong prognostic power for future ischemic events. *J Mol Cell Cardiol.* 2008; 45(3):446-452

Hassan AKM, Liem SS, van der Kley F, Bergheanu SC, Wolterbeek R, Bosch J, van der Laarse A, Atsma DE, Jukema JW, Schalij MJ
In-ambulance abciximab administration in STEMI patients prior to primary PCI is associated with smaller infarct size, improved LV function and lower incidence of heart failure. *Eur Heart J.* 2008; *Supplement*:136

Liem SS, van der Hoeven BL, Mollema SA, Bosch J, van der Bom JG, Viergever EP, van Rees C, Bootsma M, van der Velde ET, Jukema JW, van der Wall EE, Schalij MJ
Optimization of acute and long-term care for acute myocardial infarction patients: The Leiden MISSION! project. *Submitted*

Liem SS, Oemrawsingh PV, Cannegieter SC, Le Cessie S, Schreur J, Rosendaal FR, Schalij MJ
Cardiovascular risk in young apparently healthy descendants from Asian Indian migrants in the Netherlands: the SHIVA study. *Netherlands Heart Journal (in press)*

Hassan AKM, Bergheanu SC, Hasan-Ali H, Liem SS, van der Laarse A, Wolterbeek R, Atsma DE, Schalij MJ, Jukema JW
Usefulness of peak troponin-T to predict infarct size and long-term outcome in patients with first acute myocardial infarction after primary percutaneous coronary intervention. *Am J Cardiol. (in press)*

Curriculum Vitae

Su-San Liem, the author of this thesis, was born on June 18, 1976 in Tegelen, The Netherlands. After having been awarded her *Gymnasium* (high school) diploma by the Collegium Marianum in Venlo, she started studying medicine at the Catholic University of Leuven in Belgium in 1994. There she obtained her candidature diploma and completed the first two doctoral years. She returned to the Netherlands and carried out research at the Department of Anatomy at the Erasmus University of Rotterdam for a period of seven months. The research was in the field of "Auditory Brainstem Response" in mice and was carried out under the supervision of Prof. Dr. L. Feenstra and Prof. Dr. C.I. de Zeeuw. In 2001 she started her internship at the Erasmus University and obtained her medical degree with distinction in April 2003. For a short period of time she worked as a resident at the Department of Internal Medicine at the Reinier de Graaf Hospital in Delft. In February 2004, she started her official training in cardiology under an "AGIKO" scholarship at the Leiden University Medical Center. Under the supervision of Prof. Dr. M.J. Schalij and Prof. Dr. E.E. van der Wall she implemented an all-phased integrated care program for patients with an acute myocardial infarction: the MISSION! protocol. The results of this protocol and other studies carried out are described in this thesis. Over the course of her time carrying out scientific research she was an abstract grader of the "Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke Conference" of the American Heart Association in 2007. She was a finalist for the "Geoffrey Rose Young Investigator Award" at the "EuroPREvent" congress of the European Society of Cardiology in Madrid 2007. Furthermore, she was active in the "Committee of Cardiovascular Prevention and Cardiac Rehabilitation" of The Netherlands Society of Cardiology. Since September 2007, she has been working at the Department of Internal Medicine at the Bronovo hospital, The Hague (pre-training for cardiologist, educational head Dr. J.W. van 't Wout). Her traineeship will be continued at the Department of Cardiology at the Haga hospital in The Hague (educational head Dr. B.J.M. Delemarre), and at the Department of Cardiology at the Leiden University Medical Center (educational head Prof. Dr. E.E. van der Wall).

Su-San Liem, de auteur van dit proefschrift, werd geboren op 18 juni 1976, te Tegelen. In 1994 behaalde zij het β -gymnasium eindexamen aan het Collegium Marianum te Venlo. In hetzelfde jaar startte zij met de studie geneeskunde aan de Katholieke Universiteit Leuven in Leuven, België. Zij behaalde daar haar diploma kandidatuursjaren en de eerste twee doctoraaljaren. Hierna ging zij terug naar Nederland. Gedurende 7 maanden deed zij onderzoek op het gebied van "Auditory Brainstem Response" bij muizen, onder begeleiding van prof. dr. L. Feenstra en prof. dr. C.I. de Zeeuw op de

afdeling anatomie van de Erasmus Universiteit te Rotterdam. In 2001 startte ze met haar co-schappen geneeskunde eveneens aan de Erasmus Universiteit te Rotterdam en behaalde haar artsexamen "cum laude" in april 2003. Hierna was ze korte tijd werkzaam als AGNIO Interne geneeskunde in het Reinier de Graaf ziekenhuis te Delft. Sinds februari 2004 is zij als "AGIKO" verbonden aan de afdeling hartziekten van het Leids Universitair Medisch Centrum te Leiden. Onder begeleiding van prof. dr. M.J. Schalij en prof. dr. E.E. van der Wall zette zij een intensief zorgprogramma op voor patiënten met een acuut hartinfarct: het MISSION! protocol. De resultaten van dit protocol en andere door haar verrichte studies staan beschreven in dit proefschrift. Tijdens haar onderzoeksperiode was zij "abstract grader" voor de "Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke Conference" van de American Heart Association in 2007. Zij was finaliste voor de "Geoffrey Rose Young Investigator Award" tijdens EuroPrevent van de European Society of Cardiology in Madrid 2007. Verder was zij actief in de Commissie Cardiovasculaire Preventie en Hartrevalidatie van de Nederlandse Vereniging voor Cardiologie. Op 1 september 2007 startte zij met het klinische gedeelte van haar opleiding tot cardioloog op de afdeling Interne Geneeskunde in het Bronovo Ziekenhuis, te Den Haag (opleider dr. J.W. van 't Wout). Dit zal vervolgd worden op de afdeling cardiologie van het Haga ziekenhuis, te Den Haag (opleider dr. B.J.M. Delemarre) en de afdeling cardiologie van het Leids Universitair Medisch Centrum, te Leiden (opleider prof. dr. E.E. van der Wall).