Myocardial Infarction

Temporal trends over the past three decades

myo
cardial
infarct
ion

Sjoerd T Nauta

Myocardial infarction:
temporal trends over the past three decades

Myocardial infarction: temporal trends over the past three decades

ISBN: 9789462286054

© Sjoerd T Nauta, 2014

All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage or retrieval system, without the prior written permission of the holder of the copyright.

Lay-out and printing: Ralph Boer (ralphboer@icloud.com)

Myocardial infarction: temporal trends over the past three decades

Ziekten van de kransvaten: temporele ontwikkelingen over de afgelopen drie decennia

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

donderdag 5 maart 2015 om 15.30 uur

Sjoerd Toussaint Nauta

geboren te Wageningen

PROMOTIECOMMISSIE

Promotor:	Prof. dr. J.W. Deckers
Overige leden:	Prof. dr. M.L. Bots
	Prof. dr. P.P. de Jaegere
	Prof. dr. J.W. Roos
Copromotor:	Dr. K.M. Akkerhuis

Het verschijnen van dit proefschrift werd mede mogelijk
gemaakt door de steun van de Nederlandse Hartstichting.

Table of Contents

PART V Percutaneous coronary interventions

PART VI Methodology

PART VII Discussion

Chapter 1

Introduction

Background: population based approach

During the past three decades cardiovascular disease has been the primary cause of death in the western world.[1] Mortality due to cardiovascular disease was highest in the late 1980s, claiming over 50 000 deaths in the Netherlands each year (>40% of total mortality). From 1985 onwards, however, mortality due to cardiovascular diseases gradually decreased, whereas mortality due to cancer became more prominent (Figure 1).

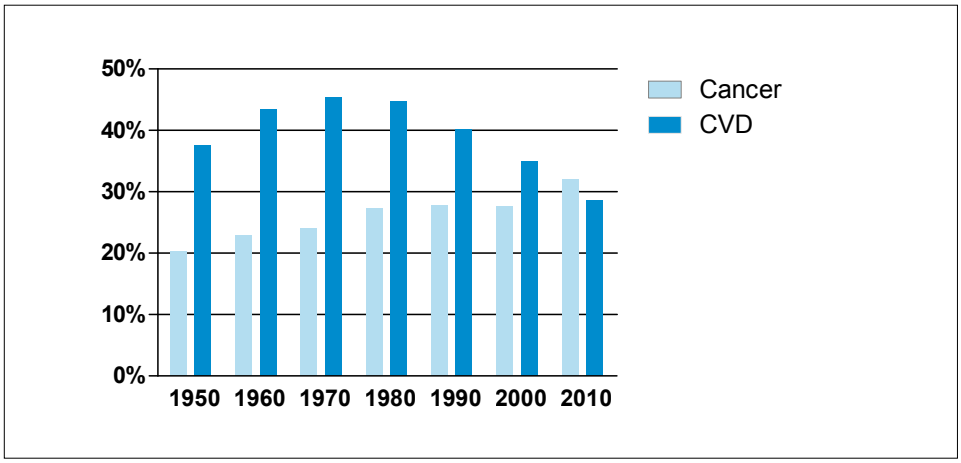

Figure 1: Number of deaths due to cancer and cardiovascular disease as a percentage of the total number of deaths for separate years between 1950 and 2010 (source: www.cbs.nl). CVD, cardiovascular disease.

Coronary artery disease has been and remains the main clinical manifestation of cardiovascular morbidity and mortality: in 1980 half of the cardiovascular mortality was due to coronary artery disease whereas less than a quarter resulted from cerebrovascular disease. In particular, the mortality due to coronary artery disease has decreased over the past decades (Figure 2).

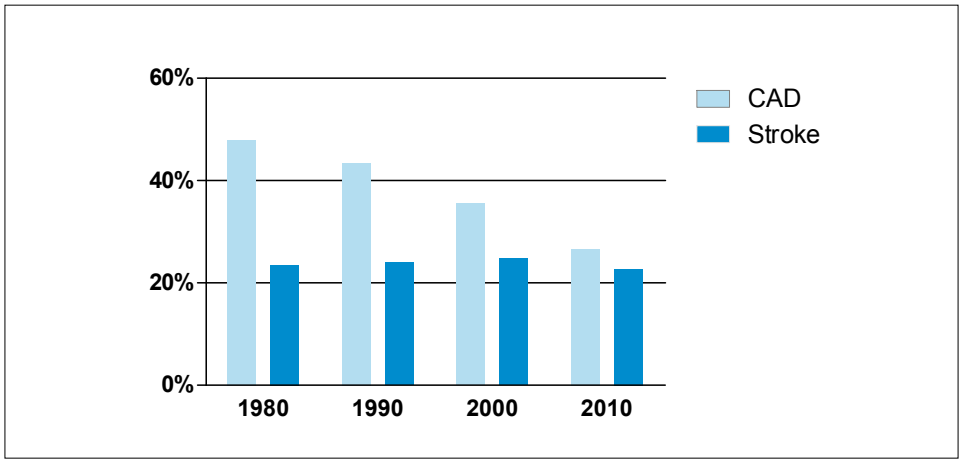

Figure 2: Number of deaths due to coronary artery disease and stroke as a percentage of the number of deaths due to cardiovascular disease for separate years between 1980 and 2010 (source: www.cbs.nl). CAD, coronary artery disease.

Interestingly, deaths from coronary artery disease occur primarily in the elderly (Figure 3). Given that the population is aging (Figure 4), the true (age corrected) mortality reduction is more substantial than the above figures suggest.

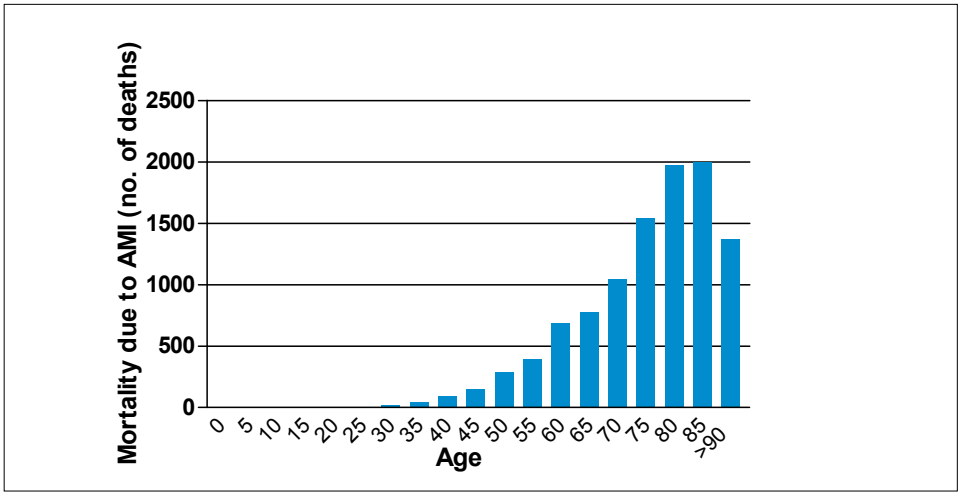

Figure 3: Number of deaths due to acute myocardial infarction in 2010 for each age group (source: www.cbs.nl). AMI, acute myocardial infarction.

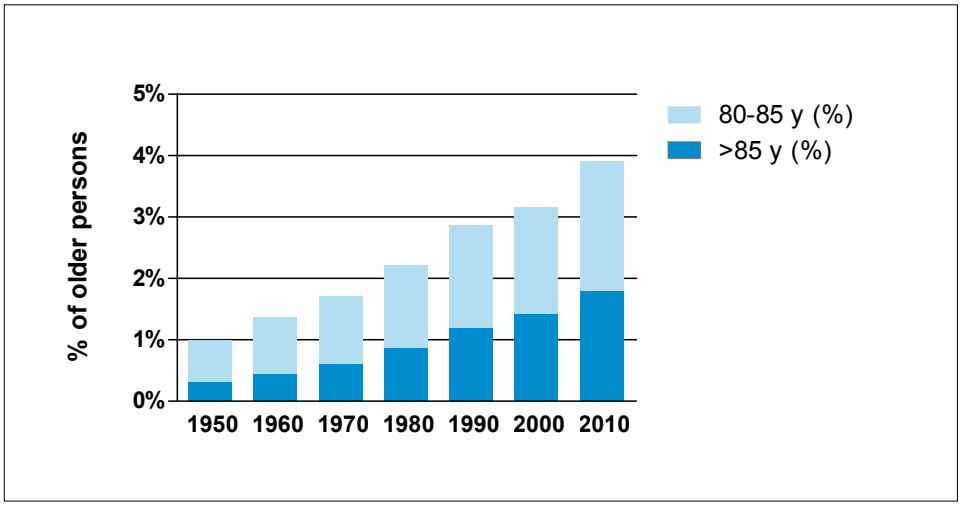

Figure 4: The aging population: number of individuals aged 80 or 85 years or older in the total population for separate years between 1960 and 2010 (source: www.cbs.nl).

Treatment

During the last 30 years, treatment of coronary artery disease has made substantial progress. The introduction of thrombolysis, percutaneous coronary intervention, aspirin, beta-blockers, ace inhibitors, statins, and novel anticoagulants should be mentioned in particular.[2] The effectiveness of these therapies have been extensively demonstrated in randomized controlled trials, however, the combined impact of these treatments remains unknown.

Risk factors

In addition to changes in treatment and demographical developments (i.e. an aging population), the clinical presenting characteristics and comorbidity of patients with coronary artery disease has changed as well. Clinical characteristics or risk factors can be used to predict adverse events. Also, comorbidity and risk factors can be used to tailor treatment, with more aggressive treatment in high risk patients and alternative treatment modalities for patients at lower risk, with comorbidity or conditions preventing the application of some treatment modality. For these reasons, it remains important to study changes in treatment and outcome in conjunction with changes in such risk factors.

References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation 2012;125(1):e2-e220.

2. Nauta ST, Deckers JW, Akkerhuis M, Lenzen M, Simoons ML, van Domburg RT. Changes in clinical profile, treatment, and mortality in patients hospitalised for acute myocardial infarction between 1985 and 2008. PLoS One 2011;6(11):e26917.

Chapter 2

Aim and thesis outline

The aim of this thesis was to expand the knowledge on treatment, outcome and risk factors for adverse outcome in coronary artery disease patients with focus on changes therein during the past three decades.

The outline of the thesis is as follows. Part I highlights changes in clinical profile, treatment and mortality in patients hospitalized for acute myocardial infarction (Chapter 3). Chapters 4 and 5 evaluate the changes in treatment and outcome of patients with either renal dysfunction or anemia.

Part II focuses on emerging risk factors. During the past decades, the population has been aging with an increase in pre-diabetes (hyperglycemia) and diabetes mellitus type II. These changes are discussed in chapters 6 to 8.

Part III addresses gender issues and focuses on prognosis of myocardial infarction patients compared with age and gender matched patients of the general population.

Part IV focuses on traditional risk factors: diabetes, hypertension, hypercholesterolemia, and family history of coronary artery disease. These risk factors are useful in the prediction of cardiovascular disease in patients with no prior history of cardiovascular disease. However, their value in myocardial infarction patients is controversial.

Part V focuses on percutaneous coronary interventions. The results of percutaneous coronary intervention in saphenous bypass grafts is discussed in chapter 12. The predictive value of the SYNTAX risk score is discussed in chapters 13 and 14. Since primary percutaneous coronary interventions might be delayed during the weekend days, chapter 15 focuses on the so called 'weekend effect' with possibly higher mortality rates during the weekend. Chapters 16 and 17 focus on the current revascularization guidelines.

Part VI of this thesis focuses on methodological issues related to clinical research. Specifically, chapter 18 describes how an appropriate control group could be selected and chapter 19 is a tutorial for analyses of clustered data.

Part I

Changes in clinical profile, treatment, and mortality

Chapter 3

Changes in clinical profile, treatment, and mortality in patients hospitalised for acute myocardial infarction between 1985 and 2008

Sjoerd T Nauta
Jaap W Deckers
Martijn Akkerhuis
Mattie Lenzen
Maarten L Simoons
Ron T van Domburg

PLoS One. 2011;6(11):e26917

Abstract

Objectives

To quantify the impact of the implementation of treatment modalities into clinical practice since 1985, on outcome of patients with ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI).

Methods

All consecutive patients admitted for STEMI or NSTEMI at the Thoraxcenter between 1985 and 2008 were included. Baseline characteristics, pharmacological and invasive treatment modalities, and survival status were collected. The study population was categorised in three groups of patients: those hospitalised between 1985-1990; 1990-2000; and 2000-2008.

Results

We identified 14,434 patients hospitalised for myocardial infarction (MI). Both STEMI and NSTEMI patients were increasingly treated with current guideline based therapy. In STEMI, at 30 days following admission, cumulative mortality rate decreased from 17% in 1985-1990 to 13% in 1990-2000, and to 6% in 2000-2008. Adjusted 30-day and three-year mortality in the last period was 80% and 68% lower than in 1985, respectively. In NSTEMI, at 30 days following admission, cumulative mortality rate decreased from 6% in 1985-1990 to 4% in 1990-2000, and to 2% in 2000-2008. Adjusted 30-day and three-year mortality in the last period was 78% and 49% lower than in 1985, respectively. For patients admitted between 2000 and 2008, 3 year survival of STEMI and NSTEMI patients was 87% and 88%, respectively.

Conclusions

Our results indicate substantial improvements in acute- and long-term survival in patients hospitalised for MI, related to improved acute- as well as long-term treatment. Early medical evaluation in suspected MI and intensive early hospital treatment both remain warranted in the future.

Keywords

ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, Survival, Trends

Introduction

During the last 25 years, the management of patients presenting with an acute myocardial infarction (MI) has undergone many transformations. Until 1984, treatment was limited to providing symptomatic relief, and management of complications as arrhythmia's, acute heart failure, or post-infarction angina. In the 1980s, the introduction of antithrombotic treatment with aspirin and intravenous (or intracoronary) fibrinolysis resulted in significant mortality reductions in patients with ST-segment elevation myocardial infarction (STEMI).[1] In the nineties, pre-hospital identification ("triage") of patients with an acute myocardial infarction with an indication for reperfusion therapy and subsequent immediate (pre-hospital) initiation of thrombolytic treatment was introduced in some areas.[2,3] Although more effective thrombolytic agents became available,[4] reperfusion of the infarct-related vessel often failed,[5] and bleeding complications were a limiting factor of fibrinolyis.[6] Gradually, mechanical percutaneous techniques improved, and in the last decade primary percutaneous coronary intervention (PCI) became the treatment of choice in patients presenting with a STEMI.[7,8]

In the same time period, patients with non-ST-elevation myocardial infarction (NSTEMI) benefitted from improved anti-thrombotic and anti-coagulant therapy,[9] better risk stratification and tailored treatment with selective coronary revascularization in high risk patients.[9,10,11,12] Additionally, effective secondary prevention was introduced with aspirin, beta-blockers, statins, and ACE inhibitors in subjects with LV dysfunction and, subsequently, in high risk MI survivors.[13,14,15,16,17] In combination, all these developments reshaped the treatment map of the patient with an MI.[18,19,20]

The impact of the implementation of all these treatment modalities into clinical practice on outcome has not yet been fully quantified. Therefore, we analysed changes in clinical practise, treatment, and 30-day as well as three-year outcome in a consecutive series of STEMI or NSTEMI patients admitted at our institution, an academic tertiary referral center, between 1985 and 2008.

Methods

We included all consecutive patients aged >18 years admitted for STEMI or NSTEMI to the Intensive Coronary Care Unit (ICCU) of the Thoraxcenter, Erasmus University Medical Center between June 1985 and December 2008. The Thoraxcenter was the referral center for all PCIs in the Rotterdam region until 2005 when a second hospital started a PCI programme. Regional arrangements were made such that patients with MI were referred to either hospital according to a pre-arranged schedule.

The primary discharge diagnosis of MI was made in the presence of the following characteristics: chest pain or equivalent symptoms in combination with dynamic ECG changes consistent with MI and a serial rise (to at least three times the upper normal value) and fall in serum biochemical markers of cardiac necrosis such as creatine kinase-MB and troponin T (as of 2002). Patients were diagnosed as STEMI in the presence of ST-segment elevation > 0.1 mV in at least two peripheral leads, or > 0.2 mV in at least two precordial leads, and as NSTEMI otherwise. For patients admitted more than once, only the first hospitalisation was taken into account.

Data collection

This is a prospective observational study. Trained physicians and nurses accustomed to the use of standardized case report forms collected the data. Demographic characteristics (age, gender), cardiac history (previous MI, PCI or coronary artery bypass surgery (CABG)), risk factors (hypertension, diabetes, family history, smoking status), renal dysfunction (creatinine value >150 µmol/L), and pharmacological and invasive treatment modalities (thrombolysis and PCI) were collected.

Follow-up and endpoints

The primary endpoint was all cause mortality at 30 days and at three-years. In-hospital mortality was retrieved from the medical records. Survival status was assessed through municipal Civil Registries in 2010 and was available for 99% of all patients.

Ethics Statement

This study has been approved by the Ethical Committee of the Erasmus Medical Center, Rotterdam. According to Dutch laws, informed consent is not required for register-based research of pre-existing personal data. Therefore, the Ethical Committee waived the need for informed consent.

Statistical Analysis

Data are summarized as frequencies and percentages for categorical variables. Continuous variables are presented as mean and standard deviation or median and 25th and 75th percentile. The study population was categorised in three groups of patients, those hospitalised between 1985-1990; 1990-2000; and 2000-2008, respectively. These categories were chosen according to important improvements in therapy with complete introduction of thrombolysis in 1991 and substantial increase in the use of primary PCI in 2001. Categorized variables among the three groups were compared with the chi-square test and continuous variables by ANOVA with Bonferroni corrections. In addition, we compared changes in mortality in time periods of three year, and these changes are presented in Forrest plots.

Cumulative survival and one-minus-survival curves were constructed using the Kaplan–Meier method according to date of hospitalization as presented above. A log-rank test was used to compare survival curves. We examined the independent association between year of hospitalization and mortality using logistic regression for 30-day outcome and the Cox proportional hazards model for long-term outcome, with adjustment for age, gender, previous MI, previous CABG, diabetes, hypertension and smoking status. Results are reported as odds or hazard ratios of mortality and their respective 95% confidence intervals. Proportionality of hazards was tested graphically by inspection of log–log survival curves and by a formal test of proportionality based on Schoenfeld residuals for each variable in the model. Calibration refers to whether the model agrees with the observed probabilities and was assessed with the Hosmer–Lemeshow statistic.

All statistical tests were 2-tailed, and p-values were significant at <0.05. Analysis was performed using SPSS software version 17.0 (SPSS, Chicago, USA).

Results

We identified 14,434 consecutive patients hospitalised for MI in our center between 1985 and 2008: 6,820 STEMI and 7,614 NSTEMI patients. At three years follow-up, mortality had occurred in 2,190 patients, 1,232 in STEMI and 958 in NSTEMI patients.

ST-segment elevation myocardial infarction

The characteristics of the STEMI patients are depicted in Table 1. With time, STEMI patients presented older, were more likely to have diabetes, hyperlipidemia, anemia, and a history of PCI. Further, STEMI patients were less likely to present with renal dysfunction or a history of MI.

The percentage of STEMI patients treated with PCI increased gradually. Before 1985, neither intracoronary- nor intravenous thrombolytic therapy was employed, while intravenous fibrinolysis was the main treatment modality from 1985 to 1998. From 1998 onwards, treatment with thrombolysis was gradually replaced by primary PCI (Figure 1). Since our institution was initially the only hospital with PCI facilities in the region, the number of patients with STEMI admitted increased as a result of the decision to offer primary PCI to all STEMI patients in the Rotterdam Region. In the most recent cohort, drug therapy with aspirin, beta-blockers, statins, and ACE inhibitors or angiotensin receptor blockers was quite common, but calcium antagonists, diuretics or nitrates were prescribed less frequently.

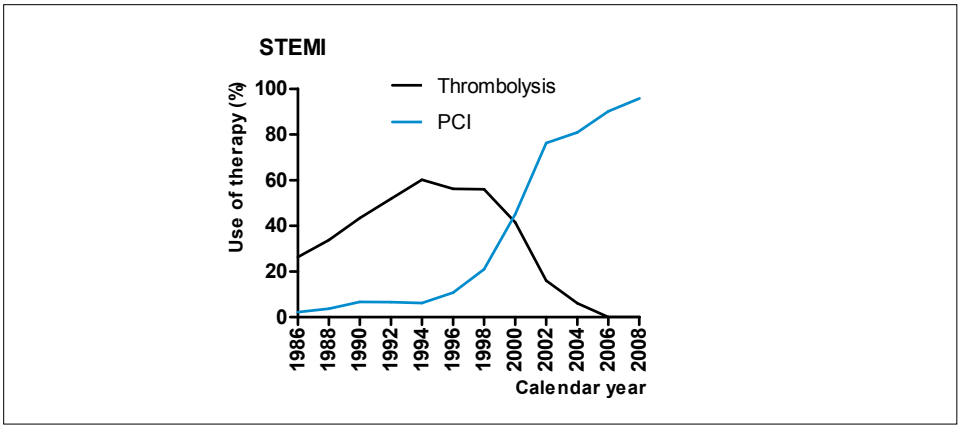

Figure 1: Treatment of STEMI patients over time

Table 1: Baseline characteristics, clinical presentation, and discharge medication of patients hospitalised for STEMI

	Period of admission			P
	1985-1990	1990-2000	2000-2008	
No. of patients	947	1928	3945	
Baseline				
Age (years)	60 ±11.6	60 ±12.7	61 ±12.6	0.01
Gender (male)	731 (77%)	1432 (74%)	2937 (75%)	0.20
Cardiac history				
Previous MI	334 (35%)	463 (24%)	1075 (27%)	<0.001
Previous PCI	43 (5%)	127 (7%)	653 (17%)	<0.001
Previous CABG	83 (9%)	124 (6%)	282 (7%)	0.09
Risk factors				
Hypertension	320 (34%)	549 (29%)	1295 (33%)	<0.01
Diabetes	79 (8%)	204 (11%)	571 (14%)	<0.001
Hyperlipidemia	76 (8%)	295 (15%)	919 (23%)	<0.001
Family history	201 (21%)	400 (21%)	1062 (27%)	<0.001
Current smoker	403 (43%)	675 (35%)	1518 (39%)	<0.001
Renal dysfunction	104 (11%)	229 (12%)	179 (5%)	<0.001
Anemia	309 (33%)	818 (42%)	1464 (37%)	<0.001
Medication at ICCU discharge				
Statin	0 (.)	NA	2996 (76%)	<0.001
Aspirin	97 (10%)	1200 (62%)	3510 (89%)	<0.001
Beta-blocker	412 (44%)	958 (50%)	2341 (59%)	<0.001
Calcium antagonist	306 (32%)	315 (16%)	174 (4%)	<0.001
Nitrates	220 (23%)	241 (13%)	190 (5%)	<0.001
Diuretics	334 (35%)	306 (16%)	321 (8%)	<0.001
ACE inhibitor or ARB	0 (.)	403 (21%)	1308 (33%)	<0.001

ACE, Angiotensin-Converting Enzyme; ARB, Angiotensin receptor blocker; CABG, coronary artery bypass grafting surgery; ICCU, intensive coronary care unit; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention; STEMI, ST-elevation MI.

At 30 days following admission, cumulative mortality rate decreased from 17% in 1985-1990 to 13% in 1990-2000, and to 6% in 2000-2008 ($p < 0.001$; Figure 2). Adjusted 30-day mortality in the last period was 80% lower than in 1985 (adjusted odds ratio (OR) 0.20, 95%CI 0.14-0.28, $p < 0.001$) (Figure 3).

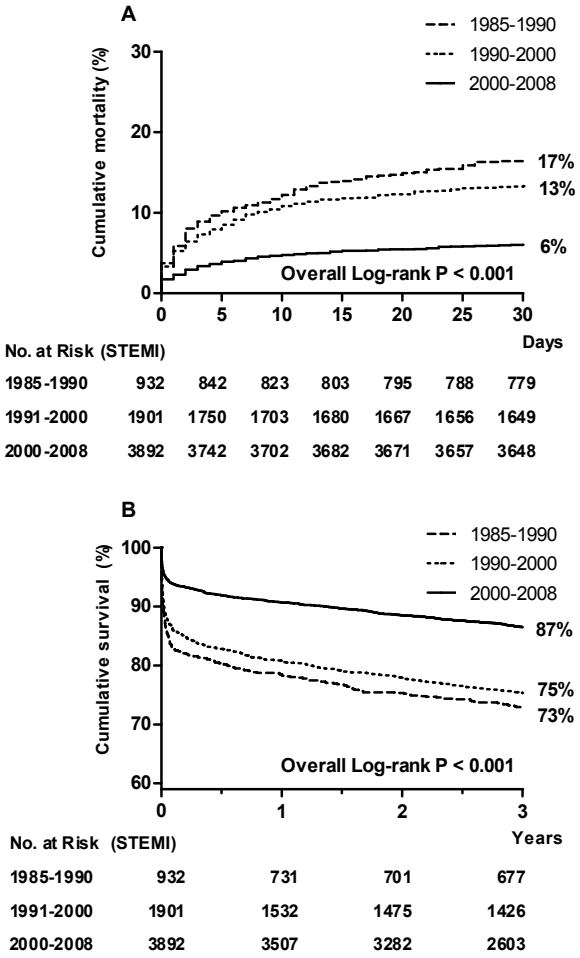

Figure 2: Kaplan-Meier curves for 30-day cumulative mortality (Figure 2A) or three-year cumulative survival (Figure 2B) according to calendar period of admission

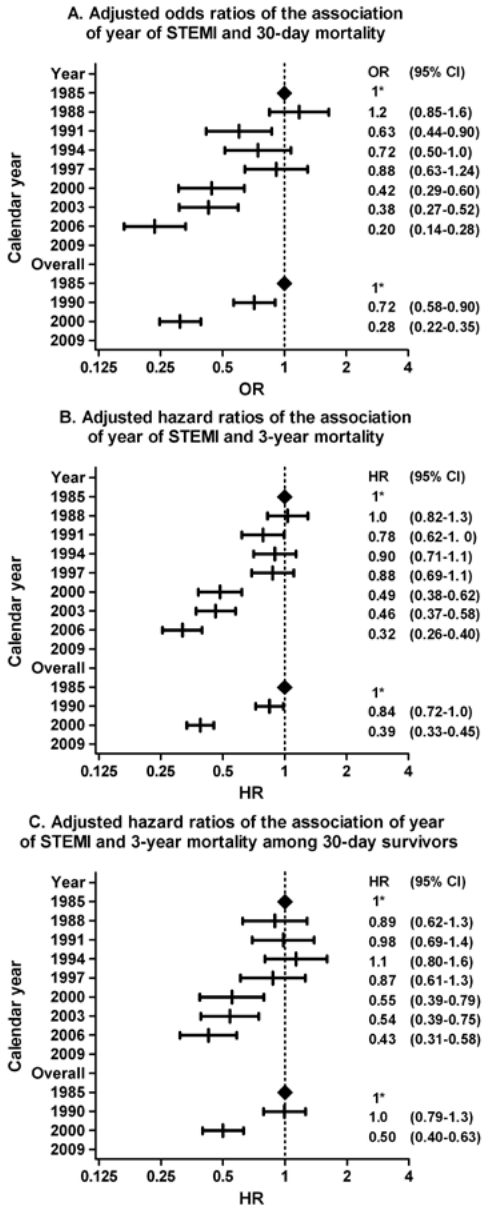

Figure 3: Adjusted odds or hazard ratios of secular trends in mortality after STEMI at 30-days (Figure 3A), at 3-year (Figure 3B), and at 3-year among 30-day survivors (Figure 3C). The upper part of the figure compares changes in mortality in time periods of three year, the lower part among patients hospitalised between 1985-1990; 1990-2000; and 2000-2008

* Reference category for the subsequent ratios CI, confidence interval; HR, Hazard ratio; OR, Odds ratio, STEMI, ST-elevation myocardial infarction

Cumulative three-year survival rate increased from 73% in 1985-1990 to 75% in 1990-2000 and to 87% in 2000-2008 ($p < 0.001$). Adjusted three-year mortality in the last period was 68% lower than in 1985 (adjusted hazard ratio (HR) 0.32, 95%CI 0.26-0.40, $p < 0.001$). In a landmark analysis, including only patients who survived the first 30 days, adjusted three-year mortality was 57% lower in the most recent period than in 1985 (adjusted HR 0.43, 95%CI 0.31-0.58, $p < 0.001$, Figure 3).

Non-ST-segment elevation myocardial infarction

With time, NSTEMI patients presented older, were more likely to have hypertension, diabetes, hyperlipidemia, or anemia and less likely to be a smoker (Table 2). Furthermore, NSTEMI patients more often presented with a history of PCI and less often presented with a history of MI in the most recent study period. As in STEMI, prescription of aspirin, beta-blockers, statins, and ACE inhibitors or angiotensin receptor blockers increased while the use of calcium antagonists and nitrates decreased.

At 30 days following admission, cumulative mortality rate decreased from 6% in 1985-1990 to 4% in 1990-2000, and to 2% in 2000-2008 ($p < 0.001$; Figure 4). Adjusted 30-day mortality in the last period was 78% lower than in 1985 (adjusted OR 0.22, 95%CI 0.13-0.37, $p < 0.001$; Figure 5).

Cumulative three-year survival rate did not significantly change between 1985-1990 (85%) and 1990-2000 (86%). Three-year survival in the last period was 88% ($p < 0.001$). Adjusted three-year mortality in the last period was 49% lower than in 1985 (adjusted HR 0.51, 95%CI 0.39-0.68, $p < 0.001$). In a landmark analysis, including only patients who survived the first 30 days, adjusted three-year mortality was 29% lower in the most recent period than in 1985 (adjusted HR 0.71, 95%CI 0.52-0.99, $p = 0.042$, Figure 5).

For patients admitted between 2000 and 2008, long term survival of STEMI and NSTEMI patients was comparable, 87% and 88%, respectively (Figures 2 and 4). The higher subsequent mortality in non-STEMI patients resulted from their older age. After correction for this confounder, the risk of 30-day to three-year mortality was similar in NSTEMI and STEMI (adjusted HR 1.0, 95%CI 0.86-1.2).

Table 2: Baseline characteristics, clinical presentation, and discharge medication of patients hospitalised for NSTEMI

	Period of admission			P
	1985-1990	1990-2000	2000-2008	
No. of patients	1269	2672	3673	
Baseline				
Age (years)	61 ±10.3	63 ±11.7	63 ±11.8	<0.001
Gender (male)	921 (73%)	1806 (68%)	2575 (70%)	<0.01
Cardiac history				
Previous MI	581 (46%)	1050 (39%)	1290 (35%)	<0.001
Previous PCI	130 (10%)	356 (14%)	757 (21%)	<0.001
Previous CABG	196 (15%)	292 (12%)	390 (11%)	<0.001
Risk factors				
Hypertension	455 (36%)	881 (34%)	1604 (44%)	<0.001
Diabetes	95 (8%)	321 (12%)	745 (20%)	<0.001
Hyperlipidemia	159 (13%)	736 (24%)	1785 (49%)	<0.001
Family history	331 (26%)	666 (25%)	1122 (31%)	<0.001
Current smoker	459 (36%)	741 (28%)	880 (24%)	<0.001
Renal dysfunction	102 (8%)	222 (8%)	349 (10%)	0.20
Anemia	489 (39%)	1153 (43%)	1783 (49%)	<0.001
Medication at ICCU discharge				
Statin	0 (.)	NA	1962 (68%)	<0.001
Aspirin	225 (18%)	1169 (55%)	3125 (85%)	<0.001
Beta-blocker	865 (68%)	1271 (60%)	2334 (64%)	<0.001
Calcium antagonist	884 (70%)	972 (46%)	515 (14%)	<0.001
Nitrates	475 (37%)	393 (19%)	335 (9%)	<0.001
Diuretics	240 (19%)	276 (13%)	337 (9%)	<0.001
ACE inhibitor or ARB	0 (.)	191 (7%)	1134 (31%)	<0.001

ACE, Angiotensin-Converting Enzyme; ARB, Angiotensin receptor blocker; CABG, coronary artery bypass grafting surgery; ICCU, intensive coronary care unit; MI, myocardial infarction; NA, not available; NSTEMI, non-ST-elevation MI; PCI, percutaneous coronary intervention.

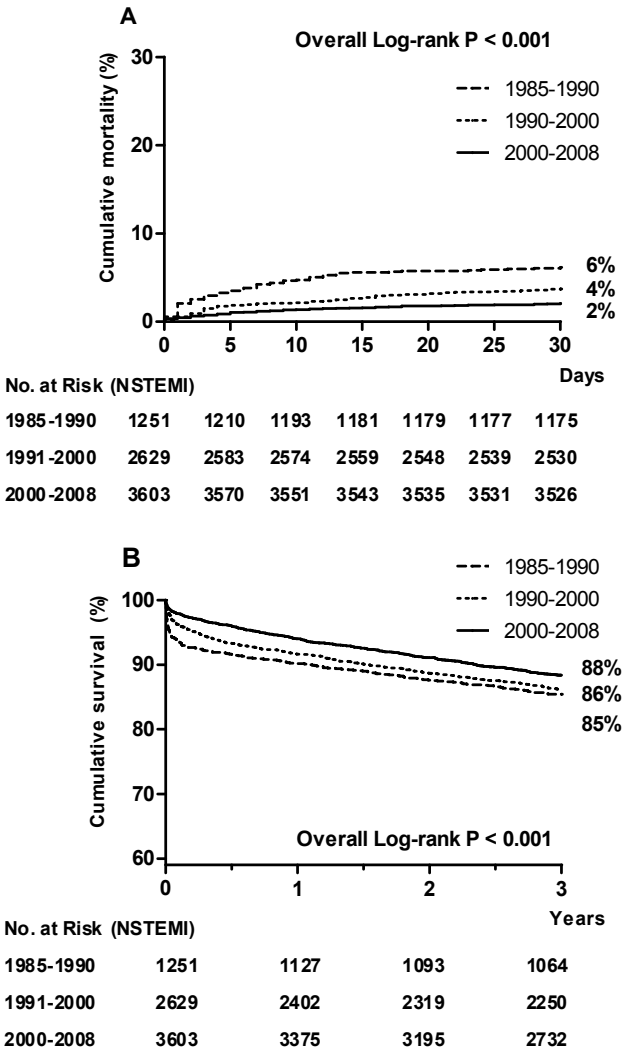

Figure 4: Kaplan-Meier curves for 30-day cumulative mortality or (Figure 4A) or three-year cumulative survival (Figure 4B) according to calendar period of admission

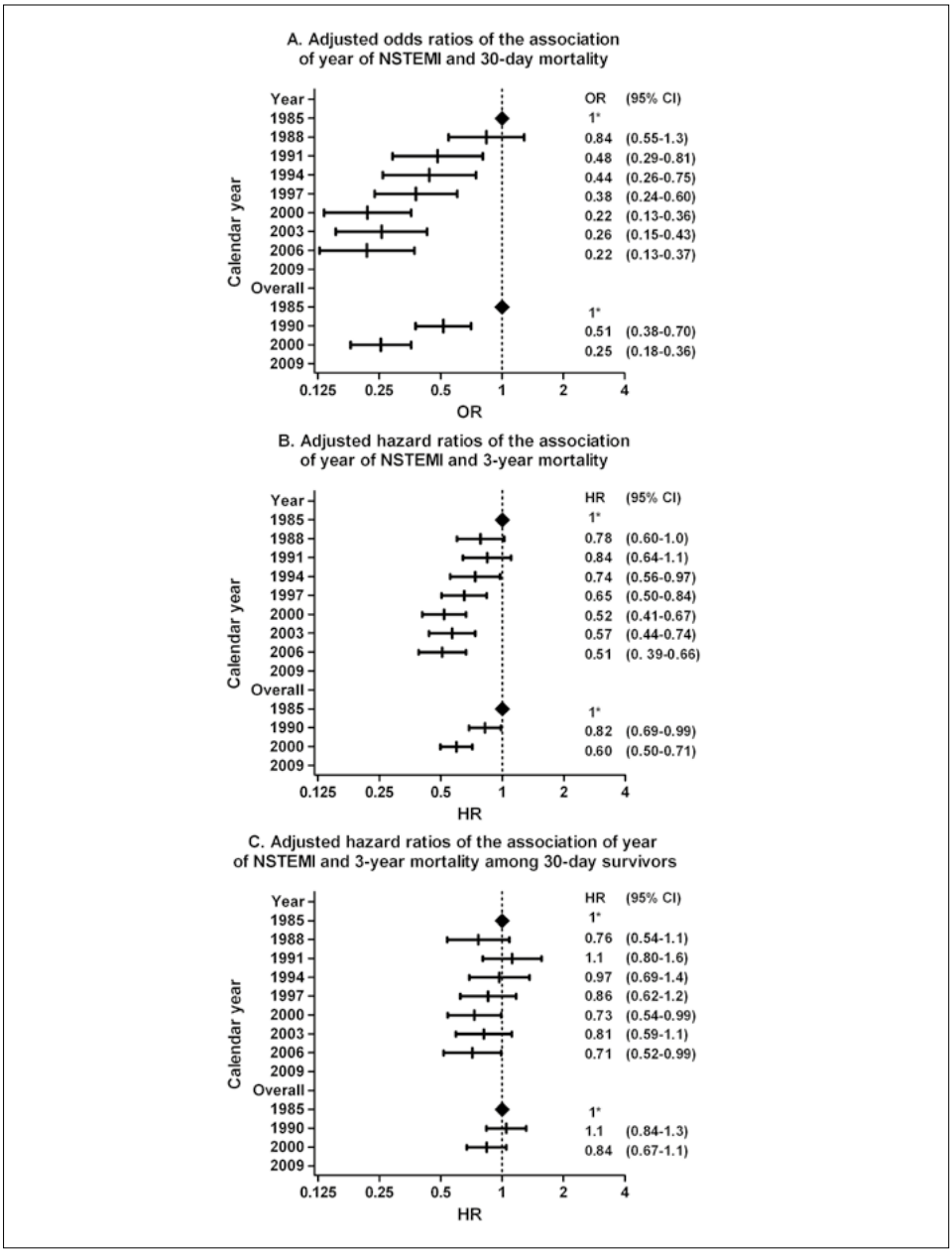

Figure 5: Adjusted odds or hazard ratios of secular trends in mortality after NSTEMI at 30- days (Figure 5A), at 3-year (Figure 5B), and at 3-year among 30-day survivors (Figure 5C).
The upper part of the figures compares changes in mortality in time periods of three year, the lower part among patients hospitalised between 1985-1990; 1990-2000; and 2000-2008

* Reference category for the subsequent ratios CI, confidence interval; NSTEMI, non-ST-elevation myocardial infarction; HR, Hazard ratio; OR, Odds ratio

Discussion

We have shown that, during a period of almost 25 years, overall 30 day mortality in patients hospitalised for MI was reduced with 80%. In patients admitted for ST-segment elevation MI (STEMI), 30-day mortality declined from 17% to 6%. In patients with a smaller, non ST-segment elevation MI (NSTEMI) 30-day mortality declined from 6% to 2%. In addition, we demonstrated that this early survival benefit was maintained over three years of follow-up, with long term survival increasing from 73% to 87% and from 85% to 88% in STEMI and NSTEMI, respectively. The reduction in long- term all-cause mortality is illustrative of the strength of the improvement of the combined treatment effects.

There can be little doubt that such improvements have resulted from changes in medical therapy, both pharmacological as well as interventional.[20] The most important factors must have been the introduction of reperfusion therapy in the form of fibrinolytic therapy and later primary PCI for STEMI,[1,8] as well as the more frequent use of revascularization in selected patients with NSTEMI. Also, the introduction and subsequent employment of medical therapies including statins, and ACE inhibitors or angiotensin receptor blockers must have played a role. Of course, patient characteristics also gradually changed during the observation period. However, most of the observed alterations in our patient's phenotypes, like increasing age and more co-morbidity such as diabetes and renal dysfunction, have previously been associated with impaired outcomes and do not account for the observed outcome improvement. A reduction in case fatality in spite of treating older patients with co-morbidity has also been observed in other observational studies.[20,21,22] Earlier clinical presentation could have contributed to improved prognosis, but we found no evidence for this.

Better primary prevention could have influenced the severity of the acute clinical event, and better secondary prevention must also have contributed significantly. Exact details of the medication use of our patients after discharge are not known, but registries in our region in 1995, 2001 and 2006 indicated that the use of preventive medication significantly intensified during that time.[14] For instance, statins were used by 36%, 72% and 93% of the patients respectively, with a subsequent drop in

mean cholesterol level from 6.2 mmol/l in 1995 to 4.2 mmol/l in 2006. Aspirin was used by >90% of the patients from 1995 onwards, and smoking trends decreased from 32% to 15% between 1995 and 2006.[14]

With time, the number of patients admitted with myocardial infarction increased. This was mainly the result of changes in referrals: when primary PCI became the treatment of choice in STEMI patients, they were specifically referred to our center from 2000 onwards. Our STEMI patients can therefore be considered to be representative for this syndrome and we thus believe that the decrease in mortality in this group is broadly illustrative of current clinical practice. The number of NSTEMI patients also increased. Most likely, this was also due to changes in referrals, in particular of high risk patients in whom invasive therapy was warranted. Therefore, our population with this type of acute coronary syndrome will probably be less representative for that group at large. Still, given their already low mortality, the further decline in 30-day mortality in this group with time was also impressive.

Other studies, such as The National Registry of Myocardial Infarction, Worcester Heart Attack Study and Minnesota Heart Survey,[19,20,23,24,25,26,27,28] have described prognostic time trends after acute MI, but none of these covered both i) secular trends for a period longer than 10 years from 1990 and ii) follow-up data after the first 30-days; as the present study does.

Although the present study thus has unique strengths, some of its limitations must be emphasized. First, the present data are derived from a single center. Although this will have enhanced the quality of the data and the observed secular trends, this could result in a lower external validity. However, this is unlikely, since a nation wide study in Sweden and a state wide study in the US reported quite comparable results.[21,29] Second, based on our data, it is not possible to establish changes in MI incidence as other studies have shown. Still, the increasing age of our population provides indirect evidence of a lower incidence rate of myocardial infarction. Lastly, the current report is based on hospitalised patients, and we are therefore unable to assess the changes in mortality of all patients who suffered a myocardial infarction but died before clinical presentation.

Conclusions

Our results indicate very substantial improvements in acute and long term survival in patients hospitalised for MI, related to improved acute- as well as long-term treatment. Since the early survival benefit is maintained over time, the present results emphasize that efforts to further reduce in-hospital mortality must be rigorously pursued, and that early medical evaluation in suspected MI and intensive early hospital treatment remain warranted. Although one might envisage even lower hospital mortality rates associated with acute MI in the future, absolute treatment benefits will become smaller because of the current low mortality levels. Indirectly therefore, our data emphasize the need for better and more effective primary prevention, as well as the necessity to target high risk MI subgroups such as the elderly and those with heart failure.

References

1. Simoons ML, Serruys PW, vd Brand M, Bar F, de Zwaan C, Res J, Verheugt FW, Krauss XH, Remme WJ, Vermeer F, Lubsen J. Improved survival after early thrombolysis in acute myocardial infarction. A randomised trial by the Interuniversity Cardiology Institute in The Netherlands. Lancet 1985;2(8455):578-82.

2. Grijseels EW, Deckers JW, Hoes AW, Boersma E, Hartman JA, van der Does E, Simoons ML. Implementation of a pre-hospital decision rule in general practice. Triage of patients with suspected myocardial infarction. Eur Heart J 1996;17(1):89-95.

3. Grijseels EW, Deckers JW, Hoes AW, Hartman JA, Van der Does E, Van Loenen E, Simoons ML. Pre-hospital triage of patients with suspected myocardial infarction. Evaluation of previously developed algorithms and new proposals. Eur Heart J 1995;16(3):325-32.

4. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. N Engl J Med 1993;329(10):673-82.

5. Reiner JS, Lundergan CF, Fung A, Coyne K, Cho S, Israel N, Kazmierski J, Pilcher G, Smith J, Rohrbeck S, Thompson M, Van de Werf F, Ross AM. Evolution of early TIMI 2 flow after thrombolysis for acute myocardial infarction. GUSTO-1 Angiographic Investigators. Circulation 1996;94(10):2441-6.

6. Simoons ML, Maggioni AP, Knatterud G, Leimberger JD, de Jaegere P, van Domburg R, Boersma E, Franzosi MG, Califf R, Schroder R, Knatterud G, Braunwald E. Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. Lancet 1993;342(8886-8887):1523-8.

7. Grines CL, Cox DA, Stone GW, Garcia E, Mattos LA, Giambartolomei A, Brodie BR, Madonna O, Eijgelshoven M, Lansky AJ, O'Neill WW, Morice MC. 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(26):1949-56.

8. Zijlstra F, Hoorntje JC, de Boer MJ, Reiffers S, Miedema K, Ottervanger JP, van 't Hof AW, Suryapranata H. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1999;341(19):1413-9.

9. Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E, Wallentin L. 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. Lancet 2006;368(9540):998-1004.

10. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 2000;284(7):835-42.

11. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, Akkerhuis KM, Harrington RA, Deckers JW, Armstrong PW, Lincoff AM, Califf RM, Topol EJ, Simoons ML. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. Circulation 2000;101(22):2557-67.

12. Hirsch A, Windhausen F, Tijssen JG, Verheugt FW, Cornel JH, de Winter RJ. Long-term outcome after an early invasive versus selective invasive treatment strategy in patients with non-ST-elevation acute coronary syndrome and elevated cardiac troponin T (the ICTUS trial): a follow-up study. Lancet 2007;369(9564):827-35.

13. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344(8934):1383-9.

14. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyorala K, Keil U. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. Lancet 2009;373(9667):929-40.

15. 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.

16. Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, Westendorp RG, de Craen AJ, Knopp RH, Nakamura H, Ridker P, van Domburg R, Deckers JW. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ 2009;338:b2376.

17. Cleland JG, Erhardt L, Murray G, Hall AS, Ball SG. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure. A report from the AIRE Study Investigators. Eur Heart J 1997;18(1):41-51.

18. Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, Filippatos G, Fox K, Huber K, Kastrati A, Rosengren A, Steg PG, Tubaro M, Verheugt F, Weidinger F, Weis M. 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):2909-45.

19. Fox KA, Steg PG, Eagle KA, Goodman SG, Anderson FA, Jr., Granger CB, Flather MD, Budaj A, Quill A, Gore JM. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. JAMA 2007;297(17):1892-900.

20. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med 2010;362(23):2155-65.

21. Kostis WJ, Deng Y, Pantazopoulos JS, Moreyra AE, Kostis JB. Trends in mortality of acute myocardial infarction after discharge from the hospital. Circ Cardiovasc Qual Outcomes 2010;3(6):581-9.

22. Chew DP, Anderson FA, Avezum A, Eagle KA, FitzGerald G, Gore JM, Dedrick R, Brieger D. Six-month survival benefits associated with clinical guideline recommendations in acute coronary syndromes. Heart 2010;96(15):1201-6.

23. Arciero TJ, Jacobsen SJ, Reeder GS, Frye RL, Weston SA, Killian JM, Roger Vr VL. Temporal trends in the incidence of coronary disease. Am J Med 2004;117(4):228-33.

24. McGovern PG, Jacobs DR, Jr., Shahar E, Arnett DK, Folsom AR, Blackburn H, Luepker RV. Trends in acute coronary heart disease mortality, morbidity, and medical care from 1985 through 1997: the Minnesota heart survey. Circulation 2001;104(1):19-24.

25. Masoudi FA, Foody JM, Havranek EP, Wang Y, Radford MJ, Allman RM, Gold J, Wiblin RT, Krumholz HM. Trends in acute myocardial infarction in 4 US states between 1992 and 2001: clinical characteristics, quality of care, and outcomes. Circulation 2006;114(25):2806-14.

26. Floyd KC, Yarzebski J, Spencer FA, Lessard D, Dalen JE, Alpert JS, Gore JM, Goldberg RJ. A 30-year perspective (1975-2005) into the changing landscape of patients hospitalized with initial acute myocardial infarction: Worcester Heart Attack Study. Circ Cardiovasc Qual Outcomes 2009;2(2):88-95.

27. McManus DD, Gore J, Yarzebski J, Spencer F, Lessard D, Goldberg RJ. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. Am J Med 2011;124(1):40-7.

28. Rogers WJ, Frederick PD, Stoehr E, Canto JG, Ornato JP, Gibson CM, Pollack CV, Jr., Gore JM, Chandra-Strobos N, Peterson ED, French WJ. Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. Am Heart J 2008;156(6):1026-34.

29. Jernberg T, Johanson P, Held C, Svennblad B, Lindback J, Wallentin L. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. JAMA 2011;305(16):1677-84.

Chapter 4

Decline in 20-year mortality after myocardial infarction in patients with chronic kidney disease: evolution from the prethrombolysis to the percutaneous coronary intervention era

Sjoerd T Nauta
Ron T van Domburg
Rutger-Jan Nuis
Martijn Akkerhuis
Jaap W Deckers

Kidney Int. 2013 Aug;84(2):353-8

Abstract

Cardiovascular disease is the main cause of death in patients with renal impairment. We examined temporal trends in treatment and mortality after myocardial infarction (MI) depending on renal function at presentation. Therefore, we studied 12 087 patients admitted for MI to a coronary care unit from 1985 to 2008. In line with the Kidney Foundation practice guidelines patients were categorized into normal renal function (eGFR >90 ml/min per 1.73 m^2) stage 2 (60-89), stage 3 (30-59), and stage 4-5 (<30) chronic kidney disease (CKD). A total of 8632 (71%) of the 12 087 patients had stage 2-5 CKD. Use of evidence-based care increased over time in all groups according to renal function. Mortality rates fell over the period. Adjusted 30-day mortality fell (adjusted odds (2000-2008 vs. 1985-1990) 0.33 (95% CI 0.18-0.60) in patients with stage 4-5 CKD, and 0.21 (95% CI 0.10-0.42) in those without renal impairment). This mortality decrease sustained during long-term follow-up. There was no significant interaction between renal function and decade of admission. Overall, median survival was >20, 15, 8 and 1.8 years for patients with normal renal function, stage 2, stage 3 and stage 4-5 CKD, respectively. In conclusion, during the past 25 years, treatment of patients with an MI improved substantially with a concomitant decline in mortality that was similar for all stages of renal function, however, prognosis remains poor after stage 4-5 CKD.

Introduction

Cardiovascular disease is the single largest cause of death in patients with renal impairment or progressive primary renal disease, and these cardiovascular deaths often occur before end stage renal failure has been reached.[1] Studies of myocardial infarction (MI) have reported that MI patients with renal dysfunction have a worse in-hospital survival.[1-5] Furthermore, recent data suggests that such patients are less likely to receive evidence-based therapies, although increased usage of evidence-based medical treatment has significant potential to reduce mortality in MI patients with renal dysfunction.[6-7]

Within the past 25 years, major improvements in the treatment of MI have been implemented, including thrombolytic therapy and primary percutaneous coronary intervention (PCI) for ST-elevation MI (STEMI), as well as more intensive management according to individual risk assessment in patients with a non-STEMI (NSTEMI).[8] A longitudinal analysis of MI patients with different stages of renal dysfunction will identify temporal changes in the use of treatment modalities, as well as temporal trends in early and late outcomes according to renal function.

Against this background, the aims of our study were threefold. First, to determine inequalities and changes in medical care in patients with MI with different levels of renal dysfunction over a 24-year period. Second, to compare temporal trends in mortality according to renal function for patients admitted with an MI. And third, to quantify the effect of different stages of renal impairment on short- and long-term mortality after MI.

Results

Patient characteristics

A total of 12 087 patients were included, of whom, 5 598 (46%), 2 504 (21%) and 530 (4%) had stage 2, stage 3 and stage 4-5 chronic kidney disease (CKD), respectively (Table 1). A total of 92 712 person-years were analyzed. The number of patients and total number of events after MI according to decade of hospitalization and renal function is shown in Table 2.

Table 1: Baseline characteristics and clinical presentation of patients hospitalized for myocardial infarction according to renal function at hospitalization.

	Renal function (eGFR) on admission				P for trend
	Normal (>90 ml/ min per 1.73 m²)	Stage 2 CKD (60 to 90)	Stage 3 CKD (30 to 60)	Stage 4-5 CKDa (<30)	
No. of patients	3455 (29%)	5598 (46%)	2504 (21%)	530 (4%)	
Baseline					
Age (±SD)	53±10	63±11	69±10	68±11	<0.001
Gender (female)	19%	27%	40%	37%	<0.001
Cardiac history					
Previous MI	30%	34%	39%	40%	<0.001
Previous PCI	15%	15%	12%	12%	<0.01
Previous CABG	7%	10%	13%	12%	<0.001
Risk factors					
Hypertension	31%	35%	41%	56%	<0.001
Diabetes	13%	13%	17%	24%	<0.001
Hyperlipidemia	29%	28%	22%	22%	<0.001
Family history	32%	27%	19%	14%	<0.001
Current smoker	47%	30%	20%	16%	<0.001
Anemia	19%	21%	34%	69%	<0.001
eGFR (median, IQR)	102 (94-114)	76 (69-83)	52 (45-57)	21 (12-27)	<0.001
Diagnosis					
STEMI	53%	43%	44%	49%	<0.001
Medication at ICCU discharge					
Ca-antagonist	19%	26%	30%	32%	<0.001
Diuretics	8%	12%	27%	30%	<0.001
Nitrates	10%	15%	20%	25%	<0.001
Antiarrhythmics	3%	4%	7%	8%	<0.001

CABG, coronary artery bypass surgery; ICCU, intensive coronary care unit; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2: Study population outline: the number of patients at risk and total number of events after myocardial infarction stratified by decade of hospitalization and renal function.

	Decade of hospitalization for myocardial infarction		
	1985-1990	1990-2000	2000-2008
	Total no. events/ No. at risk		
Renal (dys)function			
Normal (>90)	172/343	372/1183	179/1929
Stage 2 CKD (60 to 90)	667/1073	953/1824	452/2701
Stage 3 CKD (30 to 60)	520/607	697/900	370/997
Stage 4-5 CKD (<30)	99/105	191/209	139/216

Renal (dys)function in ml/min per 1.73 m^2.

With increasing renal impairment, patients were older, more often female; more often had a history of MI or coronary artery bypass surgery (CABG), hypertension, diabetes and anemia. In contrast, with increasing renal impairment patients were less often current smokers, less often had hypercholesterolemia, or a family history of previous MI (Table 1). With time, more patients presented with normal renal function and less with moderate to severe renal dysfunction (Figure 1).

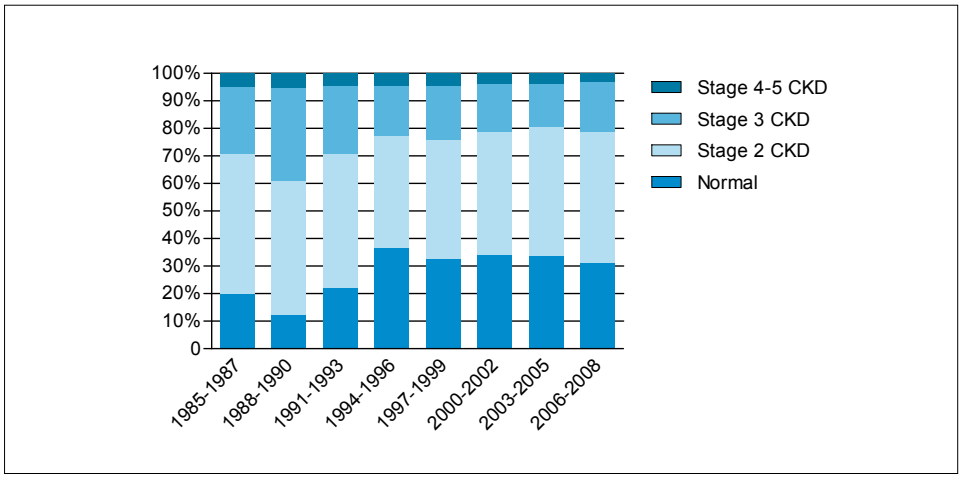

Figure 1: Distribution of study population according to renal function and study period.

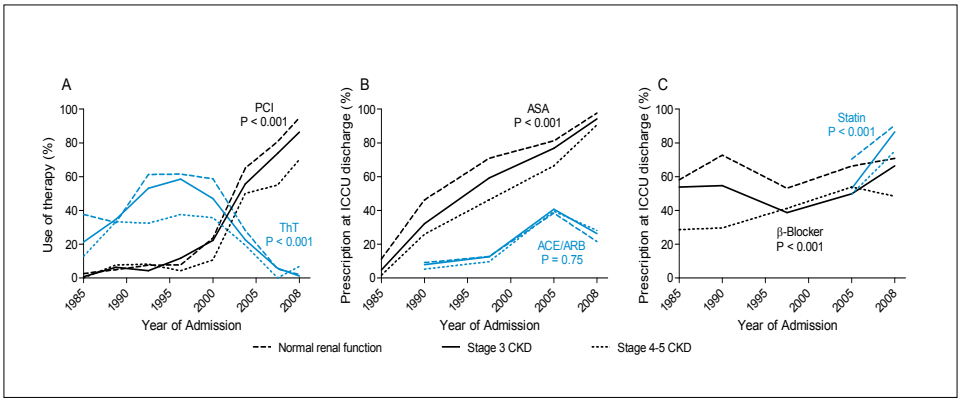

Figure 2: Treatment of patients over time: use of reperfusion therapy in ST-segment elevation myocardial infarction (A) and use of evidence-based medical care in myocardial infarction patients (B and C). ACE denotes angiotensin-converting enzyme inhibitor; ASA, aspirin; ARB, angiotensin receptor blocker; PCI, percutaneous coronary intervention; ThT, thrombolytic therapy. Cochran statistic with correction for calendar period was used to calculate P values between normal and severe renal impairment.

Table 3: Temporal trends of 30-day and 5-year mortality for all patients and for subgroups according to renal function at hospitalization for myocardial infarction.

	All patients	Normal (>90 ml/ min per 1.73 m^2)	Stage 2 CKD (60 to 90)	Stage 3 CKD (30 to 60)	Stage 4-5 CKD (<30)
Calendar period					
			Adjusted odds ratios for 30-day mortality		
1985-90	Reference	Reference	Reference	Reference	Reference
1990-2000	0.75 (0.62-0.91)	0.38 (0.19-0.75)	0.61 (0.44-0.84)	1.0 (0.75-1.4)	0.60 (0.35-1.1)
2000-08	0.40 (0.32-0.49)	0.21 (0.10-0.42)	0.33 (0.24-0.47)	0.54 (0.38-0.76)	0.33 (0.18-0.60)
			Adjusted hazard for mortality during 5 year among 30-day survivors		
1985-90	Reference	Reference	Reference	Reference	Reference
1990-2000	1.2 (1.1-1.4)	1.1 (0.70-1.7)	1.2 (0.97-1.5)	1.2 (0.97-1.5)	1.23 (0.83-1.8)
2000-08	0.90 (0.78-1.0)	0.85 (0.55-1.31)	0.80 (0.63-1.0)	0.96 (0.76-1.23)	0.90 (0.60-1.4)

Adjusted for age, gender, previous MI, previous CABG, hypertension, diabetes, hyperlipidemia, family history, smoking status, renal dysfunction, anemia and diagnosis.
P interaction = 0.15 and = 0.68, at 30 days and 5 years, respectively.

Medical and invasive treatment during the study period

The use of reperfusion therapy (either by thrombolytic therapy or primary PCI) increased over time in all four groups according to renal function with STEMI (p<0.001). However, patients with severe renal impairment in particular were less likely to receive reperfusion therapy during the entire study period as compared to patients with normal renal function (p<0.001) (Figure 2 A). In addition, prescription of evidence-based medical care (class 1A), including aspirin, ß-blockers, and statins increased over time, but was less frequent in patients with severe renal impairment (p<0.001 for all) (Figure 2 B and C). Prescription of other medical therapy with a lower level of evidence for the treatment of MI, including calcium-antagonists, nitrates and diuretics at Intensive Coronary Care Unit (ICCU) discharge was higher in patients with renal impairment (Table 1).

Temporal trends in mortality

In the overall study population, Kaplan-Meier short-term (30-day) mortality decreased from 10% in 1985-90 to 4% in 2000-08. The magnitude of this decrease was comparable for the merged group of patients with stage 2-5 CKD (estimated Glomerular Filtration Rate (eGFR) < 90 ml/min per m^2): their 30-day mortality decreased from 11% in 1985-90 to 6% in 2000-08. Similarly, for the study population as a whole, 5-year Kaplan-Meier mortality decreased from 24% in 1985-90 to 19% in 2000-08; for patients with stage 2-5 CKD a reduction in 5-year mortality was observed from 26% in 1985-90 to 24% in 2000-08.

From 1985 to 2008, the adjusted risk of 30-day mortality decreased by about 60% in the whole study population (adjusted OR 0.40, 95%CI: 0.32-0.49). Although there was no statistical heterogeneity in this temporal mortality decrease among all four subgroups according to renal function (p = 0.15), 30-day mortality appeared to decrease less over time in patients with stage 2-5 CKD (Table 3).

The improvement of short-term mortality was sustained during long-term follow-up. Among 30-day survivors, the long-term mortality hazard was 10% lower in 2000-2008 compared to 1985-1990 (adjusted hazard ratio, HR 0.90, 95%CI: 0.78-1.0). Again, there was no statistical heterogeneity in this temporal mortality decrease among all four subgroups according to renal function (p = 0.68) (Table 3).

Renal function and Mortality

Unadjusted mortality at 30 days after MI was much higher in patients with renal impairment (25% in patients with severe renal impairment vs. 2% in those with normal renal function, p<0.001). This was also true during long-term follow-up (92% at 15 year in patients with severe renal impairment vs. 47% at 20 year in those with normal renal function, p<0.001) (Figure 3). Median survival in patients with stage 2, stage 3 and stage 4-5 was 15 years, 8 years and 22 months (1.8 years) respectively, compared to >20 years in patients with normal renal function. Adjusted mortality for stage 2, stage 3 and stage 4-5 CKD was 2.1, 4.3, and 8.6 fold higher at 30 days, while the long-term hazard was 1.0, 1.5, and 3.4, fold higher, respectively, compared to patients with normal renal function (Table 4).

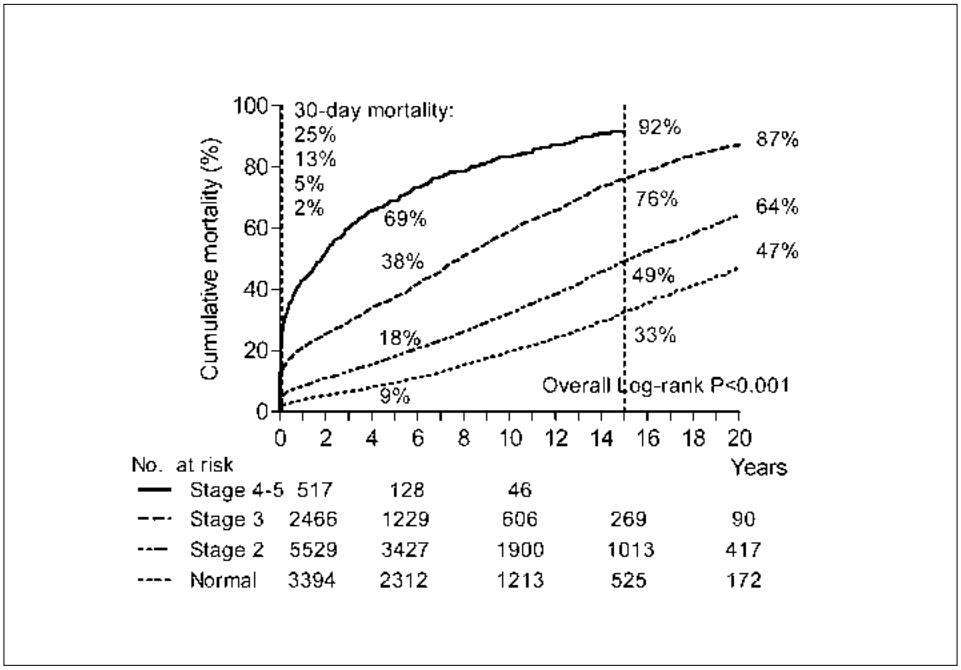

Figure 3: Kaplan-Meier curves of mortality according to renal function.

In a secondary analysis, unadjusted mortality at 30 days was comparable between patients with stage 4 CKD (eGFR 15-30, n = 332) and stage 5 CKD (eGFR<15, n = 198) (26% vs. 22%, respectively, p = 0.28), but, compared to stage 4 CKD, unadjusted 5-year mortality was higher in patients with stage 5 CKD (63% vs. 79%, respectively; p < 0.01). Compared to normal renal function, adjusted 30-day mortality was 8.5 (95%CI: 5.7-13) and 8.8-fold (5.5-14) higher in patients with stage 4 and stage 5 CKD, respectively. The adjusted hazard for mortality between 30 days and 5 year was 3.3 (2.6-4.2) and 8.0-fold (6.3-10) higher in patients with stage 4 and stage 5 CKD, respectively, compared to normal renal function.

Table 4: Unadjusted and adjusted odds and hazard ratios of mortality depending on renal function at hospitalization for myocardial infarction.

	Odds ratios for 30-day mortality	
	Unadjusted	**Adjusted***
Renal (dys)function		
Normal (>90 ml/min per m^2)	Reference	Reference
Stage 2 CKD (60 to 90)	2.8 (2.1-3.7)	2.1 (1.5-2.8)
Stage 3 CKD (30 to 60)	8.0 (6.1-10)	4.3 (3.2-5.9)
Stage 4-5 CKD (<30)	17 (13-24)	8.6 (6.0-12)
Hazard for mortality during 20 year among 30-day survivors		
Normal	Reference	Reference
Stage 2	1.7 (1.5-1.8)	1.0 (0.91-1.1)
Stage 3	3.6 (3.2-3.9)	1.5 (1.3-1.6)
Stage 4-5	8.3 (7.2-9.5)	3.4 (2.9-4.0)

* Adjusted for the same variables as Table 2 and decade of hospitalization.

Discussion

This analysis of MI patients showed changes in treatment and outcome depending on renal function over 24 years of observation. During the past decades, treatment of MI improved in all groups of renal function, but patients with stage 4-5 renal dysfunction were less likely to receive evidence-based medical treatment and reperfusion therapy. Temporal trends in 30-day mortality reveal impressive mortality reductions during this 24-year period that were comparable for all stages of renal function and were sustained during long-term follow-up. Although the outcome after MI improved across the whole range of renal function, we showed that renal dysfunction remains a strong risk factor for increased both short- and long-term mortality.

Treatment of patients with MI and renal dysfunction is a challenge. As in the present study, previous studies[2-6, 9-10] showed that patients with increasing renal dysfunction and MI are less likely to receive cardio-protective therapies, including invasive treatment or reperfusion therapy. Some studies have reported that patients with stage 3-4 CKD and impeding dialysis, are less likely to receive percutaneous coronary interventions compared to patients already on dialysis.[6, 11] This suggests that fear for contrast-induced nephropathy influences treatment decisions. However, we as well as others[3-5,12-13] observed a proportional decrease in the use of percutaneous coronary interventions and other cardio-protective therapies with decreasing renal function. Other reasons for withholding treatment modalities might include medical uncertainty as most randomized controlled trials of MI have excluded subjects with renal dysfunction.[14] In addition, renal dysfunction is associated with anemia and an increased risk of bleeding .[2,15] Furthermore, patients with renal dysfunction more often have a delayed or an atypical presentation.[16] All these factors could affect treatment decisions, lead to reduced use of evidence-based reperfusion therapy and, ultimately, result in impaired outcome. The treatment discrepancies provide a window of opportunity to improve care in MI patients with renal impairment.[17-21] It is therefore encouraging to observe a persistent temporal increase in the use of such therapies among all groups according to renal function during our 24-year study period, and this provides evidence that improved clinical care in these patients is indeed possible.

No previous study compared temporal improvement in outcome according to different stages of renal function for almost a quarter of a century. We observed comparable temporal reductions in adjusted 30-day and long-term mortality across all stages of renal function. There can be little doubt that such improvements have resulted from changes in medical therapy, both pharmacological as well as interventional.[4, 17-21] The most important factors must have been the introduction of reperfusion therapy in the form of fibrinolytic therapy and later primary PCI for STEMI, as well as the more frequent use of revascularization in selected patients with NSTEMI.[8] Also, the introduction and subsequent employment of medical therapies including aspirin, statins, and ACE inhibitors or angiotensin receptor blockers must have played a role. In our study, there was no statistically significant heterogeneity for temporal trends according to renal function. The observation that the mortality reduction in the contemporary era was least prominent in patients with moderate renal impairment was probably due to chance. Our results are encouraging and the application of evidence-based MI therapies to appropriate patients regardless of renal function may even further improve these outcomes in the future.

Short-term mortality after MI deteriorated with every decline in renal function, including the decline from normal to mild renal (dys-)function (i.e. to stage 2 CKD). Patients with stage 4-5 CKD had a more than eight fold increased mortality rate compared to normal renal function after adjustment for baseline characteristics. These findings are consistent with previous studies.[3, 6, 22] Our data is unique in that it comprises survival data for up to 20 years after MI which is a whole life course for patients with stage 4-5 CKD. On the long-term, renal dysfunction remained associated with increased mortality.

Limitations

There are some limitations to the present study. First, because the data is derived from a hospital-based registry, patients who died before admission to the hospital were by definition excluded from the registry. This might be in particular NSTEMI patients with advanced renal disease because in those patients the diagnosis of NSTEMI may be problematic due to the absence of “typical” symptoms and uninterpretable ECGs.[16] Therefore, the detrimental effect of stage 4-5 CKD on short-term mortality could have been underestimated. However, this has unlikely affected our temporal

trend analyses because these diagnostic issues were present during all past decades studied. Second, the assessment of creatinine at admission for MI might have resulted in unfavorable renal function estimates due to the effect of the acute event –including acute kidney injury– on the creatinine concentration. However, this is unlikely, since hemodynamic instability leading to renal dysfunction typically occurs later during the course of MI. Also, renal function was estimated using creatinine-based GFR equations, and these estimates might not perfectly correlate with actual renal function.23 Still, this should not affect the validity of our results since these estimates are central for clinical assessment of kidney function. Third, the present data are derived from a single center. Although this could result in a lower external validity, we think that this is unlikely because the observed association between renal impairment and 30-day mortality corresponds well with that in previous reports. The relatively high proportion of patients with STEMI reflects the function of our center as referral center for these patients. Fourth, information on left ventricular ejection fraction or Killip class is unavailable for analyses.

Conclusion

Renal function is an important and independent predictor for both short- and long-term mortality after acute MI. Even though patients with stage 4-5 CKD remained less likely to receive evidence-based medical care and reperfusion therapy, temporal reductions in 30-day and long-term mortality during the past decades were substantial and were independent of renal function. Thus, patients with renal impairment also benefitted from improved outcomes over the past decades. This encouraging observation should stimulate the use of evidence based treatment in MI patients regardless of renal dysfunction.

Methods

We considered all 14 434 consecutive patients aged >18 years admitted with STEMI or NSTEMI to the ICCU of the Thoraxcenter, Erasmus University Medical Center between June 1985 and December 2008. Of these 12 087 patients (84%) had at least one baseline creatinine value, and these patients thus constitute the study population.

The diagnosis of MI was made by the attending physician in the presence of the following characteristics: chest pain or equivalent symptoms in combination with dynamic ECG changes consistent with MI and a serial rise (to at least three times the upper normal value) and fall in serum biochemical markers of cardiac necrosis such as creatine kinase-MB and troponin-T (as of 2002). Patients were diagnosed as STEMI in the presence of ST-segment elevation > 0.1 mV in at least two peripheral leads, > 0.2 mV in at least two precordial leads or new left bundle branch block, and as NSTEMI otherwise. The proportion of patients with STEMI or NSTEMI was about 50% in each decade of study. For patients admitted more than once, only the first hospitalization was taken into account.

In line with the US National Kidney Foundation practice guidelines,[24] patients were categorized as having normal renal function (eGFR > 90 ml/min per 1.73 m^2 body surface area), stage 2 (60-89), stage 3 (30-59), and stage 4-5 (<30) CKD. In a secondary analysis, patients with severe renal impairment were recategorized into those with stage 4 (eGFR 15-30) and stage 5 (eGFR < 15) CKD.

Serum creatinine was assessed by a nonkinetic alkaline picrate (Jaffe) method.[25] GFR was estimated with the CKD-EPI equation[23]: eGFR (ml/min per 1.73 m^2 body surface area) = 141 x min(creatinine/κ, 1) α x max(creatinine /κ, 1)$^{-1.209}$ x 0.993^{age} x 1.018 (if female) x 1.159 (if black), where κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of creatinine/κ or 1, and max indicates the maximum of creatinine/κ or 1. All analyses were also performed using the Modification of Diet in Renal Disease (MDRD) equation,[26] this did not result in significantly different results (not shown).

Trained physicians and nurses accustomed to the use of standardized case report forms collected the data, using definitions that have previously been described.[27] The study endpoint was all-cause mortality at 30 days and at 20 years. Survival status was assessed through municipal Civil Registries in 2010 and was available for 99% of all patients.

This project was carried out in accordance with current rules of ethics and legislature. No additional actions involving the study participants were undertaken because of this registry. Register-based studies are approved by the ethical committee of the Erasmus Medical Center.

Statistical Analysis

Categorical variables were summarized as percentages and the chi-square test for trend was used to calculate p-values. Age was normally distributed according to the Kolmogorov-Smirnov test and therefore summarized as mean and 95% confidence interval. The analysis of variance test (ANOVA) was used to calculate a p-value for age differences. Renal function values were presented as medians and interquartile range and compared with the Kruskal-Wallis test.

Patients were stratified in three groups according to decade of hospitalization: 1985-1990; 1990-2000; 2000-2008. We assessed temporal trends in outcome by comparing these three periods. We examined the independent association between decade of hospitalization and mortality, for each stage of renal function, using logistic regression for 30-day outcome and the Cox proportional hazards model for long-term outcome (among 30-day survivors). Adjustment was performed for age, gender, previous MI, previous CABG, hypertension, diabetes, hyperlipidemia, family history, smoking status, anemia and STEMI/NSTEMI diagnosis. Information on anemia was missing in 324 of the patients (2.7%). The influence of decade on mortality was examined with a formal interaction test by adding decade crossed with renal function to the model. In addition, we examined the independent association between renal function and mortality using the analyses described above.

Results are reported as odds ratios (OR) –for 30-day mortality– and hazard ratios (HR) –for long-term mortality– and their respective 95% confidence intervals. All statistical tests were 2-tailed, and p-values were considered significant at <0.05. Analysis was performed using SPSS software version 20.0 (SPSS, Chicago, Ill).

Disclosure

All the authors declared no competing interests.

References

1. Johnston N, Dargie H, Jardine A. Diagnosis and treatment of coronary artery disease in patients with chronic kidney disease: Ischaemic heart disease. Heart 2008;94(8):1080-8.

2. Medi C, Montalescot G, Budaj A, Fox KA, Lopez-Sendon J, FitzGerald G, Brieger DB. Reperfusion in patients with renal dysfunction after presentation with ST-segment elevation or left bundle branch block: GRACE (Global Registry of Acute Coronary Events). JACC Cardiovasc Interv 2009;2(1):26-33.

3. Szummer K, Lundman P, Jacobson SH, Schon S, Lindback J, Stenestrand U, Wallentin L, Jernberg T. Relation between renal function, presentation, use of therapies and in-hospital complications in acute coronary syndrome: data from the SWEDEHEART register. J Intern Med 2010;268(1):40-9.

4. Wong JA, Goodman SG, Yan RT, Wald R, Bagnall AJ, Welsh RC, Wong GC, Kornder J, Eagle KA, Steg PG, Yan AT. Temporal management patterns and outcomes of non-ST elevation acute coronary syndromes in patients with kidney dysfunction. Eur Heart J 2009;30(5):549-57.

5. Szummer K, Lundman P, Jacobson SH, Schon S, Lindback J, Stenestrand U, Wallentin L, Jernberg T. Influence of renal function on the effects of early revascularization in non-ST-elevation myocardial infarction: data from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). Circulation 2009;120(10):851-8.

6. Fox CS, Muntner P, Chen AY, Alexander KP, Roe MT, Cannon CP, Saucedo JF, Kontos MC, Wiviott SD. Use of evidence-based therapies in short-term outcomes of ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction in patients with chronic kidney disease: a report from the National Cardiovascular Data Acute Coronary Treatment and Intervention Outcomes Network registry. Circulation 2010;121(3):357-65.

7. Hanna EB, Chen AY, Roe MT, Wiviott SD, Fox CS, Saucedo JF. Characteristics and in-hospital outcomes of patients with non-ST-segment elevation myocardial infarction and chronic kidney disease undergoing percutaneous coronary intervention. JACC Cardiovasc Interv 2011;4(9):1002-8.

8. Nauta ST, Deckers JW, Akkerhuis M, Lenzen M, Simoons ML, van Domburg RT. Changes in clinical profile, treatment, and mortality in patients hospitalised for acute myocardial infarction between 1985 and 2008. PLoS One 2011;6(11):e26917.

9. Berger AK, Duval S, Krumholz HM. Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction. J Am Coll Cardiol 2003;42(2):201-8.

10. Szummer K, Lundman P, Jacobson SH, Schon S, Lindback J, Stenestrand U, Wallentin L, Jernberg T. Association between statin treatment and outcome in relation to renal function in survivors of myocardial infarction. Kidney Int 2011;79(9):997-1004.

11. Shroff GR, Frederick PD, Herzog CA. Renal failure and acute myocardial infarction: clinical characteristics in patients with advanced chronic kidney disease, on dialysis, and without chronic kidney disease. A collaborative project of the United States Renal Data System/National Institutes of Health and the National Registry of Myocardial Infarction. Am Heart J 2012;163(3):399-406.

12. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, Zelenkofske S, Leimberger JD, Califf RM, Pfeffer MA. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004;351(13):1285-95.

13. Charytan D, Mauri L, Agarwal A, Servoss S, Scirica B, Kuntz RE. The use of invasive cardiac procedures after acute myocardial infarction in long-term dialysis patients. Am Heart J 2006;152(3):558-64.

14. Coca SG, Krumholz HM, Garg AX, Parikh CR. Underrepresentation of renal disease in randomized controlled trials of cardiovascular disease. JAMA 2006;296(11):1377-84.

15. Latif F, Kleiman NS, Cohen DJ, Pencina MJ, Yen CH, Cutlip DE, Moliterno DJ, Nassif D, Lopez JJ, Saucedo JF. In-hospital and 1-year outcomes among percutaneous coronary intervention patients with chronic kidney disease in the era of drug-eluting stents: a report from the EVENT (Evaluation of Drug Eluting Stents and Ischemic Events) registry. JACC Cardiovasc Interv 2009;2(1):37-45.

16. Herzog CA, Littrell K, Arko C, Frederick PD, Blaney M. Clinical characteristics of dialysis patients with acute myocardial infarction in the United States: a collaborative project of the United States Renal Data System and the National Registry of Myocardial Infarction. Circulation 2007;116(13):1465-72.

17. Januzzi JL, Cannon CP, DiBattiste PM, Murphy S, Weintraub W, Braunwald E. Effects of renal insufficiency on early invasive management in patients with acute coronary syndromes (The TACTICS-TIMI 18 Trial). Am J Cardiol 2002;90(11):1246-9.

18. Johnston N, Jernberg T, Lagerqvist B, Wallentin L. Early invasive treatment benefits patients with renal dysfunction in unstable coronary artery disease. Am Heart J 2006;152(6):1052-8.

19. Charytan DM, Wallentin L, Lagerqvist B, Spacek R, De Winter RJ, Stern NM, Braunwald E, Cannon CP, Choudhry NK. Early angiography in patients with chronic kidney disease: a collaborative systematic review. Clin J Am Soc Nephrol 2009;4(6):1032-43.

20. McCullough PA, Sandberg KR, Borzak S, Hudson MP, Garg M, Manley HJ. Benefits of aspirin and beta-blockade after myocardial infarction in patients with chronic kidney disease. Am Heart J 2002;144(2):226-32.

21. Wright RS, Reeder GS, Herzog CA, Albright RC, Williams BA, Dvorak DL, Miller WL, Murphy JG, Kopecky SL, Jaffe AS. Acute myocardial infarction and renal dysfunction: a high-risk combination. Ann Intern Med 2002;137(7):563-70.

22. van Domburg RT, Hoeks SE, Welten GM, Chonchol M, Elhendy A, Poldermans D. Renal insufficiency and mortality in patients with known or suspected coronary artery disease. J Am Soc Nephrol 2008;19(1):158-63.

23. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604-12.

24. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003;139(2):137-47.

25. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem 1992;38(10):1933-53.

26. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145(4):247-54.

27. Nauta ST, Deckers JW, Akkerhuis KM, van Domburg RT. Short- and Long-Term Mortality After Myocardial Infarction in Patients With and Without Diabetes: Changes from 1985 to 2008. Diabetes Care 2012.

Chapter 5

Effect of anemia on short- and long-term outcome in patients hospitalized for acute coronary syndromes

John O Younge
Sjoerd T Nauta
K Martijn Akkerhuis
Jaap W Deckers
Ron T van Domburg

Am J Cardiol. 2012 Feb 15;109(4):506-10

Abstract

Anemia is not uncommon in hospitalized cardiac patients and is associated with adverse outcomes. The aim of this study was to identify the association of anemia with early and long- term outcome in patients with Acute Coronary Syndromes (ACS). A total of 5304 consecutive patients (73% men, 61 ±12 years of age) admitted to a coronary care unit between 1985 and

2008 for ACS, were included. According to the WHO, anemia was defined as serum hemoglobin levels <13 g/dl for men and <12 g/dl for women. Anemia was divided into tertiles to compare mild, moderate and severe anemia with nonanemia. With respect to trend analyses, the study population was categorized in three groups: 1985-1990; 1991-2000; and 2001-2008. Outcome measurements were all-cause mortality at 30-days and 20 years.

Anemia was present in 2016 (38%) patients, of whom 655 had mild anemia, 717 moderate anemia and 646 severe anemia. Median follow-up duration was 10 years and ranged from 2 to 25 years. When comparing to nonanemia, adjusted hazard ratios for mortality at 30-days were 1.40 for moderate anemia (95%CI 1.04-1.87) and 1.67 for severe anemia (95%CI 1.25-2.24). At 20-year, hazard ratios were 1.13 for moderate anemia (95%CI 1.01-1.27), and 1.39 for severe anemia (95%CI 1.23-1.56). Additionally, survival during hospitalization improved over time. Compared to 1985-1990 adjusted hazard ratios were 0.52 for 1991-2000 (95%CI 0.41-0.66) and 0.36 for 2001-2008 (95%CI 0.25-0.51). In conclusion, the presence and severity of anemia is an important predictor of higher in-hospital- and long-term-mortality after ACS. Additionally, since the 1980's, in-hospital outcome of ACS patients with anemia has improved.

Keywords

Anemia, acute coronary syndromes, trends, prognosis.

Introduction

Anemia is not uncommon in patients hospitalized for Acute Coronary Syndromes (ACS) and its prevalence ranges from 6.4% to 45%.[1-5] It is associated with adverse outcomes during hospitalisation.[2,4-6] Although adverse outcomes in other populations due to anemia have been described,[7-11] only a very few studies have examined the long-term effects of anemia in ST-elevation Myocardial Infarction (STEMI) and nothing is yet known whether this association changed over the last 25 years. In the past decades, new therapeutical and medical treatment interventions were introduced that reduced morbidity and enhanced survival after acute myocardial infarction. These strategies include the use of reperfusion therapy, antiplatelet agents, ACE- inhibitors, and β-blockers.[12-15] Furthermore, percutaneous coronary intervention (PCI) became the therapeutic modality of first choice in STEMI patients.[13,16,17] The effect of anemia in these patients has not been studied yet. And therefore, the main goal of this study was to identify the association of anemia on early and long-term outcome in a cohort of ACS patients hospitalized between 1985 and 2008 and whether this association is independent of renal insufficiency.

Methods

All patients aged >18 years admitted with a first admission for STEMI or Non-ST-elevated Myocardial Infarction (NSTEMI) in the Coronary Care Unit (CCU) of the Thorax-center, Erasmus University Medical Center between January 1985 and December 2008, from whom the first haemoglobin value was obtained, were included.

The primary discharge diagnosis of STEMI was made in the presence of the following characteristics: chest pain or equivalent symptoms in combination with dynamic ECG changes consistent with MI and a serial rise and fall in serum biochemical markers of cardiac necrosis such as creatine kinase-MB and troponin T. Patients were diagnosed as STEMI in the presence of ST-segment elevation > 0·1 mV in at least two extremity leads, or > 0·2 mV in at least two precordial leads, and as NSTEMI otherwise.

Data was acquired retrospectively by retrieving the hospital medical records. Demographic characteristics (age, gender), cardiac history (previous MI, PCI or CABG), risk factors (hypertension, diabetes, hypercholesterolemia, family history, smoking status, renal dysfunction), discharge diagnosis (STEMI or NSTEMI), and therapy (PCI, antithrombotic treatment), were collected.

The primary endpoint was mortality at 30-days and at 20 years follow-up. Survival status was assessed through municipal Civil Registries.

Haemoglobin value was determined on first admission. We adopted the definition of anemia by the World Health Organization , which defines anemia as a serum hemoglobin level <13 g/dl for men and a level <12 g/dl for women.[18] Patients with anemia were divided into tertiles to compare to prognosis of patients with mild (12.2-13.0 g/dl men, 11.2-12.0 g/dl women), moderate (10.9-12.1 g/dl men, 10.3-11.1 g/dl women) and severe anemia (≤10.8 g/dl men, ≤10.2 g/dl women) to subjects without anemia.

Patient's characteristics were given as mean± standard deviation for continuous variables, compared by one-way ANOVA test and Bonferroni correction. Pearson chi-squared test was used for categorical variables and were presented in percentages. Cumulative survival was constructed using the Kaplan–Meier method. Logrank tests were used to compare curves. Logistic regression analyses were performed to adjust anemia for the other baseline characters of 30-day outcome. Cox regression analyses were performed to identify 20-year outcome. Adjustments were made for the variables age, gender, hypertension, diabetes, renal insufficiency defined in patients who had a creatinine value >150 mmol/L, hypercholesterolemia, smoking, clinical presentation, treatment, prior CABG, prior myocardial infarction, prior PTCA, and trends. Results are reported as hazard ratios of mortality and their respective 95% confidence intervals. All statistical tests were 2-tailed, and p-values were significant at <0.05. When analysing for trends, the study population was categorised in three groups of patients hospitalized between 1985-1990; 1991-2000; and 2001-2008. Furthermore, when analysing for trends, we tried to find a possible interaction with anemia or renal insufficiency. All data were analyzed with SPSS software (SPSS 17.0, SPSS Inc., Chicago, IL, USA).

Results

Of the 5304 patients included in the study, 73% were men. Mean age was 61 years. In total, 38% of the patients were anemic. When this last group was divided in tertiles, 655 had mild anemia (12.3%), 717 moderate anemia (13.5%) and 646 severe anemia (12.2%). Mean haemoglobin levels were 14.2 ± 1.2 g/dL in nonanemic patients and 11.0 ± 1.6 g/dL in patients with anemia.

Patients with anemia were more likely to be older, male, smoking, to have more renal insufficiency, diabetes or hypertension, family history, prior MI and arrhythmia (Table 1). Patients with anemia were more often treated with aspirin, antiarrhythmics, digitalis, diuretics and less with β-blockers oral anticoagulants as compared with nonanemic patients. Furthermore, patients with anemia received less additional therapy at admission. The prevalence of mild anemia increased from 8.5% in 1985-1990 to 12.6% in 1991-2000 and 16.0% in 2001-2008 ($p<0.001$). The prevalence of moderate anemia increased from 10.2 % in 1985-1990 to 14.2% in 1991-2000 and 15.6% in 2001-2008 ($p<0.001$). The prevalence of severe anemia increased from 10.5% in 1985-1990 to 13.3% in 1991-2000, and to 11.8% in 2001-2008 ($p<0.05$).

In the total study population, mean follow-up duration was 10 years and ranged from 2 to 25 years. Overall cumulative survival was 91% at 30 days, and 49% at 20-years. Cumulative 30-day survival was 93% in nonanemic patients and 88% in anemic patients ($p<0.001$) (Figure 1A). Cumulative 30-day survival rate, in patients with anemia increased from 87.2% in 1985-1990 to 91.3% in 1991-2000 ($p=0.002$) and 94.1% in 2001-2008 ($p<0.001$) (Figure 2A).

Cumulative 20-year survival was 52.9% for nonanemic patients and 42.8% in anemic patients ($p<0.001$) (Figure 1B). The difference was predominantly made in the first year. Thereafter, the curves were parallel. Over time, cumulative 20-year survival rate was 33.8% in 1985-1990, which decreased to 33.7% in 1991-2000 and in 2001-2008 66.8% (Figure 2B).

Table 1: Baseline characteristics according to anemia categories.

Variable	Nonanemia (n=3288) (61.9%)	Mild anemia (n=655,) (12.3%)	Moderate anemia (n=715) (13.5%)	Severe anemia (n=646) (12.2%)	p
Demographic					
Age (years), mean±sd	60±12.0	63±11.6	64±11.3	65±11.8	<0.001
Gender (male), %	76	65	72	68	<0.001
Risk factors, %					
Diabetes Mellitus	11	12	14	16	0.001
Hypertension	33	32	35	40	0.01
Hypercholesterolemia	29	21	22	22	0.2
Smoking	40	33	31	25	<0.001
Family history	27	24	23	20	<0.001
Renal insufficiency	4	6	14	27	<0.001
History, %					
Prior MI	29	34	34	36	<0.001
Prior PCI	8	9	11	10	0.1
Prior CABG	8	8	9	8	0.6
Arrhythmia	1.7	2.6	2.7	3.4	0.02
Clinical presentation, %					0.1
STEMI	53	50	49	49	
NSTEMI	47	50	51	51	
Medication, %					
Aspirin	54	57	56	51	0.05
ACE inhibitor	20	19	21	22	0.5
Antiarrhythmics	5	6	7	9	0.004
Beta blocker	64	60	56	52	<0.001
Calcium antagonist	33	34	35	33	0.7
Digitalis	5	6	7	8	0.01
Diuretics	16	18	21	25	<0.001
Oral anticoagulant	57	57	56	51	0.03
Treatment, %					<0.001
PCI	35	43	42	36	
Antithrombotic treatment	16	15	12	9	
None	49	41	45	55	

* P calculated with ANOVA for continuous variables and with chi-square for categorical variables. MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting surgery.

Anemia was divided into tertiles by; mild anemia (12.2-13.0 g/dl men, 11.2-12.0 g/dl women), moderate (10.9-12.1 g/dl men, 10.3-11.1 g/dl women) and severe anemia (≤ 10.8 g/dl men, ≤ 10.2 g/dl women)

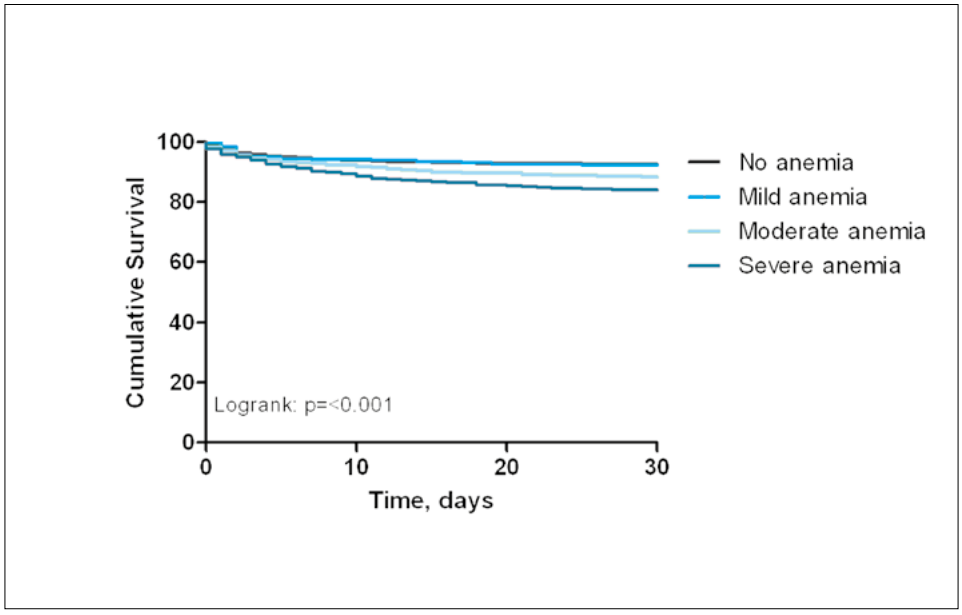

Figure 1A: Cumulative survival of severity of anemia at 30-days follow-up.

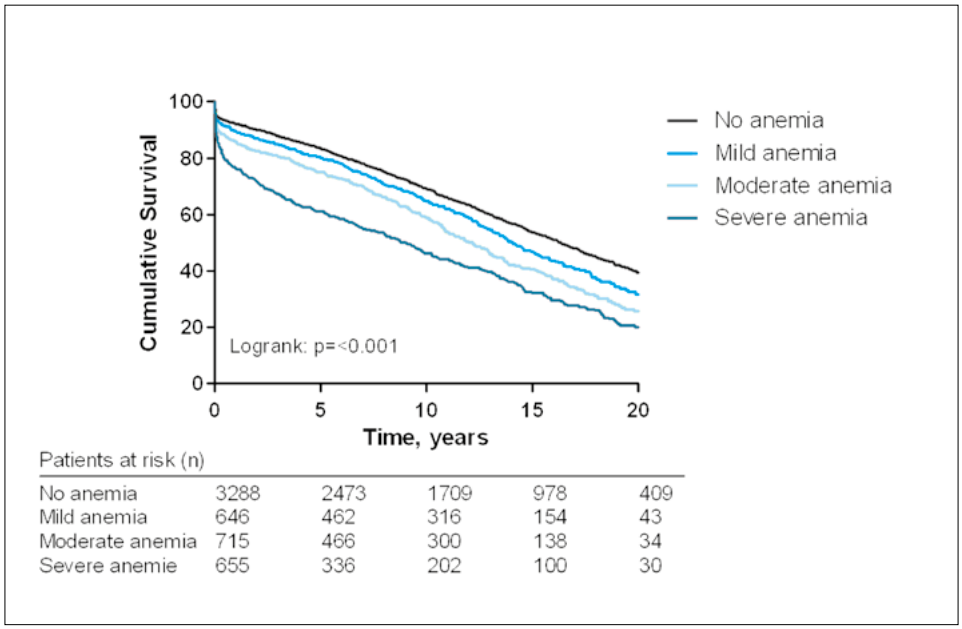

Figure 1B: Cumulative long-term survival according to severity of anemia.

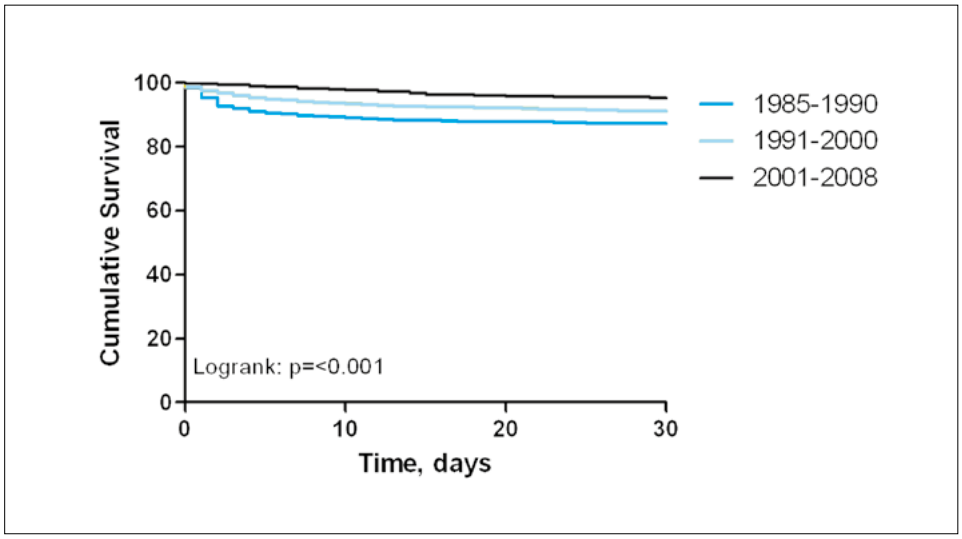

Figure 2A: Cumulative survival of trends in anemia patients at 30-days follow-up.

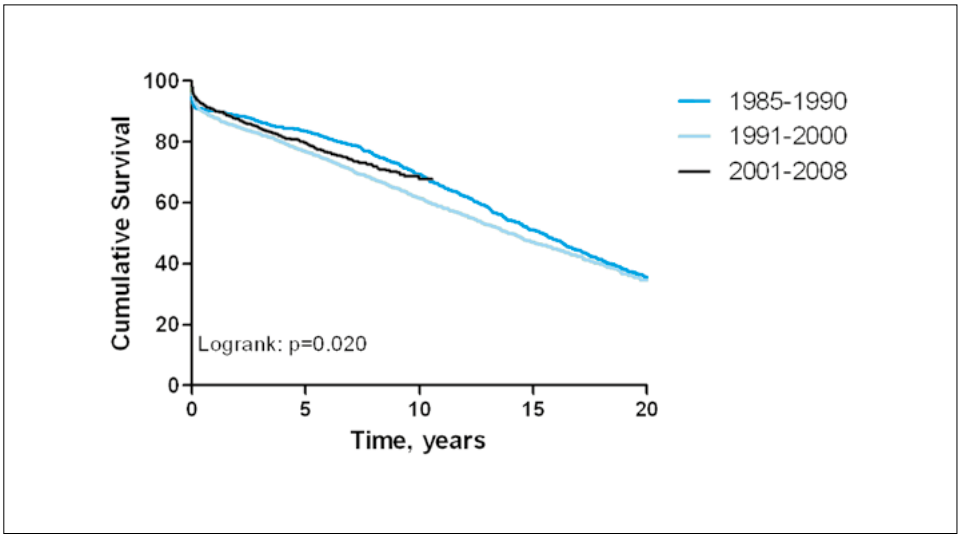

Figure 2B: Long-term cumulative survival of trends in anemia patients.

Table 2: Univariate and multivariate logistic hazards regression 30-day outcome

	Univariate HR (95% CI)	Multivariate* HR (95% CI)
Nonanemia	Reference	Reference
Mild anemia	0.82(0.60-1.11)	0.99(0.71-1.39)
Moderate anemia	1.40(1.09-1.80)	1.40 (1.04-1.87)
Severe anemia	2.16(1.71-2.73)	1.67(1.25-2.24)
Renal insufficiency	3.31(2.96-3.70)	4.11(3.14-5.38)
1985-1990	Reference	Reference
1990-2000	1.10(1.02-1.18)	0.52(0.41-0.66)
2000-2008	0.86(0.77-0.97)	0.36(0.25-0.51)

* Adjusted for: age, gender, hypertension, diabetes mellitus, hypercholesterolemia, smoking, prior MI, PCI, CABG, Renal insufficiency, trends and tertiles anemia.

MI = myocardial infarction; PCI= percutaneous coronary intervention; CABG= coronary artery bypass grafting; HR= Hazard Ratio; 95% CI= 95% Confidence Interval

Table 3: Univariate and multivariate cox proportional hazards regression for twenty-year outcome

	Univariate HR (95% CI)	Multivariate* HR (95% CI)
Nonanemia	Reference	Reference
Mild anemia	1.01(0.90-1.13)	1.05(0.93-1.18)
Moderate anemia	1.29 (1.16-1.44)	1.13 (1.01-1.27)
Severe anemia	1.83(1.65-2.01)	1.39 (1.23-1.56)
Renal insufficiency	3.31(2.96-3.70)	2.28 (2.02-2.57)
1985-1990	Reference	Reference
1990-2000	1.10(1.02-1.18)	0.99(0.90-1.08)
2000-2008	0.86(0.77-0.97)	0.85(0.73-0.99)

* Adjusted for: age, gender, hypertension, diabetes mellitus, hypercholesterolemia, smoking, prior MI, PCI, CABG, Renal insufficiency, trends and tertiles anemia.

MI = myocardial infarction; PCI= percutaneous coronary intervention; CABG= coronary artery bypass grafting; HR= Hazard Ratio; 95% CI= 95% Confidence Interval

After adjusting for baseline characteristics including renal insufficiency, moderate and severe anemia were associated with an increased risk of 30 day-mortality (adjusted HR 1.40, 95% CI 1.04-1.87 and adjusted HR 1.67, 95% CI 1.25-2.24) (Table 2).

Hospital mortality during the 1990s and 2000s was lower than in the 1980s (adjusted HR 0.52, 95% CI 0.41-0.66 and adjusted HR 0.36, 95% CI 0.25-0.51).

On the long-term outcome, respectively moderate and severe anemia were associated with higher mortality (adjusted HR 1.13, 95% CI 1.01-1.27 and adjusted HR 1.39, 95% CI 1.23-1.56) despite the predictor renal insufficiency on mortality (HR 2.28, 95% CI 2.02-2.57). (Table 3)

Long-term mortality in 1991-2000 was similar with 1985-1990 (adjusted HR 0.99, 95% CI 0.99-1.08). However, between 2001-2008 the mortality was lower (adjusted HR 0.85, 95% CI 0.73-0.99). No interaction was found between the time trends and anemia, nor with renal insufficiency.

Discussion

Our results show that the extent of anemia at hospital admission and renal dysfunction is associated with in hospital and long-term mortality. Despite renal insufficiency, a higher mortality was observed both in moderate and severe anemia. In addition, we showed that over the years in-hospital survival of patients with anemia has improved from 83% in the 1980s to 88% in the 1990s and 92% in the 2000s.

Anemia has the potential to worsen the myocardial ischemic insult in acute MI and other acute coronary syndromes, both by decreasing the oxygen content of the blood supplied to the endangered myocardium and by increasing myocardial oxygen demand through necessitating a higher cardiac output to maintain adequate systemic oxygen delivery.[19,20] The origin of anemia is mostly multifactorial. The cause of anemia in heart failure patients is understood to be caused by malnutrition, iron deficiency, bone marrow depression and certain medication.[8,21-23] Renal dysfunction is a known marker with adverse prognosis in patients with ischemic

heart disease,[24] especially in those who have anemia.[25] Also demographic factors like age and gender have an important role. Furthermore, anemia is associated with changes in left ventricular anatomy among patients with chronic kidney disease and it is possible that these changes could contribute to worsening left ventricular diastolic and/or systolic dysfunction and consequent increased risk of death.[26] Westenbrink et al.[27] also showed that besides impaired renal perfusion and blunted erythropoietin production, fluid retention can cause anemia as well in chronic heart failure patients. The effect is caused by an increase in plasma volume which leads to pseudo-anemia due to hemodilutation. Anemia is a modifiable clinical marker. Haemotransfusion is considered for Hb values > 10gr/dL.[28] Studies with regard to blood transfusion show different results on 30-day mortality in patients with ACS.[2,5] But since the absence of randomized controlled trials the negative and positive effects of blood transfusion are not fully established. Other treatment approaches, like epoetin-α and darbepoetin-α, are showing promising results. Silverberg et al.[29] randomized 32 patients with mild anemia. One group was given rhEPO and intravenous iron, while the comparing group didn't receive any treament. Results showed an significant improvement in New York Heart Association (NYHA) functional class, left ventricular function, renal function and heart failure hospitalisations. Ponikowski et al.[30] randomized 41 patients in a placebo controlled trial. The group which was given darbepoeitin-α had an improvement in quality of life. Van Veldhuisen et al.[31] randomized chronic heart failure patients with anemia and they also found an improvement in certain quality of life indexes in those who received darbepoetin-α. A gradually rise in haemoglobin levels was achieved. Still, it is uncertain whether these treatment options will decrease mortality and morbidity in ACS patients.

Our findings support the results from prior studies which showed an association between anemia and adverse outcomes on short and long-term follow-up. Wu et al [5] found, in an elderly population, an association between low hematocrit level on admission and 30-day mortality. The results were graded, a lower survival was found in a lower degree of anemia. Sabatine et al.[2] examined 40,000 ACS patients and concluded that anemia is a powerful and independent predictor of major cardiovascular events on 30-day outcome, whereas STEMI patients were more at risk. In a study of 1,122 STEMI patients, treated with PCI, results showed that prior chronic anemia was an independent predictor for intra-hospital mortality. Patients

with new anemia showed a higher mortality rate and incidence of major bleedings.[4] Dunkelgrun et al. reported that, in patients, scheduled for elective vascular surgery, anemia was an independent predictor for perioperative and long-term cardiovascular outcome (30-day and 5 year), regardless of underlying heart failure or renal disease.[7]

On the long-term the effect of anemia is still unclear, with different results. In STEMI patients anemia was associated with an increased 1 and 5-year mortality.[1,3] Aronson et al.[1] found a hazard ratio of 1.27 (95% CI 1.16-1.40; p<0.001) of anemia at 48 months. Salisbury et al.[3] founds similar results, whereas moderate-severe hospital acquired anemia had a higher mortality at 1-year (HR 1.82, 95% CI 1.11-2.98). On the contrary, Falluji et al.[32] found similar outcome at 1-year mortality in the anemia and nonanemia group in 1986 (RR 1.005, p=0.93) and 1996 (RR 1.084, p=0.11) and concluded there was no difference in survival between anemic and non anemic patients.

Our study shows that also severity of anemia is associated with long-term outcome. The higher mortality in patients with anemia is predominantly made in the first year. Beyond one year the survival of both patients with and without anemia are similar. Our study showed for the first time that hospital mortality in ACS patients with anemia has improved. However, after hospital discharge, no improvements in the treatment of anemia was observed over the years. The improvements over time must, without any doubt, be attributed to improvements in treatment and changes in high profile of these patients during hospital admission. New medical treatment options made their attendance such as antiplatelet agents, ACE- inhibitors, β-blockers. Furthermore, fibrinolitic therapy and anti-coagulation improved survival significantly.[12,14,15,33] Also interventions like primary PCI improved survival in STEMI patients.[13,16,17]

In conclusion, the presence and severity of anemia is an important predictor of higher in hospital and long-term mortality after ACS. However, beyond one year the increased mortality stabilizes. Additionally, we showed that since the 1980's, in-hospital outcome of ACS patients with anemia has been improved.

References

1. Aronson D, Suleiman M, Agmon Y, Suleiman A, Blich M, Kapeliovich M, Beyar R, Markiewicz W, Hammerman H. Changes in haemoglobin levels during hospital course and long-term outcome after acute myocardial infarction. *Eur Heart J* 2007;28:1289-1296.

2. Sabatine MS, Morrow DA, Giugliano RP, Burton PB, Murphy SA, McCabe CH, Gibson CM, Braunwald E. Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. *Circulation* 2005;111:2042-2049.

3. Salisbury AC, Alexander KP, Reid KJ, Masoudi FA, Rathore SS, Wang TY, Bach RG, Marso SP, Spertus JA, Kosiborod M. Incidence, correlates, and outcomes of acute, hospital-acquired anemia in patients with acute myocardial infarction. *Circ Cardiovasc Qual Outcomes* 2010;3:337-346.

4. Valente S, Lazzeri C, Chiostri M, Sori A, Giglioli C, Gensini GF. Prior and new onset anemia in ST-elevation myocardial infarction: a different prognostic role? *Intern Emerg Med* 2010.

5. Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001;345:1230-1236.

6. Lipsic E, van der Horst IC, Voors AA, van der Meer P, Nijsten MW, van Gilst WH, van Veldhuisen DJ, Zijlstra F. Hemoglobin levels and 30-day mortality in patients after myocardial infarction. *Int J Cardiol* 2005;100:289-292.

7. Dunkelgrun M, Hoeks SE, Welten GM, Vidakovic R, Winkel TA, Schouten O, van Domburg RT, Bax JJ, Kuijper R, Chonchol M, Verhagen HJ, Poldermans D. Anemia as an independent predictor of perioperative and long-term cardiovascular outcome in patients scheduled for elective vascular surgery. *Am J Cardiol* 2008;101:1196-1200.

8. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new- onset heart failure. *Circulation* 2003;107:223-225.

9. Hamaguchi S, Tsuchihashi-Makaya M, Kinugawa S, Yokota T, Takeshita A, Yokoshiki H, Tsutsui H. Anemia is an independent predictor of long-term adverse outcomes in patients hospitalized with heart failure in Japan. A report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circ J* 2009;73:1901-1908.

10. McKechnie RS, Smith D, Montoye C, Kline-Rogers E, O'Donnell MJ, DeFranco AC, Meengs WL, McNamara R, McGinnity JG, Patel K, Share D, Riba A, Khanal S, Moscucci M. Prognostic implication of anemia on in-hospital outcomes after percutaneous coronary intervention. *Circulation* 2004;110:271-277.

11. Stewart T, Freeman J, Stewart J, Sullivan A, Ward C, Tofler GH. Anaemia in heart failure: a prospective evaluation of clinical outcome in a community population. *Heart Lung Circ* 2010;19:730-735.

12. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC, Jr., Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Circulation* 2004;110:588-636.

13. Grines CL, Cox DA, Stone GW, Garcia E, Mattos LA, Giambartolomei A, Brodie BR, Madonna O, Eijgelshoven M, Lansky AJ, O'Neill WW, Morice MC. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* 1999;341:1949-1956.

14. Van de Werf F, Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KA, Julian D, Lengyel M, Neumann FJ, Ruzyllo W, Thygesen C, Underwood SR, Vahanian A, Verheugt FW, Wijns W. 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.

15. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med* 2010;362:2155-2165.

16. Weaver WD, Simes RJ, Betriu A, Grines CL, Zijlstra F, Garcia E, Grinfeld L, Gibbons RJ, Ribeiro EE, DeWood MA, Ribichini F. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. *JAMA* 1997;278:2093-2098.

17. Zijlstra F, Hoorntje JC, de Boer MJ, Reiffers S, Miedema K, Ottervanger JP, van 't Hof AW, Suryapranata H. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1999;341:1413-1419.

18. Nutritional anaemias. Report of a WHO scientific group. *World Health Organ Tech Rep Ser* 1968;405:5-37.

19. Levy PS, Quigley RL, Gould SA. Acute dilutional anemia and critical left anterior descending coronary artery stenosis impairs end organ oxygen delivery. *J Trauma* 1996;41:416-423.

20. Most AS, Ruocco NA, Jr., Gewirtz H. Effect of a reduction in blood viscosity on maximal myocardial oxygen delivery distal to a moderate coronary stenosis. *Circulation* 1986;74:1085-1092.

21. Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, Yusuf S. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet* 2003;361:1077-1083.

22. Ishani A, Weinhandl E, Zhao Z, Gilbertson DT, Collins AJ, Yusuf S, Herzog CA. Angiotensin-converting enzyme inhibitor as a risk factor for the development of anemia, and the impact of incident anemia on mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2005;45:391-399.

23. van der Meer P, Lipsic E, Westenbrink BD, van de Wal RM, Schoemaker RG, Vellenga E, van Veldhuisen DJ, Voors AA, van Gilst WH. Levels of hematopoiesis inhibitor N-acetyl-seryl-aspartyl-lysyl-proline partially explain the occurrence of anemia in heart failure. *Circulation* 2005;112:1743-1747.

24. Gibson CM, Dumaine RL, Gelfand EV, Murphy SA, Morrow DA, Wiviott SD, Giugliano RP, Cannon CP, Antman EM, Braunwald E. Association of glomerular filtration rate on presentation with subsequent mortality in non-ST-segment elevation acute coronary syndrome; observations in 13,307 patients in five TIMI trials. *Eur Heart J* 2004;25:1998-2005.

25. Lee PC, Kini AS, Ahsan C, Fisher E, Sharma SK. Anemia is an independent predictor of mortality after percutaneous coronary intervention. *J Am Coll Cardiol* 2004;44:541-546.

26. Langston RD, Presley R, Flanders WD, McClellan WM. Renal insufficiency and anemia are independent risk factors for death among patients with acute myocardial infarction. *Kidney Int* 2003;64:1398-1405.

27. Westenbrink BD, Visser FW, Voors AA, Smilde TD, Lipsic E, Navis G, Hillege HL, van Gilst WH, van Veldhuisen DJ. Anaemia in chronic heart failure is not only related to impaired renal perfusion and blunted erythropoietin production, but to fluid retention as well. *Eur Heart J* 2007;28:166-171.

28. Practice Guidelines for blood component therapy: A report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. *Anesthesiology* 1996;84:732-747.

29. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, Brosh D, Laniado S, Schwartz D, Yachnin T, Shapira I, Gavish D, Baruch R, Koifman B, Kaplan C, Steinbruch S, Iaina A. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 2000;35:1737-1744.

30. Ponikowski P, Anker SD, Szachniewicz J, Okonko D, Ledwidge M, Zymlinski R, Ryan E, Wasserman SM, Baker N, Rosser D, Rosen SD, Poole-Wilson PA, Banasiak W, Coats AJ, McDonald K. Effect of darbepoetin alfa on exercise tolerance in anemic patients with symptomatic chronic heart failure: a randomized, double-blind, placebo- controlled trial. *J Am Coll Cardiol* 2007;49:753-762.

31. van Veldhuisen DJ, Dickstein K, Cohen-Solal A, Lok DJ, Wasserman SM, Baker N, Rosser D, Cleland JG, Ponikowski P. Randomized, double-blind, placebo-controlled study to evaluate the effect of two dosing regimens of darbepoetin alfa in patients with heart failure and anaemia. *Eur Heart J* 2007;28:2208-2216.

32. Al Falluji N, Lawrence-Nelson J, Kostis JB, Lacy CR, Ranjan R, Wilson AC. Effect of anemia on 1-year mortality in patients with acute myocardial infarction. *Am Heart J* 2002;144:636-641.

33. Simoons ML, Serruys PW, vd Brand M, Bar F, de Zwaan C, Res J, Verheugt FW, Krauss XH, Remme WJ, Vermeer F, et al. Improved survival after early thrombolysis in acute myocardial infarction. A randomised trial by the Interuniversity Cardiology Institute in The Netherlands. *Lancet* 1985;2:578-582.

Part II

Ageing and glucose metabolsims: emerging risk factors

Chapter 6

Age-dependent care and long-term (20year) mortality of 14,434 myocardial infarction patients: Changes from 1985 to 2008

Sjoerd T Nauta
Jaap W Deckers
K Martijn Akkerhuis
Ron T van Domburg

Int J Cardiol. 2013 Aug 10;167(3):693-7

Abstract

Objectives

To determine whether age-dependent inequalities in care and outcome changed over a 24 year period for patients admitted with a myocardial infarction (MI).

Methods

We examined four age groups (<55, 55-65, 65-75, and >75 years) and treatment and mortality in 14 434 consecutive patients admitted for MI to an intensive coronary care unit from 1985 to 2008. Temporal trend analyses were performed by comparing decades of admission (1985-1990 vs. 1990-2000 vs. 2000-2008).

Results

A total of 2040 (14%) of the patients were >75 years of age. Older patients more often were female and less often presented with an ST-segment elevation MI (STEMI). Systematic differences in care were present between the age groups: older patients were less likely to receive evidence-based medical care and reperfusion therapy during the last 24 years, although the differences became smaller over time. In 2000-2008, 30-day (adjusted OR 0.28, 95%CI: 0.23-0.34) and 5-year (adjusted HR 0.61, 95%CI: 0.54-0.68) mortality were lower compared to 1985-1990. These temporal trends were equal across all age groups. Hence, the change in mortality over the 24-year study period is similar among the spectrum of ages. Patients aged <55, 55-65, 65-75, and >75 years had a 20-year mortality of 38, 63, 87 and >95%, respectively.

Conclusions

Older patients with an MI remained less likely to receive evidence-based care during 24 years of observation. Temporal reductions in mortality were similar among all age groups. The application of proven MI therapies to appropriate patients regardless of age may even further improve these outcomes.

Introduction

Due to ageing of the general population in the Western world, more elderly patients present to hospital with a myocardial infarction (MI).[1] Previous studies have suggested that elderly patients with an MI are less likely to receive evidence-based therapies and have a worse survival after hospitalization compared to younger patients.[2-4] Recent data has underlined the need for increased use of evidence-based management among the elderly and has shown potential for a reduction in mortality in this age group.[3, 5]

Within the past 25 years, substantial improvements in the treatment and outcome of MI have been made with, for example the implementation of thrombolytic therapy in the 1990s, primary percutaneous coronary intervention (PCI) in the beginning of the new century and tailored treatment according to individual risk.[6-10] A long-term analysis of patients admitted to hospital with an MI might identify changes in the use of treatment modalities, and early and late outcomes for the whole spectrum of ages. Therefore, the aims of this study were threefold. First, to determine whether, in accordance with the guideline recommendations,[11-12] age-dependent inequalities in care changed over a 24-year period. Second to compare temporal trends in mortality according to age for patients admitted with an MI. And third, to quantify the effect of age on 30-day and long-term mortality.

Methods

We included all consecutive patients aged >18 years admitted for ST-segment elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI) to the Intensive Coronary Care Unit (ICCU) of the Thoraxcenter, Erasmus University Medical Center between June 1985 and December 2008.

The primary discharge diagnosis of MI was made in the presence of the following characteristics: chest pain or equivalent symptoms in combination with dynamic ECG changes consistent with MI and a typical serial rise (to at least three times the upper normal value) and fall in serum biochemical markers of cardiac necrosis such

as creatine kinase-MB or troponin-T (as of 2002). Patients were diagnosed as STEMI in the presence of ST-segment elevation > 0.1 mV in at least two peripheral leads, or > 0.2 mV in at least two contiguous precordial leads, and as NSTEMI otherwise. For patients admitted more than once, only the first hospitalization was taken into account.

Data collection

Trained physicians and nurses accustomed to the use of standardized case report forms collected the data. Demographic characteristics (age, gender), cardiac history (previous MI, PCI or coronary artery bypass surgery (CABG)), risk factors (hypertension, diabetes, family history, smoking status), anemia (Hemoglobin level < 13.0 g/dl men, <12.0 g/dl women), renal dysfunction (creatinine > 150 μmol/l), and pharmacological and invasive treatment modalities (thrombolysis and PCI) were collected. The decision to use or not use specific pharmacological and invasive treatment modalities was made according to the level of evidence and recommendations in the guidelines available at that time.

Follow-up and endpoints

The primary endpoint was all cause mortality at 30 days and at 20 years. In-hospital mortality was retrieved from the medical records. Long-term survival status was assessed through municipal Civil Registries in 2010 and was available for 99% of all patients.

Ethics

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.[13]

Statistical Analysis

The study patients were categorized in four groups of patients according to age: those aged <55, 55-65, 65-75, and >75 years. Categorical variables were summarized as percentages and chi-square test for trend was used to calculate p-values. Patients were stratified in three groups according to decade of hospitalization: 1985-1990; 1990-2000; 2000-2008. We assessed temporal trends in outcome by comparing these three periods. Cumulative survival curves were constructed using the Kaplan–Meier method for patients aged >75 years. The log-rank test was used to compare survival

curves. We examined the independent association between decade of hospitalization and mortality, for the whole study population and for the elderly, respectively, using logistic regression for 30-day outcome and the Cox proportional hazards model for long-term outcome. Since complete long-term (20-year) follow-up of patients admitted after 1991 is unavailable, we used 5-year outcomes for comparing the influence of decades of hospitalization on outcome. Adjustment was performed for gender, previous MI, previous CABG, hypertension, diabetes, hyperlipidemia, family history, smoking status, renal dysfunction, anemia and discharge diagnosis. In addition, we examined the independent association between age and mortality using the analyses described above.

Results are reported as odds ratios (OR) –for 30-day mortality– and hazard ratios (HR) –for long-term mortality– and their respective 95% confidence intervals. All statistical tests were 2-tailed, and p-values were considered significant at <0.05. Analysis was performed using SPSS software version 17.0 (SPSS, Chicago, USA).

Results

We included 14,434 patients, of whom 2,040 (14%) were >75 years of age. The distribution of age categories is shown in Table 1. A total of 110,690 person-years were analyzed.

Patient characteristics

Patient characteristics are shown in Table 1. Older patients were more often female; more often had a history of CABG, anemia and renal impairment. Older patients were less often current smokers, less often had hypercholesterolemia, a family history of previous MI, or a discharge diagnosis of STEMI. For each decade of age, the odds of presenting with a STEMI decreased by 15% (odds ratio, OR 0.85, 95%CI: 0.83-0.88).

Medical and invasive care during the study period

Age-dependent inequalities in care were present in 1985 and persisted during the 24-year study period. While use of reperfusion therapy (either by thrombolytic therapy or PCI) increased over time in all groups with STEMI ($p<0.001$), older patients were less likely to receive reperfusion therapy ($p<0.001$), although the differences appeared to become smaller during the study period (Figure 1A). Prescription of evidence-based medical care (class 1A), including aspirin, Β-blockers, and statins was and remained lower in the elderly during the whole study period ($p<0.001$ for all). The prescription of ACE-inhibitors/ angiotensin-receptor blockers was lower for older patients in the

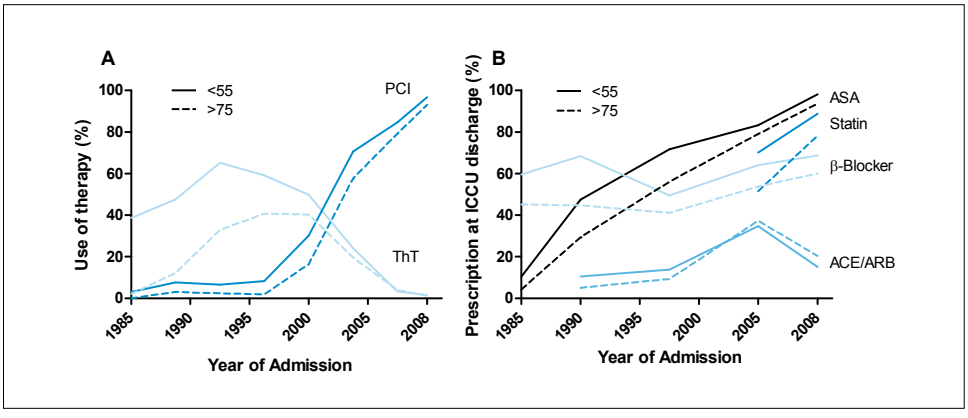

Figure 1: Treatment of patients over time: use of reperfusion therapy in STEMI (A) and use of evidence-based medical care in MI patients (B). ACE denotes angiotensin-converting enzyme inhibitor; ASA, aspirin; ARB, angiotensin receptor blocker; ThT, thrombolytic therapy.

1990s, but not thereafter (Figure 1B). Prescription of other medical therapy with a lower level of evidence for the treatment of MI, including calcium-antagonists, nitrates and diuretics at ICCU discharge was higher in the elderly (Table 1).

Table 1: Baseline characteristics and clinical presentation of patients hospitalized for MI according to age on admission.

	Age on admission				P for trend
	<55	55-65	65-75	>75	
No. of patients	4319 (30%)	4113 (29%)	3962 (27%)	2040 (14%)	
Baseline					
Gender (female)	20%	23%	32%	45%	<0.001
Cardiac history					
Previous MI	30%	34%	36%	34%	<0.001
Previous PCI	14%	15%	15%	15%	0.37
Previous CABG	7%	10%	12%	10%	<0.001
Risk factors					
Hypertension	29%	37%	39%	39%	<0.001
Diabetes	11%	14%	16%	17%	<0.001
Hyperlipidemia	29%	30%	26%	21%	<0.001
Family history	35%	29%	21%	14%	<0.001
Current smoker	51%	35%	21%	11%	<0.001
Renal dysfunction	5%	7%	12%	14%	<0.001
Anemia	30%	39%	50%	58%	<0.001
Discharge diagnosis					
STEMI	54%	47%	41%	45%	<0.001
Medication at ICCU * discharge					
Ca-antagonist	19%	24%	27%	21%	<0.001
Diuretics	8%	11%	16%	20%	<0.001
Nitrates	11%	13%	14%	16%	<0.001
Antiarrhythmics	4%	4%	4%	4%	0.20

* ICCU, intensive coronary care unit.

Temporal trends in mortality

In the total study population, the risk of 30-day mortality decreased between 1985 and 2008 from 11% in 1985-90 to 4% in 2000-8. This decrease was more pronounced for patients aged >75 years, from 27% in 1985-90 to 9% in 2000-8 (Figure 2A). Also, for the study population as a whole, 5-year mortality decreased between 1985 and 2008, from 24% in 1985-90 to 17% in 2000-8, and for patients aged >75 years from 55% in 1985-90 vs. 40% in 2000-8 (Figure 2B).

From 1985 to 2008, the adjusted risk of 30-day mortality decreased by nearly 75%, in both the overall study population (adjusted OR 0.28, 95%CI: 0.23-0.34) as well as in the elderly (adjusted OR 0.29, 95%CI: 0.18-0.45; Table 2). The risk of 5-year mortality decreased by nearly 40% in both the overall study population (adjusted hazard ratio, HR 0.61, 95%CI: 0.54-0.68) and in the elderly (adjusted HR 0.63, 95%CI: 0.49-0.80; Table 2). Hence, the relative risk reduction in 30-day and long-term mortality over the 24-year study period was similar among the spectrum of ages.

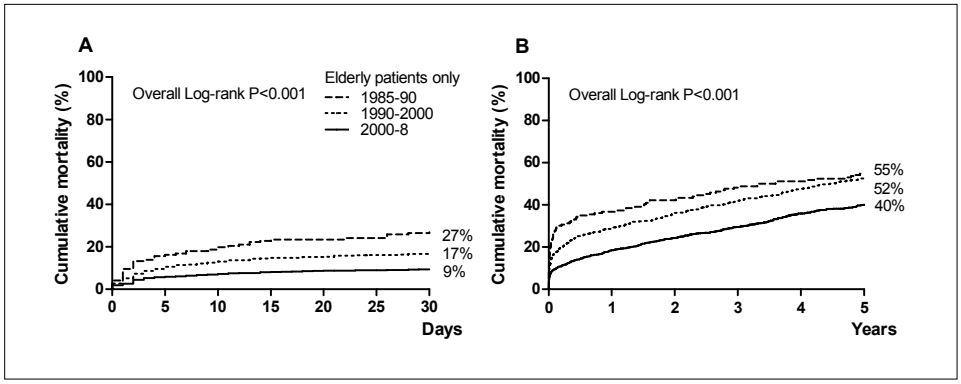

Figure 2: Temporal trends: Kaplan-Meier curves of mortality according to decade of admission in elderly patients (aged >75).

Table 2: Temporal trends of 30-day and 5-year mortality in MI patients.

Calendar period	All patients	>75
Odds ratios for 30-day mortality		
1985-90	Reference	Reference
1990-2000	0.61 (0.51-0.74)	0.59 (0.38-0.91)
2000-08	0.28 (0.23-0.34)	0.29 (0.18-0.45)
Hazard ratios for 5-year mortality		
1985-90	Reference	Reference
1990-2000	0.93 (0.83-1.0)	0.98 (0.77-1.2)
2000-08	0.61 (0.54-0.68)	0.63 (0.49-0.80)

Adjusted for gender, previous MI, previous CABG, hypertension, diabetes, hyperlipidemia, family history, smoking status, renal dysfunction, anemia and discharge diagnosis.

Age and Mortality

As expected, the risk of mortality was higher in older MI patients at 30 days follow-up (13% for patients >75 years vs. 3% for those <55 years, p<0.001) and during long-term follow-up (Figure 3: after 16 years, 95% for patients >75 years vs. 29% for those <55 years, p<0.001). The (adjusted) mortality rates for 30-day and 20-year outcomes are presented in Table 3. There were no significant interactions between the baseline characteristics and age and mortality. One in seven of the patients were >75, but one third of the deaths within 30 days occurred in this group.

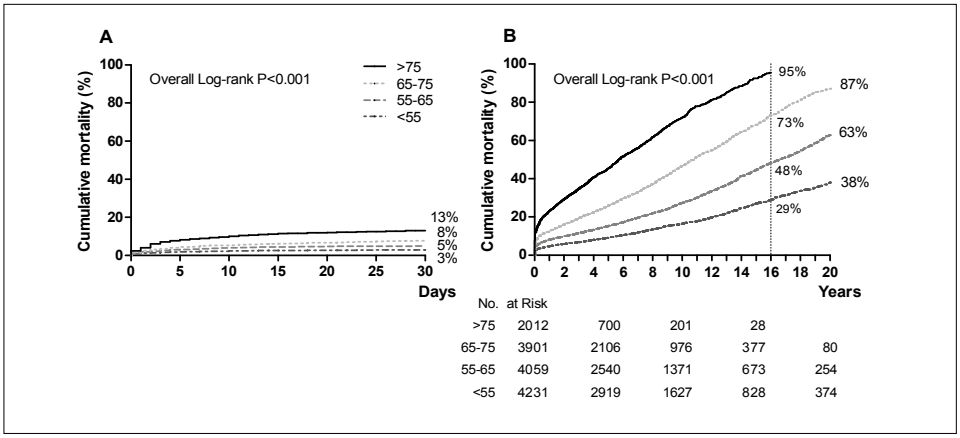

Figure 3: Kaplan-Meier curves of mortality according to age.

Table 3: Unadjusted and adjusted odds and hazard ratios of mortality according to age at hospitalization.

Age category	Unadjusted	Adjusted*
Odds ratios for 30-day mortality		
<55	Reference	Reference
55-65	1.8 (1.4-2.2)	1.6 (1.3-2.1)
65-75	2.8 (2.3-3.5)	2.5 (2.0-3.1)
>75	5.0 (4.0-6.2)	4.6 (3.6-5.8)
Hazard ratios for 20-year mortality		
<55	Reference	Reference
55-65	1.9 (1.7-2.1)	1.8 (1.7-2.0)
65-75	3.6 (3.4-4.0)	3.5 (3.2-3.8)
>75	7.3 (6.6-8.0)	7.3 (6.6-8.1)

*Adjusted for the same variables as Table 2 and decade of hospitalization.

Discussion

In this study conducted in a cohort of 14,434 MI patients, we showed that systematic differences in care were present between patients from different age groups: older patients were less likely to receive evidence-based medical care and reperfusion therapy during all 24 years of observation, although the differences became smaller over time. Furthermore, temporal trends in 30-day and long-term mortality showed substantial improvements in outcome during this 24-year period that were independent of age. Thus, these improvements in outcome were similar for all age groups. Finally, we demonstrated the association between age and mortality with follow-up data up to 20 years.

The better outcomes in younger patients could in part be due to the fact that effective therapies are better implemented among these patients. Previous studies[11, 14] showed that older patients with an STEMI who are eligible for reperfusion therapy, actually less often receive this treatment. Furthermore, other studies[11] showed that elderly patients with a NSTEMI are substantially less likely to undergo an invasive treatment strategy, while individual trials[15-16] have suggested that the benefit from an invasive strategy is mainly observed in patients >65 years of age (the "risk-treatment paradox"). Other proven therapies are also underused in the elderly[2, 17], even in the absence of contra-indications.[18] These age-related treatment patterns persisted in the present study, although the overall temporal increase in the use of evidence-based therapies (especially primary PCI for STEMI) among the elderly is encouraging and confirms other recent observations in older patients with STEMI.[19]

Thirty-day and long-term mortality after MI have decreased during the past decades.[10, 20] However, two recent studies suggest that temporal mortality improvements did not occur in older patients.[21-22] However, data from our study clearly demonstrates that, in our center, similar reductions in 30-day and long-term mortality have occurred across all age groups. In fact, the i) numerically similar relative reductions over time and ii) the higher absolute mortality in the elderly, imply that in absolute terms, elderly patients benefit most from improved medical care during the past 24 years. Still, the application of evidence-based MI therapies to appropriate patients regardless of age may even further improve these outcomes.

Age is one of the most important predictors of risk in MI patients.[23] Relative odds of 6.2 to 7.8 for in-hospital mortality in patients >75 years compared to <55 years have previously been reported,[3, 22, 24] figures similar to that of the present study. Relative hazards for long-term mortality in the elderly are presented in this study, with follow-up data comprising almost a whole life course.

Strengths and limitations

To our knowledge, this is the first paper investigating temporal trends in clinical characteristics, treatment and outcome of older patients (>75 years) with an MI over a time period of 24 years and with follow-up data for up to 20 years. Although the present study has unique strengths, some limitations should be mentioned. First, the discharge diagnosis of MI was based on the diagnosis of the attending physician. Newer definitions of MI have been published within the study period; these might interfere with the probability of an acute coronary syndrome patient to be diagnosed with MI. Still, these inconsistencies reflect clinical practice during these transitional periods. Second, given the nature of ageing this study reveals important associations but cannot prove causation. Finally, the present data are derived from a single center. Although this could result in a lower external validity, we think that this is unlikely to be the case since the definition of myocardial infarction and its therapeutic modalities are quite uniform, certainly in the Western world.

Conclusion

The elderly contribute a substantial proportion to MI mortality. Subjects > 75 years of age were less likely to receive evidence-based medical care and reperfusion therapy over the 24-year study period. Despite this, improvements in the application of evidence-based MI care were evident across all age groups from 1985 to 2008. There were significant temporal reductions in 30-day and long-term mortality, that were equal across all age groups. In absolute terms, therefore, older patients benefit most from the improved medical care for MI during the last 24 years. It is likely that a further increase in the application of evidence-based therapies for MI in the elderly will further improve their short- and long term outcome.

References

1. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med 2010;362(23):2155-65.

2. Avezum A, Makdisse M, Spencer F, Gore JM, Fox KA, Montalescot G, Eagle KA, White K, Mehta RH, Knobel E, Collet JP. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). Am Heart J 2005;149(1):67-73.

3. Rosengren A, Wallentin L, Simoons M, Gitt AK, Behar S, Battler A, Hasdai D. Age, clinical presentation, and outcome of acute coronary syndromes in the Euroheart acute coronary syndrome survey. Eur Heart J 2006;27(7):789-95.

4. Skolnick AH, Alexander KP, Chen AY, Roe MT, Pollack CV, Jr., Ohman EM, Rumsfeld JS, Gibler WB, Peterson ED, Cohen DJ. Characteristics, management, and outcomes of 5,557 patients age > or =90 years with acute coronary syndromes: results from the CRUSADE Initiative. J Am Coll Cardiol 2007;49(17):1790-7.

5. Devlin G, Gore JM, Elliott J, Wijesinghe N, Eagle KA, Avezum A, Huang W, Brieger D. Management and 6-month outcomes in elderly and very elderly patients with high-risk non-ST-elevation acute coronary syndromes: The Global Registry of Acute Coronary Events. Eur Heart J 2008;29(10):1275-82.

6. Simoons ML, Serruys PW, vd Brand M, Bar F, de Zwaan C, Res J, Verheugt FW, Krauss XH, Remme WJ, Vermeer F, et al. Improved survival after early thrombolysis in acute myocardial infarction. A randomised trial by the Interuniversity Cardiology Institute in The Netherlands. Lancet 1985;2(8455):578-82.

7. Zijlstra F, Hoorntje JC, de Boer MJ, Reiffers S, Miedema K, Ottervanger JP, van 't Hof AW, Suryapranata H. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1999;341(19):1413-9.

8. Boersma E, Akkerhuis M, Simoons ML. Primary angioplasty versus thrombolysis for acute myocardial infarction. N Engl J Med 2000;342(12):890-1; author reply 891-2.

9. Hirsch A, Windhausen F, Tijssen JG, Verheugt FW, Cornel JH, de Winter RJ. Long-term outcome after an early invasive versus selective invasive treatment strategy in patients with non-ST-elevation acute coronary syndrome and elevated cardiac troponin T (the ICTUS trial): a follow-up study. Lancet 2007;369(9564):827-35.

10. Nauta S, Deckers J, Akkerhuis M, Lenzen M, Simoons M, Van Domburg R. Changes in clinical profile, treatment, and mortality in patients hospitalised for acute myocardial infarction between 1985 and 2008. PLoS ONE 2011;In Press.

11. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D, Bax JJ, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Poldermans D, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S, Achenbach S, Badimon L, Bertrand M, Botker HE, Collet JP, Crea F, Danchin N, Falk E, Goudevenos J, Gulba D, Hambrecht R, Herrmann J, Kastrati A, Kjeldsen K, Kristensen SD, Lancellotti P, Mehilli J, Merkely B, Montalescot G, Neumann FJ, Neyses L, Perk J, Roffi M, Romeo F, Ruda M, Swahn E, Valgimigli M, Vrints CJ, Widimsky P. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011.

12. Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, Filippatos G, Fox K, Huber K, Kastrati A, Rosengren A, Steg PG, Tubaro M, Verheugt F, Weidinger F, Weis M. 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):2909-45.

13. Coats AJ, Shewan LG. Statement on authorship and publishing ethics in the international journal of cardiology. Int J Cardiol 2011;153(3):239-40.

14. Gharacholou SM, Alexander KP, Chen AY, Wang TY, Melloni C, Gibler WB, Pollack CV, Jr., Ohman EM, Peterson ED, Roe MT. Implications and reasons for the lack of use of reperfusion therapy in patients with ST-segment elevation myocardial infarction: findings from the CRUSADE initiative. Am Heart J 2010;159(5):757-63.

15. Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E, Wallentin L. 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. Lancet 2006;368(9540):998-1004.

16. Fox KA, Clayton TC, Damman P, Pocock SJ, de Winter RJ, Tijssen JG, Lagerqvist B, Wallentin L. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. J Am Coll Cardiol 2010;55(22):2435-45.

17. Yan RT, Yan AT, Tan M, Chow CM, Fitchett DH, Ervin FL, Cha JY, Langer A, Goodman SG. Age-related differences in the management and outcome of patients with acute coronary syndromes. Am Heart J 2006;151(2):352-9.

18. Tran CT, Laupacis A, Mamdani MM, Tu JV. Effect of age on the use of evidence-based therapies for acute myocardial infarction. Am Heart J 2004;148(5):834-41.

19. Newell MC, Henry JT, Henry TD, Duval S, Browning JA, Christiansen EC, Larson DM, Berger AK. Impact of age on treatment and outcomes in ST-elevation myocardial infarction. Am Heart J 2011;161(4):664-72.

20. Jernberg T, Johanson P, Held C, Svennblad B, Lindback J, Wallentin L. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. JAMA 2011;305(16):1677-84.

21. Claessen BE, Kikkert WJ, Engstrom AE, Hoebers LP, Damman P, Vis MM, Koch KT, Baan J, Jr., Meuwissen M, van der Schaaf RJ, de Winter RJ, Tijssen JG, Piek JJ, Henriques JP. Primary percutaneous coronary intervention for ST elevation myocardial infarction in octogenarians: trends and outcomes. Heart 2010;96(11):843-7.

22. Goldberg RJ, McCormick D, Gurwitz JH, Yarzebski J, Lessard D, Gore JM. Age-related trends in short- and long-term survival after acute myocardial infarction: a 20-year population-based perspective (1975-1995). Am J Cardiol 1998;82(11):1311-7.

23. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA, Jr., Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ 2006;333(7578):1091.

24. Ruiz-Bailen M, Aguayo de Hoyos E, Ramos-Cuadra JA, Diaz-Castellanos MA, Issa-Khozouz Z, Reina-Toral A, Lopez-Martinez A, Calatrava-Lopez J, Laynez-Bretones F, Castillo-Parra JC, De La Torre-Prados MV. Influence of age on clinical course, management and mortality of acute myocardial infarction in the Spanish population. Int J Cardiol 2002;85(2-3):285-96.

Chapter 7

Short- and long-term mortality after myocardial infarction in patients with and without diabetes mellitus: changes from 1985 to 2008

Sjoerd T Nauta
Jaap W Deckers
K Martijn Akkerhuis
Ron T van Domburg

Diabetes Care. 2012 Oct;35(10):2043-7

Abstract

Objectives

To study temporal trends in short- and long-term outcome after myocardial infarction according to diabetes status.

Research Design and Methods

We included all 14,434 consecutive patients admitted for ST-segment elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI) at our center between 1985 and 2008. The study patients were compared according to prevalent diabetes. Temporal trend analyses were performed by comparing decades of admission (1985–1990 vs. 1990–2000 vs. 2000–2008).

Results

A total of 2,015 (14%) of the patients had prevalent diabetes. The risk of presenting with diabetes increased from 8% to 17% from 1985 to 2008. Diabetic patients presented with a higher prevalence of cardiovascular risk factors. With time, the use of evidence-based therapies increased in both patients with and without diabetes. Diabetes is associated with an 1.5-fold increased risk of mortality at 20 year follow-up. Ten-year mortality decreased over time, in patients with diabetes from 53% in 1985-90 to 39% in 2000-8 (adjusted HR 0.56, 95%CI: 0.43-0.73) and in those without diabetes from 38% in 1985-90 to 29% in 2000-8 (adjusted HR 0.66, 95%CI: 0.60-0.73; p interaction = 0.83). Patients with diabetes benefitted from a higher 30-day and 10-year absolute survival increase.

Conclusions

Temporal mortality reductions after myocardial infarction between 1985 and 2008 were at least as high in patients with diabetes compared to those without. However, long-term mortality remained higher in diabetic patients. Awareness of the high risk profile of diabetic patients is warranted and might stimulate optimal medical care and their outcome.

Over the last decades, the prevalence of diabetes mellitus in patients with a myocardial infarction (MI) has increased significantly.[1-3] Current figures indicate that cardiovascular events are responsible for 80% of all deaths in patients with diabetes.[3] Within the past 25 years, the management and prognosis of MI has shown substantial progress; clinical evidence and guidelines have introduced thrombolytic therapy, primary percutaneous coronary intervention (PCI), tailored treatment according to individual risk, as well as improved secondary prevention.[1, 4-8] However, some studies have shown that patients with diabetes suffering from acute MI are less likely to receive evidence-based therapies.[9-11] Furthermore, recent data have also suggested that patients with diabetes have not benefitted from the temporal long-term mortality reductions after MI, as opposed to patients without diabetes.[9] Therefore, the need for management that improves long-term post MI survival in patients with diabetes has been underlined.[9]

We aimed to investigate the effect of diabetes on (20 year) mortality, in a cohort of consecutive MI patients hospitalized from 1985 to 2008. Further, we aimed to determine whether temporal improvements in survival after MI have occurred equally in patients with and without diabetes.

Research design and Methods

We included all consecutive patients aged >18 years admitted for ST-segment elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI) to the Intensive Coronary Care Unit (ICCU) of the Thoraxcenter, Erasmus University Medical Center between June 1985 and December 2008.[1]

The primary discharge diagnosis of MI was made in the presence of the following characteristics: chest pain or equivalent symptoms in combination with dynamic ECG changes consistent with MI and a typical serial rise (to at least three times the upper normal value) and fall in serum biochemical markers of cardiac necrosis such as creatine kinase-MB or troponin-T (as of 2002). Patients were diagnosed as STEMI in the presence of ST-segment elevation > 0.1 mV in at least two contiguous peripheral leads, or > 0.2 mV in at least two contiguous precordial leads, and as NSTEMI otherwise.

For patients admitted more than once, only the first hospitalization was taken into account.

Data collection

Diabetes was defined as previously diagnosed by a physician or as receiving medication to lower glucose levels. Trained physicians and nurses accustomed to the use of standardized case report forms collected the data. Demographic characteristics (age, gender), cardiac history (previous MI, PCI or coronary artery bypass surgery (CABG)), risk factors (hypertension, family history, smoking status), anemia (Hemoglobin level <13.0 g/dl in men, <12.0 g/dl in women), renal dysfunction (creatinine >150 μmol/l), and pharmacological and invasive treatment modalities (thrombolysis and PCI) were collected. Hypertension was defined as previously diagnosed by a physician or receiving medication to lower blood pressure. Family history was defined as one or more relatives (parent or sibling) with an MI diagnosed before the age of 60 years.

Follow-up and endpoints

The primary endpoint was all-cause mortality. Survival status and date were assessed through municipal Civil Registries in 2010 and were available for 99% of all patients.

Ethics

This project was carried out in accordance with current rules of ethics and legislature. No additional actions involving the study participants were undertaken because of this registry. Register based studies are approved by the ethical committee of the Erasmus MC and do not require informed consent according to Dutch laws ('WMO').

Statistical Analysis

The study patients were categorized in two groups of patients according to prevalent DM. Patients were stratified in three groups according to the year of hospitalization: 1985-1990; 1990-2000; 2000-2008. These strata were chosen according to important improvements in therapy with complete introduction of thrombolytic therapy in 1990 and a substantial increase in the use of primary PCI since 2000. Categorical variables were summarized as frequencies and percentages. Cochran's statistic with correction for study period was used to calculate p-values. We assessed temporal

mortality trends by comparing one-minus-survival curves that were constructed using the Kaplan–Meier method. The log-rank test was used to compare survival curves. We examined the independent association between decade of hospitalization and mortality according to DM status, using logistic regression for 30-day outcome and the Cox proportional hazards model for long-term outcome. Adjustment was performed for age, gender, previous MI, previous CABG, hypertension, dyslipidemia, family history, smoking status, renal dysfunction, anemia and discharge diagnosis.

Results are reported as odds ratios (OR) –for 30-day mortality– and hazard ratios (HR) –for long-term mortality– and their respective 95% confidence intervals. For all analyses that compared decades of hospitalization we analyzed up to 10 years of follow-up, since longer follow-up is unavailable for patients hospitalized in the last decade (2000-2008). Interaction between DM status and study period and mortality was assessed using multivariable regression models. All statistical tests were 2-tailed, and p-values were considered significant at <0.05. Analysis was performed using SPSS software version 17.0 (SPSS, Chicago, USA).

Results

Patient characteristics

We included 14,434 patients, of whom 2015 (14%) had prevalent DM. For each calendar year, the relative risk of presenting with DM increased by 5%, from a prevalence of 8% in the 1980s to 17% in the last decade. The distribution of risk factors at baseline varied according to DM status and according to decade of admission (Table 1). Patients with DM were older and more often female, and more often had a history of previous MI, hypertension, dyslipidemia, anemia and renal impairment. Patients with DM were less often current smokers, and more often had a discharge diagnosis of NSTEMI.

Medical and invasive care during the study period

The medical care provided to MI patients with and without DM was comparable, with no clinically relevant sex-differences. The use of reperfusion therapy (either by thrombolytic therapy or PCI) increased over time in both groups with STEMI (p<0.001), and STEMI patients with DM were equally likely to receive primary PCI as

Table 1: Baseline characteristics and clinical presentation of patients hospitalized for MI according to diabetes mellitus status

	Diabetes			No diabetes			
	1985-90	1990-2000	2000-8	1985-90	1990-2000	2000-8	Overall P*
No. of patients	174	525	1316	2042	4075	6302	
(% of total in decade)	(8%)	(11%)	(17%)	(92%)	(89%)	(83%)	
Baseline							
Elderly (>65 year)	47%	45%	50%	37%	42%	41%	<0.001
Gender (female)	40%	40%	34%	24%	28%	26%	<0.001
Cardiac history							
Previous MI	49%	39%	32%	41%	32%	31%	<0.01
Previous PCI	11%	13%	18%	8%	10%	19%	0.47
Previous CABG	13%	12%	10%	13%	9%	9%	0.03
Risk factors							
Hypertension	41%	50%	59%	34%	29%	34%	<0.001
Dyslipidemia	9%	30%	50%	11%	21%	32%	<0.001
Family history	20%	21%	28%	24%	23%	29%	0.10
Current smoker	25%	26%	25%	40%	31%	33%	<0.001
Renal dysfunction	11%	15%	13%	9%	9%	6%	<0.001
Anemia	40%	47%	52%	34%	42%	42%	<0.001
Discharge diagnosis							
NSTEMI	55%	41%	57%	57%	58%	46%	<0.001
Reperfusion therapy**							
Primary PCI	8%	14%	82%	4%	12%	85%	0.45
Thrombolytic therapy	25%	47%	7%	32%	54%	8%	0.03
Medication at ICCU discharge							
Statin	0%	N.A.	74%	0%	N.A.	72%	0.12
Aspirin	17%	57%	85%	14%	61%	87%	0.02
Beta-blocker	49%	45%	62%	58%	54%	61%	0.02
ACE inhibitor or ARB	0%	15%	40%	0%	13%	27%	<0.001
Ca-antagonist	52%	30%	10%	54%	31%	9%	0.44
Nitrates	33%	13%	11%	31%	14%	6%	<0.001
Diuretics	41%	21%	16%	25%	12%	7%	<0.001
Antiarrhythmics	7%	3%	4%	7%	4%	3%	0.04

* The overall P-value compares patients with and without diabetes with adjustment for calendar decade of admission.

** STEMI patients only, n=6820.

those without DM. Prescription of evidence-based medical care (class 1A), including aspirin, β-blockers, statins and ACE-inhibitors/angiotensin-receptor blockers (ARBs) also increased over time in both groups. Overall, patients with DM were more likely to receive ACE-inhibitors/ ARBs, and less likely to receive aspirin and β-blockers. However, these differences were small and did not persist over time. Prescription of diuretics was higher in patients with DM. Other medical therapies with a lower level of evidence for the treatment of MI, including calcium-antagonists were prescribed at equal rates in both study groups (Table 1).

Temporal trends in mortality

A total of 106,517 person-years were analyzed. At 10-year follow-up a total of 663 patients with and 3,285 patients without baseline DM had died. The unadjusted risk of 30-day mortality decreased between 1985 and 2008, both in the DM group from 17% in 1985-90 to 5% in 2000-8, and from 10% in 1985-90 to 4% in 2000-8 in the non-DM group (Figure 1). Also, unadjusted 10-year mortality decreased between 1985 and 2008, both in the DM group from 53% in 1985-90 vs. 39% in 2000-8, and in the non-DM group from 38% in 1985-90 to 29% in 2000-8. Patients with DM benefitted from a higher 30-day and long-term absolute survival increase (Figure 1).

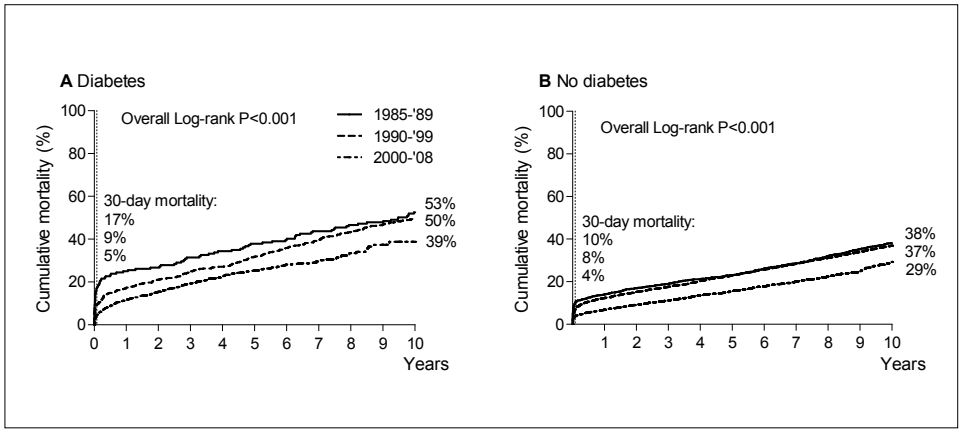

Figure 1: Temporal trends: Kaplan-Meier curves of mortality according to decade of hospitalization in patients with and without diabetes.

Table 2: Temporal trends in 30-day and 10-year mortality in MI patients.

	Diabetes		No diabetes	
Calendar period	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Odds ratios for 30-day mortality				
1985-90	Reference	Reference	Reference	Reference
1990-2000	0.49 (0.30-0.81)	0.40 (0.23-0.69)	0.73 (0.60-0.88)	0.63 (0.52-0.78)
2000-08	0.23 (0.14-0.37)	0.17 (0.10-0.30)	0.37 (0.31-0.45)	0.29 (0.24-0.37)
Hazard ratios for 10-year mortality				
1985-90	Reference	Reference	Reference	Reference
1990-2000	0.88 (0.69-1.1)	0.83 (0.65-1.1)	0.96 (0.88-1.0)	0.96 (0.88-1.1)
2000-08	0.63 (0.50-0.80)	0.56 (0.43-0.73)	0.64 (0.58-0.70)	0.66 (0.60-0.73)

Adjusted for age, gender, previous MI, previous CABG, hypertension, dyslipidemia, family history, smoking status, renal dysfunction, anemia and discharge diagnosis.

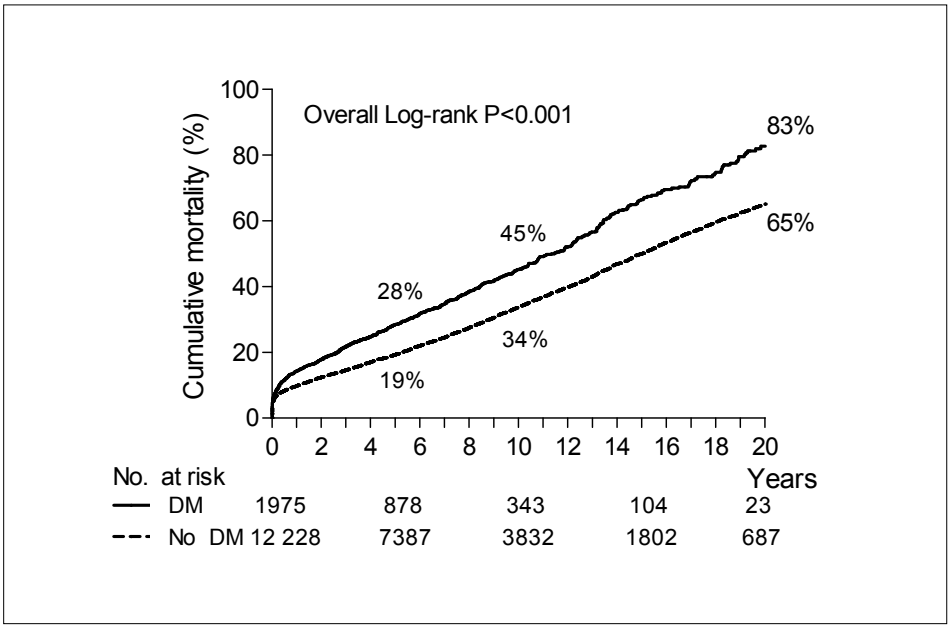

Figure 2: Kaplan-Meier curves of mortality according to diabetes for all MI patients.

From 1985 to 2008, the adjusted risk of 30-day mortality decreased by about 80%, both in the DM group (adjusted OR 0.17, 95%CI: 0.10-0.30), and in the non-DM group (adjusted OR 0.29, 95%CI: 0.24-0.37; Table 2). The risk of 10-year mortality decreased by about 40%, both in the DM group (adjusted HR 0.56, 95%CI: 0.43-0.73) and in the non-DM group (adjusted hazard ratio, HR 0.66, 95%CI: 0.60-0.73; Table 2). There was no significant interaction between DM status and study period (p = 0.39, and p = 0.83 for interaction for 30-day and 10-year mortality, respectively). Hence, the relative risk reductions in 30-day and long-term mortality over the 24-year study period were at least as high for MI patients with diabetes compared to those without.

Diabetes and Mortality

As expected, the risk of mortality was higher in MI patients with prevalent diabetes. The increased mortality risk persisted up to 20-year follow-up (Figure 2). Patients with diabetes had a median survival of 11 years compared to 15 years for those without. Patients in the diabetes group had a 50% increased adjusted long-term mortality risk in all three decades studied (adjusted HR for 10-year mortality = 1.5, 1.5, and 1.4 in 1985-90, 1990-2000, and 2000-8, respectively, p< 0.001 for all).

Conclusions

In this study comprising a cohort of 14,434 patients with acute MI, studied over a period of 24 years, we showed that there is an increasing prevalence of diabetes mellitus in patients with an acute MI. More important, we showed that the temporal reductions in all-cause mortality in patients suffering acute MI, achieved between 1985 and 2008, were at least as high in patients with diabetes as in those without diabetes. This improvement in outcome is most likely related to the fact that, during the study period, the use of MI related medical care improved significantly, both for patients with and without diabetes. Indeed, in the most recent decade, diabetes was not associated with underuse of treatment any more. Finally, we demonstrated that the increased mortality risk associated with diabetes persisted up to 20 years follow-up.

A previous study[12] demonstrated the increasing burden of diabetes in relation to cardiovascular disease mortality in the general population. Relatively few studies have evaluated temporal trends in (long-term) mortality of MI patients with and without diabetes.[9, 11, 13] Moreover, the results of these studies were inconsistent. Two studies[11, 13] show temporal mortality reductions is patients with and without diabetes, while one study[9] concludes that patients with diabetes do not benefit from a reduction in long-term post MI mortality over time.

Treatment

The awareness of the higher cardiovascular risk associated with diabetes has probably intensified cardioprotective treatment in these patients over time. We and others [9-10, 14] showed that from 1985 to 2000 the use of thrombolytic therapy and β-blockers was lower in patients with diabetes compared to those without. Studies[14-15] have shown the effectiveness of these therapies in patients with diabetes. It is therefore encouraging to observe that these inequalities in medical care are no longer present in the last decade of observation. Further, our data showed that in the last decade approximately 40% of diabetic patients were treated with ACE-inhibitors/ARBs at ICCU discharge (a median of 1 to 2 days after admission), a percentage higher than that for non-diabetic patients. ACE-inhibitors/ARBs slow myocardial remodeling and the progression of diabetic nephropathy.[16] This finding is consistent with other recent data.[10, 14] Diabetic patients received diuretics more often compared to non-diabetics, probably due to the higher risk profile in diabetic patients with more frequent hypertension and heart failure.[9]

Mortality

We found a reduction in both 30-day and long-term mortality rates over time for MI patients with and without diabetes. Patients with diabetes benefitted from a higher 30-day and long-term absolute mortality reduction. The relative morality reductions were statistically equal for patients with and without diabetes, which is consistent with another study reporting on patients hospitalized with an MI between 1979 and 1998. [11] Furthermore, other studies in the general population have shown that mortality from coronary heart disease has decreased over the past decades, and some of these studies speculated that patients with diabetes have also benefited

from this reduction.[17-19] The temporal mortality reduction observed in the present study may be a result of several factors, including improved treatment in the acute phase of MI, and increased long-term survival resulting from aggressive secondary prevention.[1,4-5,7-8,20] Although patients with diabetes benefitted at least equally from improved mortality rates over the last 25 years, their absolute long-term mortality remained about 1.5 fold higher compared to patients without diabetes. Therefore optimal medical care for diabetes patients and awareness of their high risk profile remains warranted, and may even further improve outcomes in these patients in the future.

Strengths and limitations

To our knowledge, this is the first paper investigating temporal trends in clinical characteristics, treatment and outcome of MI patients with diabetes over a time period of 24 years and with follow-up data up to 20 years.

Although the present study has unique strengths, some limitations should be mentioned. First, the present data are derived from a single center. Although this could result in a lower external validity, we think that this is unlikely to be the case given the uniform definition and therapeutic modalities of MI. Second, we did not distinguish patients with type I and type II diabetes. Also, our definition of diabetes did not include patients who were diagnosed on the basis of glucose values during hospitalization for acute MI only. Therefore, the real prevalence of diabetes might have been underestimated, alternatively, our definition is not biased by altered glucose levels resulting from the acute event,[21] and allows for better comparison of our results with previous studies. Last, given the nature of diabetes this study reveals important associations but cannot prove causation.

In conclusion, we show that there is an increasing prevalence of diabetes in patients with an MI. Medical care improved substantially for MI patients both with and without diabetes during the 24 years of observation. In the most recent decade, diabetes was not associated with underuse of evidence-based therapies any more, including primary PCI for STEMI. In the study period, outcome improved, and temporal mortality reductions were at least as high in patients with diabetes compared to those without

diabetes. However, the absolute long-term mortality rate remained about 1.5 fold higher in patients with diabetes compared those without. Therefore, optimal medical care for diabetes patients and awareness of their high risk profile remains warranted.

Author contributions

S.N., J.D., K.A. and R.v.D.: conception and design of the study, analysis and interpretation of data, drafting of the manuscript, revising the manuscript critically for important intellectual content and final approval of the manuscript submitted.

S.N. and R.v.D. are the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Nauta ST, Deckers JW, Akkerhuis M, Lenzen M, Simoons ML, van Domburg RT. Changes in Clinical Profile, Treatment, and Mortality in Patients Hospitalised for Acute Myocardial Infarction between 1985 and 2008. PLoS One 2011;6(11):e26917.

2. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med 2010;362(23):2155-65.

3. Nelson SE. Management of patients with type 2 diabetes. Curr Med Res Opin 2011;27(10):1931-47.

4. Simoons ML, Serruys PW, vd Brand M, Bar F, de Zwaan C, Res J, Verheugt FW, Krauss XH, Remme WJ, Vermeer F, et al. Improved survival after early thrombolysis in acute myocardial infarction. A randomised trial by the Interuniversity Cardiology Institute in The Netherlands. Lancet 1985;2(8455):578-82.

5. Hirsch A, Windhausen F, Tijssen JG, Verheugt FW, Cornel JH, de Winter RJ. Long-term outcome after an early invasive versus selective invasive treatment strategy in patients with non-ST-elevation acute coronary syndrome and elevated cardiac troponin T (the ICTUS trial): a follow-up study. Lancet 2007;369(9564):827-35.

6. McManus DD, Gore J, Yarzebski J, Spencer F, Lessard D, Goldberg RJ. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. Am J Med 2011;124(1):40-7.

7. Jernberg T, Johanson P, Held C, Svennblad B, Lindback J, Wallentin L. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. JAMA 2011;305(16):1677-84.

8. Zijlstra F, Hoorntje JC, de Boer MJ, Reiffers S, Miedema K, Ottervanger JP, van 't Hof AW, Suryapranata H. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1999;341(19):1413-9.

9. Cubbon RM, Wheatcroft SB, Grant PJ, Gale CP, Barth JH, Sapsford RJ, Ajjan R, Kearney MT, Hall AS. Temporal trends in mortality of patients with diabetes mellitus suffering acute myocardial infarction: a comparison of over 3000 patients between 1995 and 2003. Eur Heart J 2007;28(5):540-5.

10. Franklin K, Goldberg RJ, Spencer F, Klein W, Budaj A, Brieger D, Marre M, Steg PG, Gowda N, Gore JM. Implications of diabetes in patients with acute coronary syndromes. The Global Registry of Acute Coronary Events. Arch Intern Med 2004;164(13):1457-63.

11. Gandhi GY, Roger VL, Bailey KR, Palumbo PJ, Ransom JE, Leibson CL. Temporal trends in prevalence of diabetes mellitus in a population-based cohort of incident myocardial infarction and impact of diabetes on survival. Mayo Clin Proc 2006;81(8):1034-40.

12. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, Giles WH, Capewell S. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med 2007;356(23):2388-98.

13. Ouhoummane N, Abdous B, Louchini R, Rochette L, Poirier P. Trends in postacute myocardial infarction management and mortality in patients with diabetes. A population-based study from 1995 to 2001. Can J Cardiol 2010;26(10):523-31.

14. Norhammar A, Malmberg K, Ryden L, Tornvall P, Stenestrand U, Wallentin L. Under utilisation of evidence-based treatment partially explains for the unfavourable prognosis in diabetic patients with acute myocardial infarction. Eur Heart J 2003;24(9):838-44.

15. Lowel H, Koenig W, Engel S, Hormann A, Keil U. The impact of diabetes mellitus on survival after myocardial infarction: can it be modified by drug treatment? Results of a population-based myocardial infarction register follow-up study. Diabetologia 2000;43(2):218-26.

16. Standards of medical care in diabetes--2011. Diabetes Care 2011;34 Suppl 1:S11-61.

17. Lipscombe LL, Hux JE. Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995-2005: a population-based study. Lancet 2007;369(9563):750-6.

18. Booth GL, Kapral MK, Fung K, Tu JV. Recent trends in cardiovascular complications among men and women with and without diabetes. Diabetes Care 2006;29(1):32-7.

19. Dale AC, Vatten LJ, Nilsen TI, Midthjell K, Wiseth R. Secular decline in mortality from coronary heart disease in adults with diabetes mellitus: cohort study. BMJ 2008;337:a236.

20. Saaddine JB, Cadwell B, Gregg EW, Engelgau MM, Vinicor F, Imperatore G, Narayan KM. Improvements in diabetes processes of care and intermediate outcomes: United States, 1988-2002. Ann Intern Med 2006;144(7):465-74.

21. Timmer JR, Hoekstra M, Nijsten MW, van der Horst IC, Ottervanger JP, Slingerland RJ, Dambrink JH, Bilo HJ, Zijlstra F, van 't Hof AW. Prognostic value of admission glycosylated hemoglobin and glucose in nondiabetic patients with ST-segment-elevation myocardial infarction treated with percutaneous coronary intervention. Circulation 2011;124(6):704-11.

Chapter 8

Relation of admission glucose levels, short- and long-term (20-Year) mortality after acute myocardial infarction

Jaap W Deckers
Ron T van Domburg
K Martijn Akkerhuis
Sjoerd T Nauta

Am J Cardiol. 2013 Nov 1;112(9):1306-10

Abstract

We examined temporal trends in mortality after myocardial infarction from 1985 to 2008 depending on admission glucose levels. We included 11,324 consecutive patients admitted to our Intensive Coronary Care Unit for myocardial infarction between 1985 and 2008. Patients were categorized into normal, mild and severe hyperglycemia (admission glucose levels <140, 140-200, and ≥200 mg/dl, respectively). Temporal trends were determined using three groups: 1985-1990, 1990-2000 and 2000-2008. The prevalence of hyperglycemia increased from 26% in the 1980s to 49% in the 2000s. The prevalence of hyperglycemia primarily increased in patients without diabetes. Kaplan-Meier mortality was 4%, 8% and 17%, at 30 days, and 64%, 71% and 82%, at 20 years, in patients with normal, mild and severe hyperglycemia, respectively. Compared to normal admission glucose, adjusted 30-day mortality was 3.6-fold higher (95%CI: 2.9-4.3) in patients with severe hyperglycemia. This association was not dependent on diabetic status (p-interaction =0.43), but was dependent on decade of hospitalization with a stronger association from 2000-2008 (adjusted OR 7.7, 95%CI: 5.4-11, p-interaction <0.001). Compared to diabetes, hyperglycemia was a better discriminator for 30-day mortality. Mortality at 30 days fell between 1985 and 2008, however, it declined less in patients with hyperglycemia compared to those with normoglycemia. In conclusion, elevated admission glucose levels are common in patients with myocardial infarction and strongly associated with increased mortality. Mortality fell less from 1985 to 2008 in patients with hyperglycemia compared to those with normoglycemia. Efforts that establish optimal treatment for these patients remain warranted.

Keywords

Myocardial infarction, hyperglycemia, survival, temporal trends.

Introduction

Elevated glucose levels are common in patients hospitalized for acute myocardial infarction (MI) with a prevalence of about 40%.[1-2] Although it has been established that hyperglycemia is associated with adverse outcome during hospitalization,[2-6] only a limited number of studies has examined the long-term effects of hyperglycemia in MI.[3,5] Also, the interplay between diabetes mellitus and hyperglycemia is still unclear. In addition, no previous study has reported on the changes in the impact of hyperglycemia on mortality during the last 25 years. Therefore, the aims of the present study were 1) to determine the association of hyperglycemia at admission with both early and long-term (up to 20 years) mortality after MI, 2) to assess the effect of hyperglycemia in MI patients with diabetes versus those without diabetes, 3) to compare the predictive value of hyperglycemia with that of diabetes for long-term mortality and 4) to study the changes in these relationships over the last three decades.

Methods

We included all patients aged >18 years with a first admission for ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI) to the intensive coronary care unit (ICCU) of the Thoraxcenter, Erasmus Medical Center between June 1985 and December 2008 with an available glucose level at admission.

The primary diagnosis of MI was made in the presence of the following characteristics: chest pain or equivalent symptoms in combination with dynamic ECG changes consistent with MI and a typical serial rise (to at least three times the upper normal value) and fall in serum biochemical markers of cardiac necrosis such as creatine kinase-MB or troponin-T. Patients were diagnosed as STEMI in the presence of ST-segment elevation > 0.1 mV in at least two contiguous peripheral leads, or > 0.2 mV in at least two contiguous pre-cordial leads, and as NSTEMI otherwise.

Trained physicians and nurses accustomed to the use of standardized case report forms collected the patient data. Definitions have previously been described.[7]

Glucose value was determined on admission and was therefore non-fasting. As in the World Health Organization definition, we defined hyperglycemia as admission glucose levels ≥140 mg/dl (7.8 mmol/L).[8] Patients with hyperglycemia were further categorized into mild (140-200 mg/dl L), or severe hyperglycemia (≥200 mg/dl; ≥11.1 mmol/L) similar to ranges used by others previously.[4] Patients were categorized as diabetic if diabetes has previously been diagnosed by a physician, or when they received medication to lower blood glucose levels.[9]

The study endpoint was all-cause mortality at 30 days and at 20 years. Survival date was assessed through municipal Civil Registries which is updated regularly and therefore highly accurate in the Netherlands. Follow-up was available for 99% of all patients.

This project was carried out in accordance with current rules of ethics and legislature. The Ethical Committee of the Erasmus Medical Center waived the need for its approval because register-based studies do not require ethical approval according to Dutch law.

Categorical variables were summarized as percentages, continuous variables as mean and standard deviation. The Chi-square test or student's t-test was used to calculate p-values, as appropriate. Cumulative survival curves according to glucose levels were constructed using the Kaplan–Meier method, and compared by the log-rank test.

Logistic regression was used to model mortality at 30 days and Cox proportional hazards model to examine mortality during long-term follow-up. We separately investigated the independent association between admission glucose levels and mortality, as well as that between diabetes and mortality. Adjustment was performed for age, gender, previous MI, previous coronary artery bypass surgery (CABG), hypertension, hyperlipidemia, family history of coronary artery disease, smoking status, renal dysfunction, anemia, diagnosis (STEMI versus NSTEMI) and decade of hospital admission. A significant interaction term was found for 30-day mortality between admission glucose levels and decade of admission ($p < 0.001$) and for long-term mortality between admission glucose levels and diabetes ($p = 0.012$). Accordingly, additional analysis are presented according to decade of admission and diabetes status.

Temporal trend analyses were performed by comparing decades of admission (i.e. 2000-2008 versus 1990-2000 versus 1985-1990) in patients with and without hyperglycemia, respectively. These strata were chosen according to important improvements in therapy, with complete introduction of thrombolytic therapy in 1990 and a substantial increase in the use of primary PCI since 2000. We used 10-year outcomes for comparing the influence of decades of admission on outcome.

Results are reported as odds ratios (OR) –for 30-day mortality– and hazard ratios (HR) –for long-term mortality– and their respective 95% confidence intervals. All statistical tests were 2-tailed, and p-values were considered significant at <0.05. Analyses was performed using SPSS software version 20.0 (SPSS, Chicago, Ill).

Results

We included 11,324 patients, of whom 4,671 (41%) had elevated admission glucose levels. On average, patients with hyperglycemia were 2 years older and were more often female compared to patients with normal glucose levels. Baseline characteristics and early medical management according to admission glucose levels is shown in Table 1.

Between 1985 and 2008, the prevalence of hyperglycemia at admission increased from 26% in the 1980s to 49% in the 2000s (Figure 1A). This increase was not only due to an increase in the prevalence of diabetes at admission (from 7% to 21%; Figure 1A) but also due to an increase in hyperglycemia among patients without diabetes (from 22% to 42%; Figure 1B). In those patients with diabetes, the prevalence of admission hyperglycemia remained rather constant during the entire study period (decreased from 76% to 73%; Figure 1B).

A total of 83,585 person-years were analyzed and, during this period, 4,449 patients died. There was a gradual increase in 30-day mortality with increasing admission glucose levels (Figure 2). Kaplan-Meier 30-day mortality rates were higher in patients with mild (≥7.8 mmol/L) or severe (≥11.1 mmol/L) hyperglycemia (respectively 8% and 17%) compared to patients with normal admission glucose levels (mortality of 4%; Figure 3). This gradual increase in mortality remained unchanged after adjustment

Table 1: Baseline characteristics and clinical presentation of patients hospitalized for myocardial infarction (MI) according to admission glucose levels

Variable	Admission Glucose			p
	Normal, n = 6,653 (%)	Mild Hyperglycemia, n = 2,917 (%)	Severe Hyperglycemia, n = 1,754 (%)	
Age (yrs)	61 ± 13	63 ± 12	63 ± 12	<0.001
Women	26	28	35	<0.001
Previous MI	35	29	29	<0.001
Previous PCI	14	14	13	0.30
Previous CABG	10	9	8	0.021
Hypertension	35	37	39	<0.001
Diabetes	7	16	45	<0.001
Dyslipidemia	27	23	22	<0.001
Family history of CAD	28	24	20	<0.001
Current smoker	35	33	27	<0.001
Anemia *	23	26	27	<0.001
Renal dysfunction †				<0.001
Normal	29	29	22	
Mild	51	47	44	
Severe	20	24	34	
STEMI	52	65	66	<0.001
Reperfusion therapy ᶻ				
Primary PCI	48	57	54	0.08
Thrombolytic therapy	23	25	23	0.37

CABG = coronary artery bypass surgery; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; PCI = percutaneous coronary intervention.

* Anemia was defined as a hemoglobin level of <12.0 g/dl in women and <13.0 g/dl in men.

† Normal: eGFR 2:90 ml/min; mild: eGFR 60 to 90 ml/min; and severe: eGFR <60 ml/min per 1.73 m^2 of body surface area.

z Patients with STEMI only.

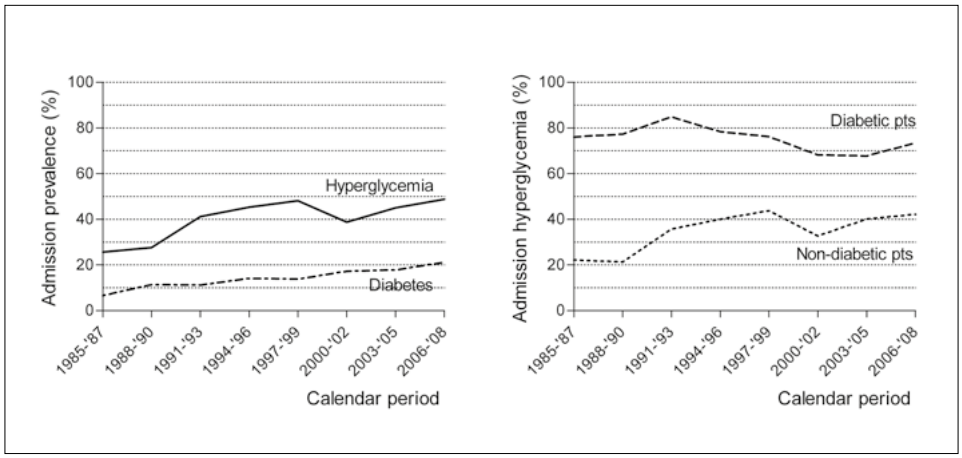

Figure 1: Prevalence of hyperglycemia and diabetes at hospitalization for myocardial infarction according to calendar year. Left: Prevalence of hyperglycemia (admission glucose ≥ 7.8 mmol/L) or diabetes over time. Right: Prevalence of hyperglycemia in subgroups of patients (pts) with and without diabetes.

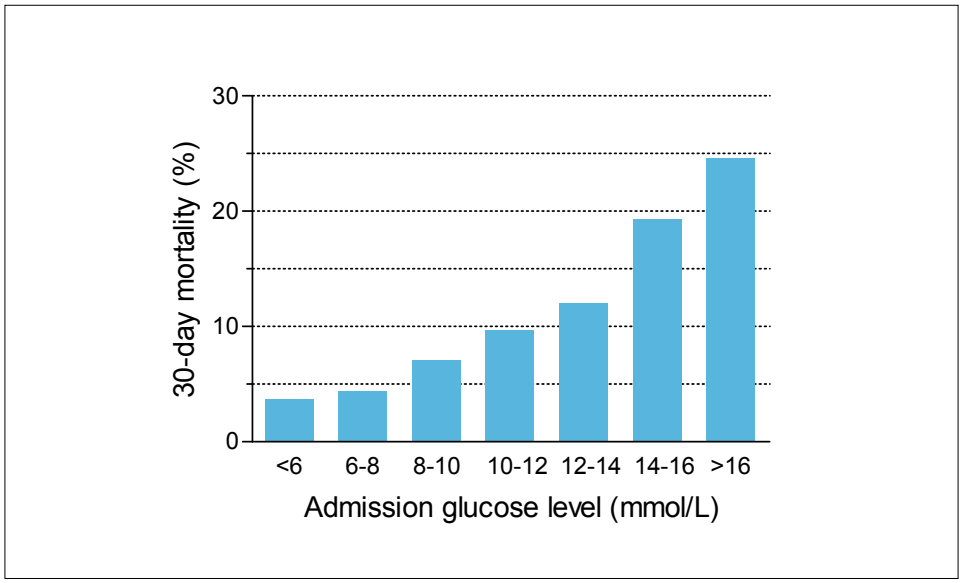

Figure 2: 30-day mortality according to the spectrum of admission glucose levels.

for potential confounders (adjusted OR 1.6, 95%CI: 1.3-2.0 for mild hyperglycemia and 3.6, 95%CI: 2.9-4.3 for severe hyperglycemia) (Table 2). Interestingly, the association between hyperglycemia at admission and 30-day mortality was stronger in patients who were hospitalized from 2000 to 2008 (adjusted OR 2.1, 95%CI: 1.5-2.9 for mild hyperglycemia and 7.7, 95%CI: 5.4-11 for severe hyperglycemia; p for interaction < 0.001) compared to those hospitalized earlier.

Table 2: Adjusted odds ratios and hazard ratios for mortality according to admission glucose levels and presence of diabetes mellitus

Variable	All Patients	Patients With Diabetes
30-Day mortality*		
Hyperglycemia:		
Normal	Reference	Reference †
Mild	1.6 (1.3–2.0)	1.6 (0.79–3.1)
Severe	3.6 (2.9–4.3)	3.4 (1.8–6.2)
Diabetes	1.2 (0.94–1.4)	NA
20-Yr mortality*		
Hyperglycemia:		
Normal	Reference	Reference z
Mild	1.1 (1.1–1.2)	0.88 (0.71–1.1)
Severe	1.6 (1.5–1.8)	1.3 (1.1–e1.5)
Diabetes	1.5 (1.3–1.6)	NA
20-Yr mortality among 30-day survivors*		
Hyperglycemia:		
Normal	Reference	Reference x
Mild	1.1 (1.0–1.2)	0.83 (0.66–1.0)
Severe	1.4 (1.3–1.5)	1.1 (0.89–1.3)
Diabetes	1.5 (1.4–1.7)	NA

NA = not applicable.

* Adjusted for age, gender, previous MI, previous coronary artery bypass surgery, hypertension, hyperlipidemia, family history, smoking status, renal dysfunction, anemia, diagnosis, and decade of hospital admission.

† Interaction for diabetes and admission glucose levels, p = 0.43.

z Interaction for diabetes and admission glucose levels, p = 0.012.

x Interaction for diabetes and admission glucose levels, p = 0.056.

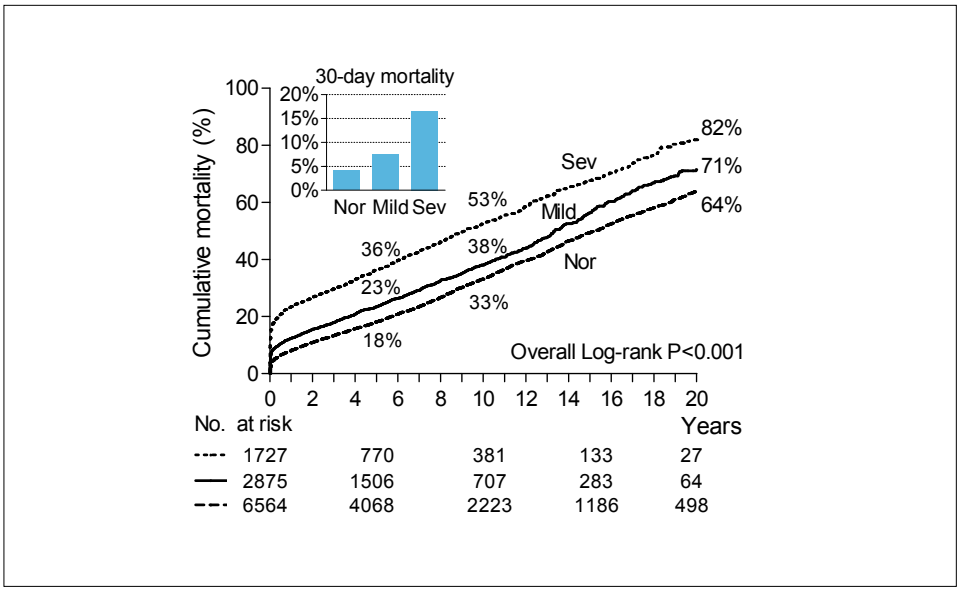

Figure 3: Kaplan-Meier curves of unadjusted mortality according to glucose levels at hospitalization. Sev: severe hyperglycemia (≥11.1 mmol/L), Mild: mild hyperglycemia (7.8-11.0 mmol/L), Nor: normal admission glucose (<7.8 mmol/L).

At 20-year follow-up, Kaplan-Meier mortality rates remained higher in patients with mild or severe hyperglycemia (respectively 71% and 82%) compared to patients with a normal admission glucose levels (mortality of 64%; Figure 3). This gradual increase in long-term mortality was also not affected by adjustment for potential confounders (Table 2).

Hyperglycemia (adjusted OR 2.3, 95%CI: 2.0-2.8) was a stronger predictor than diabetes (adjusted OR 1.2, 95%CI: 0.94-1.4), for 30-day mortality. However, diabetes (adjusted HR among 30-day survivors 1.5, 95%CI: 1.4-1.7) was a stronger predictor for long-term mortality compared to hyperglycemia (HR among 30-day survivors 1.2, 95%CI: 1.1-1.3).

There was significant heterogeneity in the association between admission glucose levels and 20-year mortality depending on diabetic status (p for interaction = 0.012). This indicates that the effect of admission glucose on long-term mortality was

significantly different in patients without compared to those with diabetes, namely increased glucose levels at admission were a strong predictor for long-term mortality in the subgroup without diabetes, but only a weak predictor in those with diabetes (Table 2). This was not the case for 30-day mortality, as the effect of admission glucose on 30-day mortality was similar in patients without and in those with diabetes (p for interaction = 0.43).

Survival after MI improved during the 24-year study period (Table 3). Compared to the period 1985-1990, 30-day mortality was 78% lower in 2000-2008 in patients without hyperglycemia (adjusted OR 0.22, 95%CI: 0.15-0.31) and 50% lower in 2000-2008 in patients with hyperglycemia (adjusted OR 0.50, 95%CI: 0.36-0.88) (p for interaction <0.001). Thus, patients without hyperglycemia benefitted from a higher reduction in 30-day mortality than subjects with hyperglycemia. During the study period, the long-term mortality decline was similar among patients with and without hyperglycemia (p for interaction = 0.49; Table 3).

Table 3: Temporal trends of 30-day and 10-year mortality in myocardial infarction patients

Calendar Period	No Hyperglycemia	Hyperglycemia (Mild and Severe)
ORs for 30-day mortality *,†		
1985-1990	Reference	Reference
1990-2000	0.51 (0.38–0.69)	0.77 (0.57–1.0)
2000-2008	0.22 (0.15–0.31)	0.50 (0.36–0.68)
Hazard ratios for 10-yr mortality*,ᶻ		
1985-1990	Reference	Reference
1990-2000	1.0 (0.92–1.2)	0.93 (0.81–1.1)
2000-2008	0.70 (0.61–0.80)	0.63 (0.53–0.73)

* Adjusted for the same variables as Table 2 and diabetes.
† Interaction for decade and hyperglycemia, p <0.001.
z Interaction for decade and hyperglycemia, p <0.49.

Discussion

In this large, contemporary cohort of acute MI patients, we demonstrated that admission glucose levels were strongly related with mortality up to 20 years during all past three decades. Compared to diabetes, hyperglycemia was a better discriminator for short-term mortality. These results are important because the prevalence of elevated admission glucose levels has increased substantially with time. The prevalence of hyperglycemia at admission increased by 22% from 1985 to almost 50% in 2008. Remarkably, the association between hyperglycemia and short-term mortality was significantly stronger in the present era. Apparently, contemporary treatment has resulted in relatively low mortality in the most healthy subjects. Therefore, although we showed that mortality after acute MI declined between 1985 and 2008, the observed decline was less pronounced in patients with hyperglycemia. Finally, we demonstrated that the association between admission glucose levels and short-term mortality was not dependent on diabetic status; a high admission glucose level was a predictor of mortality in patients with diabetes as well as in those without previously diagnosed diabetes.

Our results expand the current knowledge on the relationship between admission glucose and outcomes over the past decades in patients hospitalized with acute MI. Prior studies reported an association between elevated glucose on admission and short-term mortality in acute MI patients during limited calendar periods.[2-6,10-11] Similar to our findings, most of these studies also noted that this association is not dependent on diabetic status.[4-5,10-11] However, no previous study has compared different decades of hospitalization. This is important, not only because treatment of acute MI has changed substantially during the past three decades, but also because patient characteristics at presentation have evolved.[12] In the upper 2000s, 96% of our STEMI patients were actually treated with primary PCI.[12] Interestingly, hyperglycemia proved to be a significantly stronger predictor of adverse 30-day outcome after MI in the last decade than 25 years ago.

Hyperglycemia has potential as a treatment target in acute MI patients. Unfortunately, results of acute interventions in glucose metabolism in patients with MI are currently inconclusive.[13-16] Thus, further randomized controlled trials are needed in this patient population.[1,17]

In our study patients were categorized into admission glucose level <140, 140-200 and >200 mg/dL (<7.8, 7.8-11.0, and ≥11.1 mmol/L, respectively). Since admission glucose levels were found to be a powerful predictor of short-term mortality with a better discriminative ability than diabetes and independent of other clinical patient factors or potential confounders, risk prediction models after MI could be improved by including admission glucose level. This might affect treatment decisions in individual patients by the use of more intensive strategies in such high risk patients.

A unique observation of the present study is the 20 year long follow-up period, which is much longer than in previous studies.[3-5] Although hyperglycemia remained associated with increased long-term mortality, the actual presence of diabetes at admission proved to be a better predictor in the long term. Diabetes is a chronic disease, and its presence therefore reflects a long-term abnormal glucose metabolism, whereas admission hyperglycemia could resolve during follow-up.[6] Hyperglycemia was not associated with long-term mortality in patients with diabetes. It is conceivable that part of the association between elevated admission glucose and long-term mortality is mediated by hyperglycemia patients who develop diabetes in the near future.[3] As such, admission hyperglycemia could still function as an important discriminator of long-term mortality in non-diabetic patients.[3]

Finally, another distinctive aspect of our study includes the observed temporal trends. Importantly, a substantial increase in the prevalence of hyperglycemia at admission for acute MI was observed during the 24 year study period. This occurred in patients without diabetes and therefore was not solely the result of an increase in the prevalence of diabetes.[9] Still, it might be that both the increase in admission hyperglycemia as well as in diabetes prevalence is mediated by an increasing prevalence of insulin resistance resulting from higher population levels of adiposity, sarcopenia and physical inactivity.[18-19]

We have previously shown that 30-day mortality in subjects hospitalized for acute MI declined between 1985 and 2008.[12] We have now found that, in patients with admission hyperglycemia, mortality fell significantly less than in patients with normoglycemia at admission. Although the temporal mortality decline in patients with normoglycemia is encouraging, improved short term outcome in patients with hyperglycemia is warranted.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Deedwania P, Kosiborod M, Barrett E, Ceriello A, Isley W, Mazzone T, Raskin P. Hyperglycemia and acute coronary syndrome: a scientific statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2008;117:1610-1619.

2. Goyal A, Mehta SR, Gerstein HC, Diaz R, Afzal R, Xavier D, Zhu J, Pais P, Lisheng L, Kazmi KA, Zubaid M, Piegas LS, Widimsky P, Budaj A, Avezum A, Yusuf S. Glucose levels compared with diabetes history in the risk assessment of patients with acute myocardial infarction. Am Heart J 2009;157:763-770.

3. Timmer JR, Hoekstra M, Nijsten MW, van der Horst IC, Ottervanger JP, Slingerland RJ, Dambrink JH, Bilo HJ, Zijlstra F, van 't Hof AW. Prognostic value of admission glycosylated hemoglobin and glucose in nondiabetic patients with ST-segment-elevation myocardial infarction treated with percutaneous coronary intervention. Circulation 2011;124:704-711.

4. de Mulder M, Cornel JH, van der Ploeg T, Boersma E, Umans VA. Elevated admission glucose is associated with increased long-term mortality in myocardial infarction patients, irrespective of the initially applied reperfusion strategy. Am Heart J 2010;160:412-419.

5. Beck JA, Meisinger C, Heier M, Kuch B, Hormann A, Greschik C, Koenig W. Effect of blood glucose concentrations on admission in non-diabetic versus diabetic patients with first acute myocardial infarction on short- and long-term mortality (from the MONICA/KORA Augsburg Myocardial Infarction Registry). Am J Cardiol 2009;104:1607-1612.

6. Kosiborod M, Inzucchi SE, Krumholz HM, Xiao L, Jones PG, Fiske S, Masoudi FA, Marso SP, Spertus JA. Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. Circulation 2008;117:1018-1027.

7. Nauta ST, Deckers JW, van Domburg RT, Akkerhuis KM. Sex-related trends in mortality in hospitalized men and women after myocardial infarction between 1985 and 2008: equal benefit for women and men. Circulation 2012;126:2184-2189.

8. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. 2006. ISBN 978 92 4 159493 6.

9. Nauta ST, Deckers JW, Akkerhuis KM, van Domburg RT. Short- and long-term mortality after myocardial infarction in patients with and without diabetes: changes from 1985 to 2008. Diabetes Care 2012;35:2043-2047.

10. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet 2000;355:773-778.

11. Kadri Z, Danchin N, Vaur L, Cottin Y, Gueret P, Zeller M, Lablanche JM, Blanchard D, Hanania G, Genes N, Cambou JP. Major impact of admission glycaemia on 30 day and one year mortality in non-diabetic patients admitted for myocardial infarction: results from the nationwide French USIC 2000 study. Heart 2006;92:910-915.

12. Nauta ST, Deckers JW, Akkerhuis M, Lenzen M, Simoons ML, van Domburg RT. Changes in clinical profile, treatment, and mortality in patients hospitalised for acute myocardial infarction between 1985 and 2008. PLoS One 2011;6:e26917.

13. Cheung NW, Wong VW, McLean M. The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. Diabetes Care 2006;29:765-770.

14. Malmberg K, Ryden L, Wedel H, Birkeland K, Bootsma A, Dickstein K, Efendic S, Fisher M, Hamsten A, Herlitz J, Hildebrandt P, MacLeod K, Laakso M, Torp-Pedersen C, Waldenstrom A. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J 2005;26:650-661.

15. Mehta SR, Yusuf S, Diaz R, Zhu J, Pais P, Xavier D, Paolasso E, Ahmed R, Xie C, Kazmi K, Tai J, Orlandini A, Pogue J, Liu L. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. JAMA 2005;293:437-446.

16. Selker HP, Beshansky JR, Sheehan PR, Massaro JM, Griffith JL, D'Agostino RB, Ruthazer R, Atkins JM, Sayah AJ, Levy MK, Richards ME, Aufderheide TP, Braude DA, Pirrallo RG, Doyle DD, Frascone RJ, Kosiak DJ, Leaming JM, Van Gelder CM, Walter GP, Wayne MA, Woolard RH, Opie LH, Rackley CE, Apstein CS, Udelson JE. Out-of-hospital administration of intravenous glucose-insulin-potassium in patients with suspected acute coronary syndromes: the IMMEDIATE randomized controlled trial. JAMA 2012;307:1925-1933.

17. Kosiborod M, McGuire DK. Glucose-lowering targets for patients with cardiovascular disease: focus on inpatient management of patients with acute coronary syndromes. Circulation 2010;122:2736-2744.

18. Amati F, Dube JJ, Coen PM, Stefanovic-Racic M, Toledo FG, Goodpaster BH. Physical inactivity and obesity underlie the insulin resistance of aging. Diabetes Care 2009;32:1547-1549.

19. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.

Part III

Gender differences

Chapter 9

Sex-related trends in mortality in hospitalized men and women after myocardial infarction between 1985 and 2008: equal benefit for women and men

Sjoerd T Nauta
Jaap W Deckers
Ron T van Domburg
K Martijn Akkerhuis

Circulation. 2012 Oct 30;126(18):2184-9

Abstract

Background

We aimed to study sex-related differences in temporal trends in short- and long-term mortality from 1985 to 2008 in patients hospitalized for acute myocardial infarction (MI).

Methods and Results

We included a total of 14,434 consecutive patients admitted to our Intensive Coronary Care Unit between 1985 and 2008 for MI. A total of 4,028 (28%) patients were women. Women were more likely to present with a higher risk profile and equally likely to receive pharmacological and invasive reperfusion therapy compared to men. Women had a higher unadjusted mortality rate at 30-days (OR 1.3, 95%CI: 1.1-1.5) and during 20-years (HR 1.1, 95%CI: 1.0-1.2) follow-up. After adjustment for baseline characteristics, 30-day mortality was equal (adjusted OR 1.0, 95%CI: 0.85-1.2), but the hazard for 20-year mortality was lower (adjusted HR 0.77, 95%CI: 0.66-0.90) in women compared to men. For 30-day mortality, there was no significant interaction between sex and age, diagnosis or diabetes. Survival improved between 1985 and 2008. Temporal mortality reductions between 1985 and 2008 were at least as high in women compared to men with MI, both for 30-day mortality and long-term mortality hazard.

Conclusions

The fact that adjusted mortality rates for both the men and women treated for myocardial infarction in an Intensive Coronary Care Unit were similar and declined markedly over a 24-year period suggests that both sexes benefit from the evidence-based therapies that have been developed and implemented during this time period.

Keywords

Sex, Prognosis, Myocardial Infarction

Introduction

Cardiovascular disease is the number one cause of death in women and, the total number of women who die from cardiovascular disease is higher than this number in men.[1] Myocardial infarction (MI) is the major cardiovascular cause of death in both sexes. Since 1985, considerable progress has been made in the management of MI and treatment outcomes; clinical evidence has guided the introduction of thrombolytic therapy, primary percutaneous coronary intervention (PCI), tailored treatment according to individual risk and improved secondary prevention.[2-4]

It has been suggested that women with an MI may have benefitted less from the improvements in treatment and outcome that have occurred over the past 25 years because they were underrepresented in clinical trials.[5-9] However, no previous study has compared sex differences over a calendar period that included such marked changes in treatment and outcome of MI.

Furthermore, due to the progress made in the management of MI, at present, most patients hospitalized with MI survive until discharge.[4] For that reason, long-term outcomes after MI become increasingly important. However, only a limited number of studies have reported mortality rates after MI according to sex with a follow-up duration longer than one year.[10-12] Awareness of sex-differences in patient characteristics, treatment and outcome may eventually improve the clinical management and survival after MI in both women and men.

Therefore, the aims of the present study were to determine sex-related differences in baseline characteristics and treatment, as well as short-term mortality and long-term (20 year) mortality. Furthermore, we investigated whether the changes in mortality after MI that occurred between 1985 and 2008 were different for women and men. For this purpose, we analyzed 14,434 consecutive MI patients admitted to the Intensive Coronary Care Unit (ICCU) of the Erasmus Medical Center from 1985 to 2008.

Methods

We included all consecutive patients aged >18 years with a first admission for ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI) to the ICCU of the Thoraxcenter, Erasmus University Medical Center between June 1985 and December 2008.[13] No other inclusion or exclusion criteria were used.

The diagnosis of MI was made in the presence of the following characteristics: chest pain or equivalent symptoms in combination with dynamic ECG changes consistent with MI and a typical serial rise (to at least three times the upper normal value) and fall in serum biochemical markers of cardiac necrosis such as creatine kinase-MB or troponin-T. Patients were diagnosed as STEMI in the presence of ST-segment elevation > 0.1 mV in at least two contiguous peripheral leads, or > 0.2 mV in at least two contiguous pre-cordial leads, and as NSTEMI otherwise.

Trained physicians and nurses accustomed to the use of standardized case report forms collected the data. Demographic characteristics (age, sex), cardiac history (previous MI, PCI or coronary artery bypass surgery, CABG), risk factors (hypertension, diabetes, hyperlipidemia, family history of coronary artery disease, smoking status), anemia (hemoglobin level < 12.0 g/dl in women, <13.0 g/dl in men), renal dysfunction, and pharmacological and invasive treatment modalities (thrombolysis and PCI) were collected. Renal dysfunction was defined according to glomerular filtration rate (eGFR) estimated with the Modification of Diet in Renal Disease (MDRD) equation.[14] Hypertension, hyperlipidemia and diabetes were defined as previously diagnosed by a physician or receiving medication to lower blood pressure, cholesterol or glucose levels, respectively. Family history was defined as one or more relatives (parent or sibling) with an MI diagnosed before the age of 60 years.

The study endpoint was all-cause mortality at 30 days and during 20 years. Survival date was assessed through municipal Civil Registries which is updated regularly and therefore highly accurate in the Netherlands. Follow-up was available for 98% of all patients.

This project was carried out in accordance with current rules of ethics and legislature. The Ethical Committee of the Erasmus Medical Center waived the need for its approval because register-based studies do not require ethical approval according to Dutch law.

Statistical Analysis

Categorical variables were summarized as percentages, continuous variables as mean and standard deviation. The Chi-square test or student's t-test was used to calculate p-values, as appropriate. To ease the display of descriptive results, sex-ratios for each decade were computed to compare women and men. Cumulative survival curves according to sex were constructed using the Kaplan–Meier method, and compared by the log-rank test.

We examined the independent association between sex and mortality or mortality hazard using logistic regression for 30-day outcome and the Cox proportional hazards model for long-term outcome, respectively. Adjustment was performed for the baseline variables age, previous MI, previous CABG, hypertension, diabetes, hyperlipidemia, family history of coronary artery disease, smoking status, renal dysfunction, anemia, diagnosis and decade of hospital admission. Proportionality of hazards was tested graphically by inspection of log–log survival curves and by a formal test of proportionality based on Schoenfeld residuals. In the multivariable model, a multiple imputation algorithm with five imputations was used to handle the 2229 (15%) and 2347 (16%) patients in whom anemia status or renal function, respectively, was missing. Multiple imputation methods are known to be superior to complete case analyses.[15] In line with the literature, the association between sex and 30-day mortality was also examined in subgroups according to age (<65 year and ≥65 year), diagnosis (STEMI or NSTEMI) and diabetes status. We assessed heterogeneity within these subgroups with a statistical test for interaction.

Similar multivariable models were used to assess changes in mortality from 1985 to 2008 in women and men, separately. For this purpose, calendar periods of 3 years were compared. Results are reported as odds ratios (OR) –for 30-day mortality– and hazard ratios (HR) –for long-term mortality– and their respective 95% confidence

intervals. All statistical tests were 2-tailed, and p-values were considered significant at <0.05. To address multiplicity of testing for heterogeneity, p-values for interaction were considered significant at <0.017 (0.05 divided by three, as we defined subgroups according to three characteristics).[16] Analysis was performed using SPSS software version 20.0 (SPSS, Chicago, Ill).

Results

Patient characteristics

We included 14,434 patients, of whom 4,028 (28%) were women. On average, women were 5 years older. In addition, compared to men, women more often had hypertension, diabetes mellitus, renal dysfunction or anemia, were less often current smokers, and less often had a history of prior MI, PCI or CABG, or a diagnosis of STEMI (Table 1). From 1985 to 2008, the patients became older on presentation (Figure 1), and were

Table 1: Baseline characteristics and clinical presentation of patients hospitalized for MI according to gender.

	Women (n = 4028)	Men (n = 10,406)	P	Gender-ratios*		
				1985-'90	1990-'00	2000-'08
Characteristics						
Age (years)	65 (12)	60 (12)	<0.001			
Elderly (>65 y)	55%	37%	<0.001	1.7	1.4	1.5
Cardiac history						
Previous MI	30%	35%	<0.001	0.80	0.77	0.94
Previous PCI	13%	15%	0.032	0.82	0.74	0.94
Previous CABG	8%	10%	<0.01	0.87	0.62	0.96
Risk factors						
Hypertension	43%	32%	<0.001	1.3	1.4	1.3
Diabetes	18%	12%	<0.001	2.0	1.6	1.4
Hyperlipidemia	28%	27%	0.62	0.85	1.1	1.0
Family history	27%	26%	0.11	1.3	1.1	1.0
Current smoker	26%	35%	<0.001	0.60	0.70	0.81
Renal dysfunction †			<0.001			
Normal	20%	32%		0.31	0.68	0.66
Mild dysfunction	46%	50%		0.79	0.92	1.0
Impaired	33%	18%		2.0	1.7	1.9
Anemia	49%	39%	<0.001	1.2	1.2	1.4
Discharge diagnosis						
STEMI	43%	49%	<0.001	0.87	0.82	0.90

* Gender-ratios show the percentage of women with the specific characteristic divided by the corresponding percentage in men within a specified decade.

† Normal, estimated GFR (eGFR) >= 90 ml/min; Mild dysfunction, eGFR 60-90 ml/min; Impaired, eGFR <60 ml/ min per m^2 of body-surface area.

more likely to have diabetes or anemia (p for trend < 0.001 for all). Age at presentation increased uniformly in both women and men, therefore the age difference between women and men remained about 5 years during the study period. However, due to the changes in prevalence of risk factors over time, the cardiovascular risk profile at baseline in women became more comparable to that in men in the most recent period (Table 1).

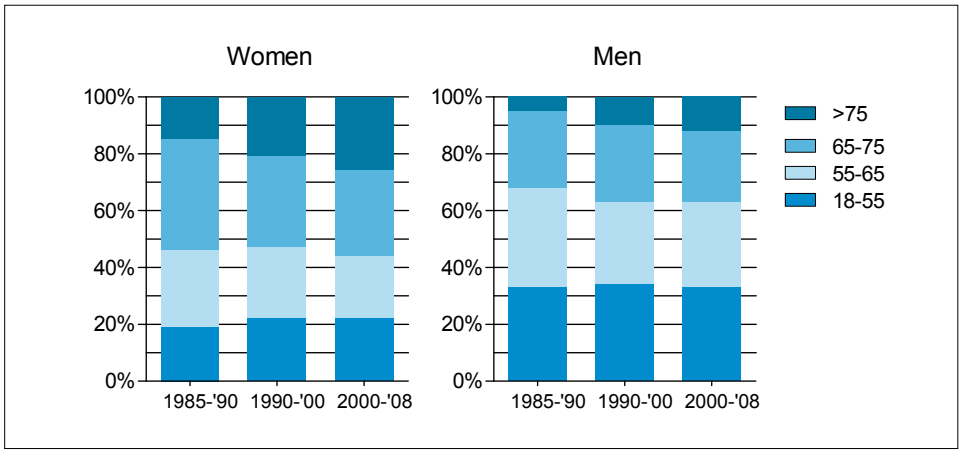

Figure 1: Distribution of study population according to age and study period.

Table 2: Initial and early management of patients hospitalized for MI according to gender.

	Women	Men	P
No. of patients	4028	10,406	
Invasive treatment			
Thrombolytic therapy *	22%	24%	0.13
PCI*	53%	53%	0.80
Medication at ICCU discharge			
Statins †	70%	73%	<0.01
Aspirin	67%	68%	0.39
β-blockers	56%	59%	<0.001
ACE-I/ARB ‡	22%	24%	0.044
Ca-antagonist	24%	22%	0.044
Nitrates	14%	12%	<0.01
Diuretics	15%	12%	<0.001
Antiarrhythmics	3%	4%	<0.01

* STEMI patients only. ICCU, intensive coronary care unit.
† Patients from 2000 to 2008 only.
‡ Patients from 1990 to 2008 only.

Patient management

Overall, sex disparities in initial and early medical management were limited (Table 2). Women with STEMI were equally likely to receive reperfusion therapy (by either thrombolytic therapy or PCI). With time, more patients received guideline-based therapy. No new sex disparities in use of evidence-based management became apparent during the study period.

Sex and mortality

A total of 106,517 person-years were analyzed. During the study period, 1,544 women and 3,708 men died. At 30 days, unadjusted mortality rates were higher in women than in men (7% vs. 6%; OR 1.3, 95%CI: 1.1-1.5; Figure 2). However, after adjustment for age, the difference in 30-day mortality between women and men was no longer present (adjusted OR 1.0, 95%CI: 0.89-1.2). After adjustment for all potential confounders, 30-day mortality remained the same (adjusted OR 1.0, 95%CI: 0.85-1.2; Table 3).

There was no heterogeneity in the association between sex and 30-day mortality in subgroups according to age (p interaction = 0.41), diagnosis (p interaction = 0.49) or diabetes (p interaction = 0.019) (with significance at $p < 0.017$ to address for multiplicity of testing).

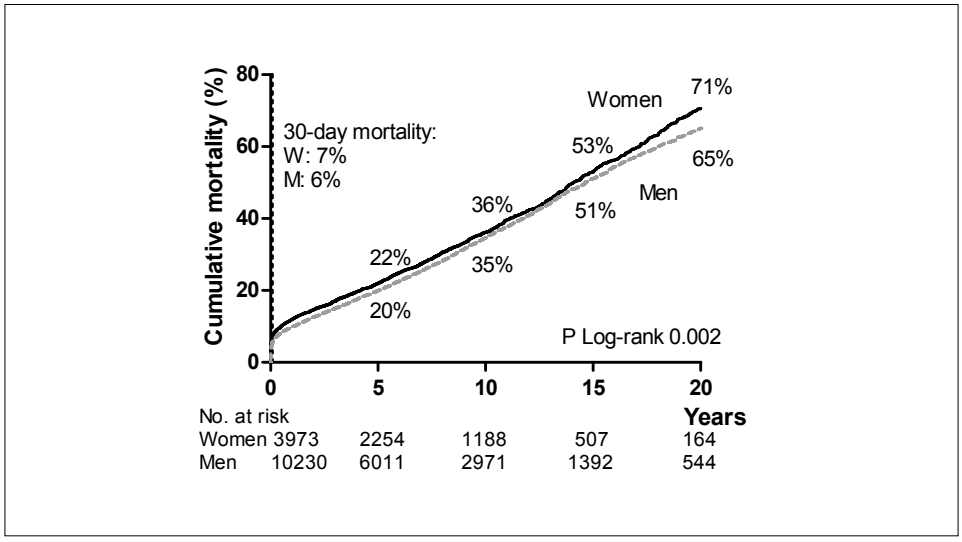

Figure 2: Kaplan-Meier curves of unadjusted 20-year mortality according to gender.

At 20-year follow-up, unadjusted mortality was slightly higher in women (71% vs. 65%, HR 1.1, 95%CI: 1.0-1.2; Figure 2), but the adjusted 20-year mortality hazard was significantly lower in women compared to men (adjusted HR 0.77, 95%CI: 0.66-0.90; Table 3).

Table 3: Unadjusted and adjusted odds ratios for 30-day mortality and hazard ratios for 20-year mortality in women vs. men.

	Unadjusted	Adjusted*			
	1985-2008	1985-2008*	1985-'90*	1990-'00*	2000-'08*
30-day mortality					
All patients	1.3 (1.1-1.5)	1.0 (0.85-1.2)	0.91 (0.64-1.3)	1.0 (0.79-1.3)	1.0 (0.79-1.3)
<65	1.1 (0.88-1.5)	1.1 (0.82-1.4) †	0.82 (0.46-1.5)	1.5 (1.0-2.3)	1.0 (0.57-1.6)
>65	1.1 (0.92-1.3)	0.95 (0.78-1.2)	0.91 (0.59-1.4)	0.83 (0.60-1.2)	1.0 (0.77-1.4)
STEMI	1.5 (1.2-1.8)	1.0 (0.85-1.3) ‡	0.93 (0.60-1.4)	1.0 (0.71-1.4)	1.1 (0.82-1.5)
NSTEMI	1.2 (0.91-1.5)	1.0 (0.72-1.3)	0.91 (0.52-1.6)	1.1 (0.72-1.7)	0.83 (0.50-1.4)
No DM	1.2 (1.0-1.4)	0.92 (0.77-1.1) §	0.80 (0.55-1.2)	0.91 (0.68-1.2)	1.0 (0.74-1.3)
DM	2.0 (1.4-2.8)	1.5 (1.1-2.2)	1.7 (0.69-4.3)	2.1 (1.1-4.2)	1.2 (0.68-2.1)
20-year mortality					
All patients	1.1 (1.0-1.2)	0.77 (0.66-0.90)	0.79 (0.67-0.93)	0.65 (0.50-0.84)	0.80 (0.67-1.0) ‖

* Adjusted for age, previous MI, previous CABG, hypertension, diabetes, hyperlipidemia, family history, smoking status, renal dysfunction, anemia, discharge diagnosis and decade of hospital admission.

† interaction age and sex p = 0.41.

‡ interaction STEMI and sex p = 0.49.

§ interaction diabetes and sex p = 0.019.

‖ 10-year mortality hazard.

Secular trends in mortality

Compared to 1985-'87, 30-day mortality after MI in 2006-'08 was significantly and substantially lower in both sexes (Figure 3). The Kaplan-Meier estimate of 30-day mortality decreased from 10% in 1985-'87 to 4% in 2006-'08. In women, adjusted 30-day mortality was 83% lower in 2006-'08 compared to 1985-'87. In men, adjusted 30-day mortality was 73% lower in 2006-'08 compared to 1985-'87 (p for interaction = 0.30).

The Kaplan-Meier estimate of 5-year mortality decreased from 24% in 1985-'87 to 14% in 2006-'08. In both women and men, the adjusted 5-year mortality hazard was 52% lower in 2006-'08 compared to 1985-'87 (p for interaction = 0.16). Thus, improvement in short- and long-term mortality during the 24-year study period was similar in women and men.

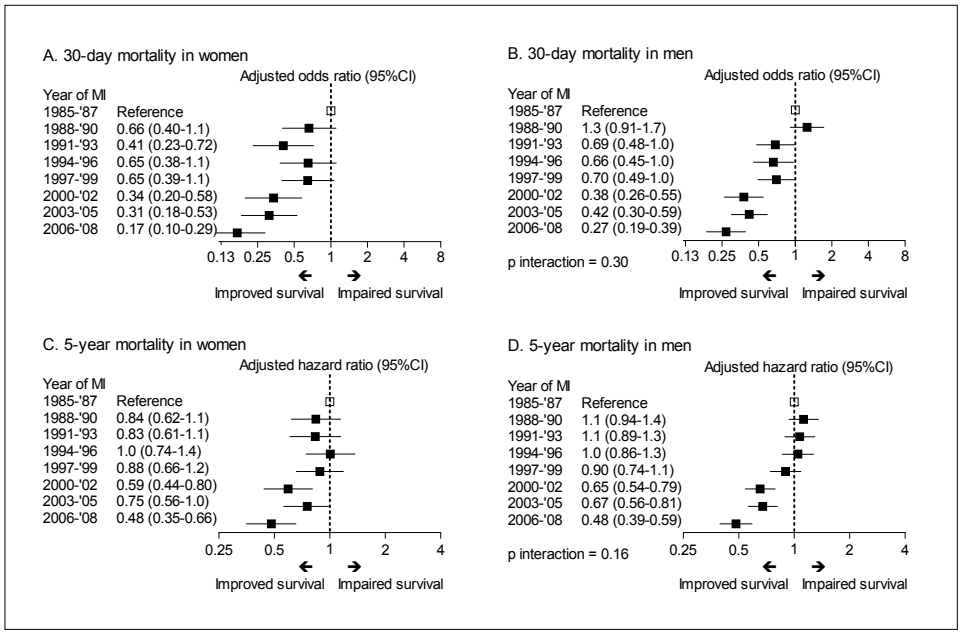

Figure 3: Temporal trends according to gender and follow-up duration. Outcome of patients who were hospitalized for MI during three-year calendar periods is compared to outcome of patients who were hospitalized in 1985-87. P-values for interaction between gender and year of MI are shown.

Discussion

This study demonstrates that, during an observation period of 24 years, women hospitalized for an acute MI were more likely to present with a higher risk profile but were equally likely to receive pharmacological and invasive reperfusion therapy compared to men. The higher risk profile was mainly determined by an average age difference of 5 years between women and men. Women and men had the same adjusted mortality rates at 30 days, while during 20 years of follow-up the mortality hazard was lower in women. Importantly, temporal improvements in 30-day mortality and long-term mortality hazard from 1985 to 2008 were substantial and at least as high in women as in men.

We showed that women were older and therefore presented with a higher risk profile compared to men, which is in line with previous studies.[11, 17-22] In our multivariable analysis, these differences fully account for the higher unadjusted mortality in women compared to men. Therefore, it is unlikely that other differences between women and men, including differences in biological factors and in treatment, caused the higher unadjusted mortality rate in women.

Previous analyses have reported that in certain subgroups, such as younger patients, the mortality risk may be a higher in women compared with men.[23, 24] Data from the US National Registry of Myocardial Infarction collected in the 1990s indicated an increased in-hospital mortality risk for young women compared with young men, with no mortality difference in the older population.[24] In our analysis, mortality appeared higher in young women compared to young men in the same calendar period (i.e. the 1990s), however, this age dependent sex gap completely disappeared in the next decade. Furthermore, no significant interaction was detected between sex and age in case the patients of all three decades were pooled together. In this study there was also no significant interaction between sex and diagnosis. Most MI studies do not report significant interaction between sex and type of MI,[20, 25, 26] it therefore is likely that our conclusions are robust for STEMI and NSTEMI patients.

We show borderline significant heterogeneity in the association between sex and 30-day mortality in subgroups according to baseline diabetes, such that among patients

with diabetes female sex might be associated with increased 30-day mortality. This finding is in part consistent with prior studies that noted increased risk of adverse events following MI among women vs. men with diabetes.[27, 28] Clinical trials in the diabetic population might help to identify specific therapies to reduce their increased risk of death.

Our study is unique in that it shows long-term (20 year) mortality depending on sex. Once admitted to the hospital, the adjusted hazard for long-term mortality is more favorable in women compared to men, similar to findings of their survival advantage in the general population. Although several studies have also shown that women are at a lower risk up to 12 months after the onset of MI,[18, 25] our adjusted analysis demonstrates – for the first time – that this assertion can be extended for up to 20 years in a contemporary population.

Contrary to previous studies that showed that mortality decreased less over time in women compared with men,[6-8] we now show that the improvement in outcome after MI over the last 24 years is at least as substantial in women as it is in men. In this respect, it should be noted that the calendar period that we studied differed from those in previous studies. Our study was initiated in 1985, at that time thrombolysis became standard therapy, and extents to the present era in which PCI became the standard therapy.[2] The conflicting observation between our study demonstrating that mortality improved over time at least as much in women as in men and previous studies that showed more improvement in men may be due to the relatively short time frame of these previous studies.[6-8] In addition, in the present study sex disparities in medical management were limited. This might have contributed to relatively favorable outcomes in women, compared to studies in countries were women less often receive evidence based management.[9] As such, the present study might demonstrate a best case scenario.

Strengths and limitations

To our knowledge, this is the first study investigating temporal trends in clinical characteristics, treatment and outcome of patients with an MI according to sex over a time period of 24 years and with follow-up data up to 20 years. Although the present study has unique strengths, some limitations should be mentioned. Firstly, given the

nature of sex this study reveals important associations but cannot prove causation. Secondly, this study is based on hospitalized patients only and did not account for possible sex differences in out-of-hospital deaths prior to admission. Finally, the present data are derived from a single center.

Conclusion

We showed that, among patients hospitalized for acute MI, women are more likely to present with a higher risk profile and were almost as likely as men to receive contemporary medical therapy. After adjustment for baseline differences, 30-day mortality was equal among women and men, while the adjusted 20-year mortality hazard was lower in women. Importantly, temporal improvements in short- and long-term mortality from 1985 to 2008 were substantial and similar for women and men. The temporal trends are encouraging and suggest that both men and women will benefit from further improvements in care for acute myocardial infarction.

Disclosures

None.

Clinical Perspective

During the past decades, medical management and outcomes of acute myocardial infarction have improved substantially. It has been suggested that women with a myocardial infarction have benefitted less from these improvements in treatment and outcome when compared to men, because they were underrepresented in clinical trials. With the present study, however, we are the first to test this suggestion over a 24 year study period. We demonstrate that adjusted short- and long-term mortality rates were similar and declined markedly and equally in women compared to men during the 24 years studied. Furthermore, we also present long-term mortality data, up to 20 years following the myocardial infarction, which is sparse. This study is important because it helps to direct both further research and further management, in which women deserve to be treated with the same evidence-based care. In addition, the observed temporal trends are encouraging and suggest that both men and women will benefit from further improvements in care for acute myocardial infarction.

References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Executive summary: heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation 2012;125(1):188-97.

2. Simoons ML, Serruys PW, vd Brand M, Bar F, de Zwaan C, Res J, Verheugt FW, Krauss XH, Remme WJ, Vermeer F, Lubsen J. Improved survival after early thrombolysis in acute myocardial infarction. A randomised trial by the Interuniversity Cardiology Institute in The Netherlands. Lancet 1985;2(8455):578-82.

3. Zijlstra F, Hoorntje JC, de Boer MJ, Reiffers S, Miedema K, Ottervanger JP, van 't Hof AW, Suryapranata H. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1999;341(19):1413-9.

4. Nauta ST, Deckers JW, Akkerhuis M, Lenzen M, Simoons ML, van Domburg RT. Changes in Clinical Profile, Treatment, and Mortality in Patients Hospitalised for Acute Myocardial Infarction between 1985 and 2008. PLoS One 2011;6(11):e26917.

5. Healy B. The Yentl syndrome. N Engl J Med 1991;325(4):274-6.

6. Peltonen M, Lundberg V, Huhtasaari F, Asplund K. Marked improvement in survival after acute myocardial infarction in middle-aged men but not in women. The Northern Sweden MONICA study 1985-94. J Intern Med 2000;247(5):579-87.

7. Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. J Am Coll Cardiol 2007;50(22):2128-32.

8. Roger VL, Jacobsen SJ, Weston SA, Goraya TY, Killian J, Reeder GS, Kottke TE, Yawn BP, Frye RL. Trends in the incidence and survival of patients with hospitalized myocardial infarction, Olmsted County, Minnesota, 1979 to 1994. Ann Intern Med 2002;136(5):341-8.

9. Chandra NC, Ziegelstein RC, Rogers WJ, Tiefenbrunn AJ, Gore JM, French WJ, Rubison M. Observations of the treatment of women in the United States with myocardial infarction: a report from the National Registry of Myocardial Infarction-I. Arch Intern Med 1998;158(9):981-8.

10. Vaccarino V, Krumholz HM, Yarzebski J, Gore JM, Goldberg RJ. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. Ann Intern Med 2001;134(3):173-81.

11. Chang WC, Kaul P, Westerhout CM, Graham MM, Fu Y, Chowdhury T, Armstrong PW. Impact of sex on long-term mortality from acute myocardial infarction vs unstable angina. Arch Intern Med 2003;163(20):2476-84.

12. Stefanini GG, Kalesan B, Pilgrim T, Raber L, Onuma Y, Silber S, Serruys PW, Meier B, Juni P, Windecker S. Impact of Sex on Clinical and Angiographic Outcomes Among Patients Undergoing Revascularization With Drug-Eluting Stents. JACC Cardiovasc Interv 2012;5(3):301-310.

13. Nauta ST, Deckers JW, Akkerhuis KM, van Domburg RT. Age-dependent care and long-term (20year) mortality of 14,434 myocardial infarction patients: Changes from 1985 to 2008. Int J Cardiol 2012: DOI: 10.1016/j.ijcard.2012.03.064.

14. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145(4):247-54.

15. He Y. Missing data analysis using multiple imputation: getting to the heart of the matter. Circ Cardiovasc Qual Outcomes 2010;3(1):98-105.

16. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine--reporting of subgroup analyses in clinical trials. N Engl J Med 2007;357(21):2189-94.

17. Berger JS, Elliott L, Gallup D, Roe M, Granger CB, Armstrong PW, Simes RJ, White HD, Van de Werf F, Topol EJ, Hochman JS, Newby LK, Harrington RA, Califf RM, Becker RC, Douglas PS. Sex differences in mortality following acute coronary syndromes. JAMA 2009;302(8):874-82.

18. Alfredsson J, Stenestrand U, Wallentin L, Swahn E. Gender differences in management and outcome in non-ST-elevation acute coronary syndrome. Heart 2007;93(11):1357-62.

19. Heer T, Gitt AK, Juenger C, Schiele R, Wienbergen H, Towae F, Gottwitz M, Zahn R, Zeymer U, Senges J. Gender differences in acute non-ST-segment elevation myocardial infarction. Am J Cardiol 2006;98(2):160-6.

20. Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Maree AO, Wells Q, Bozkurt B, Labresh KA, Liang L, Hong Y, Newby LK, Fletcher G, Peterson E, Wexler L. Sex differences in medical care and early death after acute myocardial infarction. Circulation 2008;118(25):2803-10.

21. Gan SC, Beaver SK, Houck PM, MacLehose RF, Lawson HW, Chan L. Treatment of acute myocardial infarction and 30-day mortality among women and men. N Engl J Med 2000;343(1):8-15.

22. Gottlieb S, Harpaz D, Shotan A, Boyko V, Leor J, Cohen M, Mandelzweig L, Mazouz B, Stern S, Behar S. Sex differences in management and outcome after acute myocardial infarction in the 1990s: A prospective observational community-based study. Israeli Thrombolytic Survey Group. Circulation 2000;102(20):2484-90.

23. Simon T, Mary-Krause M, Cambou JP, Hanania G, Gueret P, Lablanche JM, Blanchard D, Genes N, Danchin N. Impact of age and gender on in-hospital and late mortality after acute myocardial infarction: increased early risk in younger women: results from the French nation-wide USIC registries. Eur Heart J 2006;27(11):1282-8.

24. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. N Engl J Med 1999;341(4):217-25.

25. Mehilli J, Kastrati A, Dirschinger J, Pache J, Seyfarth M, Blasini R, Hall D, Neumann FJ, Schomig A. Sex-based analysis of outcome in patients with acute myocardial infarction treated predominantly with percutaneous coronary intervention. JAMA 2002;287(2):210-5.

26. Champney KP, Frederick PD, Bueno H, Parashar S, Foody J, Merz CN, Canto JG, Lichtman JH, Vaccarino V. The joint contribution of sex, age and type of myocardial infarction on hospital mortality following acute myocardial infarction. Heart 2009;95(11):895-9.

27. Crowley A, Menon V, Lessard D, Yarzebski J, Jackson E, Gore JM, Goldberg RJ. Sex differences in survival after acute myocardial infarction in patients with diabetes mellitus (Worcester Heart Attack Study). Am Heart J 2003;146(5):824-31.

28. Donahue RP, Goldberg RJ, Chen Z, Gore JM, Alpert JS. The influence of sex and diabetes mellitus on survival following acute myocardial infarction: a community-wide perspective. J Clin Epidemiol 1993;46(3):245-52.

Chapter 10

Relative survival estimates provide patients with prior myocardial infarction with additional insight into their long-term (20-year) prognosis

Sjoerd T Nauta
Paul W Dickman
Ron T van Domburg
Liza van Steenbergen
Maryska LG Janssen-Heijnen
Jaap W Deckers
Isabella Kardys

Accepted with minor revision. American Heart Journal 2013

Abstract

Objectives

We compared survival in patients with prior MI with survival in the general population. Methods: We examined 14,434 consecutive patients admitted for MI to an intensive coronary care unit from 1985 to 2008 and compared survival in those patients with survival in the general population using (conditional) relative survival analyses. Relative survival, meaning survival in MI patients corrected for estimated mortality from all other causes, and conditional survival (that is 'landmark' survival) was computed.

Results

Median survival from hospitalization for MI was >20, 17, 11, and 6 years in men, and >20, 19, 12, and 7 years in women, for ages <55, 55-65, 65-75 and ≥75 years, respectively. The 1-year relative survival (from hospitalization) was 98%, 97%, 95%, and 89% in men, and 97%, 95%, 94%, and 88% in women, for ages <55, 55-65, 65-75 and ≥75 years, respectively. In male patients aged 55-65 years, cumulative relative survival was 73% at 20 years, while conditional 1-year relative survival was 97%, 99% and 98%, conditional on surviving 0, 5 and 20 years after index hospitalization. For all age and sex subgroups, conditional 1-year relative survival was lower during the first year and after 15 years.

Conclusions

Survival in patients with a prior MI is only a few percent lower per year compared to the general population for both sexes and all age groups. Although these results are encouraging, continuation of optimal treatment –in particular in the first year and after 15 years– might further improve survival in the future.

Introduction

Patients who have experienced myocardial infarction (MI) often ask their physicians for an estimate of their prognosis.[1] Prognosis after MI is generally expressed as all-cause or cause-specific mortality rates. Neither approach assess the impact of the disease or health state of interest in comparison with expected survival in a similar population. Relative survival, which is the survival among patients divided by the expected survival of a the general population, is applied routinely in cancer studies and may improve on current methods for assessment of survival after MI.[2] In addition, estimates of cause-specific survival are limited by their dependence on reliable information on cause of death, whereas, relative survival is not.

Patients who have survived for a certain amount of time after their hospitalization for MI are interested in their prognosis at that particular time point. Standard survival curves after hospitalization provide an overly pessimistic picture for these patients, because these are partly based on patients who are most seriously affected and consequently die within the first month. Conditional survival analysis (or 'landmark' analysis) is a method for estimating the survival rate, given the precondition of having already survived a certain period of time. Conditional survival rates can provide patients and treating physicians with more relevant information for personal health-related future planning. Until now, relative survival analyses and conditional relative survival analyses have rarely been used in cardiovascular research.[2, 3]

With the current study, we aim to determine long-term relative survival rates in patients with a prior MI. In addition, we determine mortality for patients given they survived up to 20 years after MI by means of conditional survival estimates. For this purpose, we have analyzed data on 14,434 consecutive MI patients admitted to the Intensive Coronary Care Unit (ICCU) of the Erasmus Medical Center from 1985 to 2008.

Methods

We included all 14,434 consecutive patients aged >18 years admitted for MI to the Intensive Coronary Care Unit (ICCU) of the Thoraxcenter, Erasmus Medical Center between June 1985 and December 2008, as previously described.[4]

The diagnosis of MI was made in the presence of the following characteristics: chest pain or equivalent symptoms in combination with dynamic ECG changes consistent with MI and a typical serial rise (to at least three times the upper normal value) and fall in serum biochemical markers of cardiac necrosis such as creatine kinase-MB or troponin-T. For patients admitted more than once, only the first hospitalization was taken into account.

The study endpoint was all-cause mortality. Survival status and date were assessed through municipal Civil Registries in 2010 and were available for 98% of all patients. This project was carried out in accordance with current rules of ethics and legislature. The Ethical Committee of the Erasmus Medical Center waived the need for its approval because register-based studies do not require ethical approval according to Dutch law.

Statistical analysis

Cumulative relative survival was calculated as the observed survival among the MI patients divided by the survival of persons from the general population (publicly available from Statistics Netherlands), matched for sex, age and calendar year.[2] Thus, relative survival provides a measure of the excess mortality experienced by MI patients compared to the general population, irrespective of whether mortality is directly or indirectly related to the index MI. As such, relative survival also captures excess mortality because of, for example, treatment-related acute kidney injury or in-hospital infections, which is not possible when using cause-specific survival.

Conditional 1-year relative survival depicts the 1-year relative survival given that a patient has survived for a certain period of time (for example, 0 year, 1 month, 1year, 5, 10, 15 or 20 years). We calculated conditional 1-year survival at year x by dividing cumulative survival rates of year x+1 by the cumulative survival rate of year x. Subsequently, we combined relative and conditional survival estimates. A conditional

1-year relative survival of 100% indicates that, mortality in the patient group has become equivalent to that of the general population.

We displayed survival rates according to both sexes and four age groups: <55, 55-65, 65-75 and >75 years. Besides cumulative and conditional relative survival, we also estimated cumulative and conditional observed survival. Observed survival is the actual survival among the MI patients, considering all causes of death together.

The period approach was used to provide predictions of (both cumulative and conditional) relative and observed survival.[5] The period approach combines survival rates in a recent period (in this study, 2000-2011) to obtain up-to-date survival estimates. This approach mirrors the standard predictions of life expectancy at birth from the most recently recorded death rates at each age.[6]

Analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC, USA). Calculations were performed with a publicly available SAS macro that can be used for period analysis.[7] The macro calculated expected survival according to the Ederer II method from population life tables stratified by age, sex and calendar period. Standard errors of the survival estimates were calculated using Greenwood's method, and 95% confidence intervals were reported for cumulative survival estimates. We presented only relative survival estimates with a standard error <=10% of the survival rate and conditional survival estimates with a standard error <=5% of the survival rate.

Results

Study population and Median or Cumulative Observed Survival

We included 14,434 patients who were hospitalized for MI between 1985 and 2008. Median observed survival after MI is shown in Table 1 (and Figure 1). Observed survival after MI was inversely related to age and better for women compared to men. Median observed survival in men was >20, 17, 11, and 6 years, and median observed survival in women was >20, 19, 12, and 7 years, for ages <55, 55-65, 65-75 and ≥75 years, respectively (Table 1). The 1-year observed survival (from hospital admission) was 98%, 96%, 92%, and 82% in men, and 97%, 95%, 92%, and 83% in women, for ages <55, 55-65, 65-75 and ≥75 years, respectively. The cumulative 20-year observed survival (from hospital admission) is 61%, 39%, 13%, and 0% in men, and 67%, 42%, 16%, and 3% in women, for ages <55, 55-65, 65-75 and ≥75 years, respectively (Figure 1).

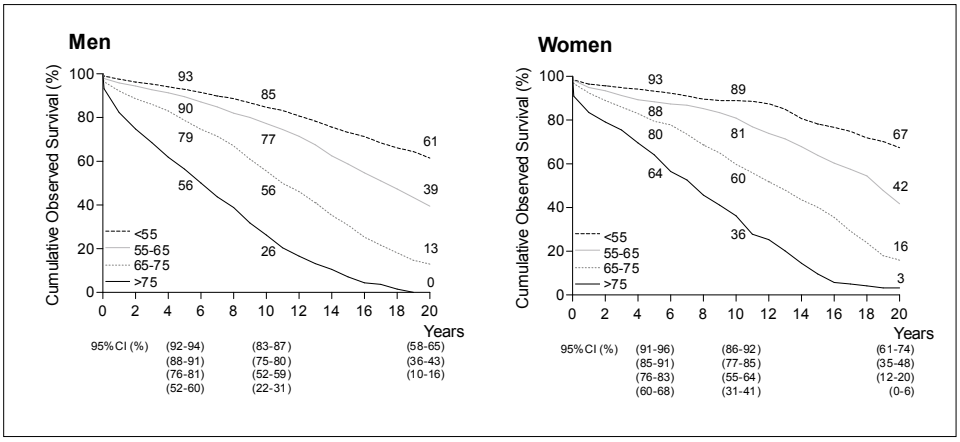

Figure 1: Observed survival after MI (follow-up period 2000-2011). Survival estimates (and 95%CIs) are shown at 5, 10 and 20 years follow-up.

Table 1: Median observed survival after MI according to age and sex.

Gender	Age	No. of MI patients	Median survival after MI (years)
Men	<55	3452	>20 [a]
	55-65	3153	17
	65-75	2684	11
	≥75	1117	6
Women	<55	867	>20 [a]
	55-65	960	19
	65-75	1278	12
	≥75	923	7

[a] Median survival is at least longer than 20 years (maximum follow-up duration).

Conditional observed survival

Conditional 1-year observed survival in male patients aged 55 to 65 years was 96%, 98%, 98%, 97%, 96%, and 88%, conditional on surviving 0 years, 1 month, 1 year, 5, 10 and 20 years after hospital admission, respectively (Table 2). Conditional observed survival was lower with increasing age.

Table 2: Conditional one-year observed survival after MI.

		Conditional one-year observed survival							Reliable estimates up to year
		No. of years already survived							
Gender	**Age**	**0 yrs**	**1/12 yr***	**1 yr**	**5 yrs**	**10 yrs**	**15 yrs**	**20 yrs**	
Men	<55	98%	98%	99%	98%	98%	97%	99%	20
	55-65	96%	98%	98%	97%	96%	93%	88%	20
	65-75	92%	95%	96%	95%	90%	82%	[a]	17
	≥75	82%	88%	91%	89%	[a]	[a]	[a]	9
Women	<55	97%	98%	99%	99%	100%	98%	97%	20
	55-65	95%	96%	99%	99%	95%	94%	89%	20
	65-75	92%	95%	96%	98%	93%	89%	[a]	17
	≥75	83%	91%	95%	88%	[a]	[a]	[a]	9

* Conditional on 1 month survival.

[a] Standard error of conditional survival proportion > 5%.

Relative survival

Relative survival rates were substantially higher than observed survival rates due to elimination of background mortality. The 1-year relative survival (from hospital admission) was 98%, 97%, 95%, and 89% in men, and 97%, 95%, 94%, and 88% in women, for ages <55, 55-65, 65-75 and ≥75 years, respectively. The cumulative 10-year relative survival (from hospital admission) was 89%, 90%, 87%, and 89% in men, and 92%, 89%, 78%, and 90% in women, for ages <55, 55-65, 65-75 and ≥75 years, respectively (Figure 2).

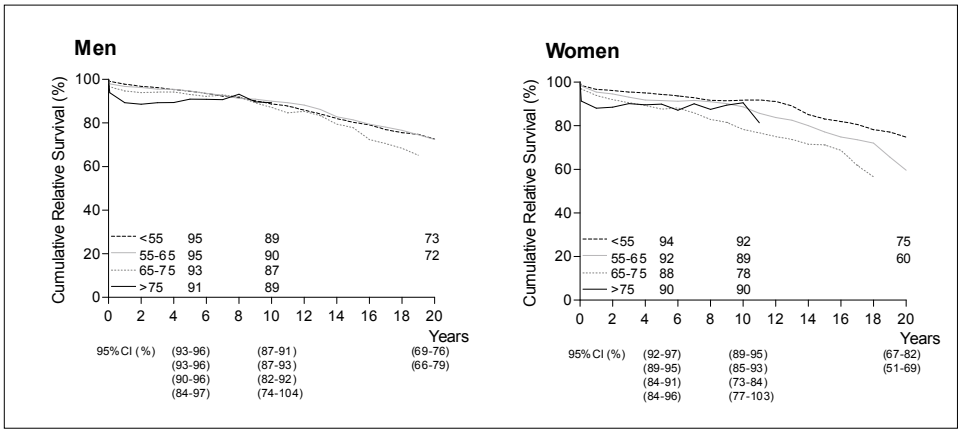

Figure 2: Relative survival after MI (follow-up period 2000-2011), as compared to survival in the general population with the same age and gender. Survival estimates (and 95%CIs) are shown at 5, 10 and 20 years follow-up.

Conditional relative survival

Conditional relative survival rates combine the information from conditional survival and from relative survival. Conditional 1-year relative survival was lower directly after hospital admission and conditional on 15 or more years survival compared to the time-period between 1 and 15 years (Table 3). For example, one-year conditional relative survival in male patients aged 55 to 65 years was 97%, 99%, 99%, 99%, 99%, and 98%, conditional on surviving 0 years, 1 month, 1 year, 5, 10, and 20 years after hospital admission, respectively. This indicates that, for example, one-year survival of a patient aged between 65 and 75 years who suffered a MI 10 years ago (age at index MI was 55 to 65 years) is 1% lower compared to 1-year survival in the general population. One-year conditional relative survival in other age groups (except ≥75 years) and in women was comparable.

Table 3: Conditional one-year relative survival after MI.

		Conditional one-year relative survival							Reliable estimates up to year
		No. of years already survived							
Gender	**Age**	**0 yrs**	**1/12 yr***	**1 yr**	**5 yrs**	**10 yrs**	**15 yrs**	**20 yrs**	
Men	<55	98%	99%	99%	99%	99%	99%	100%	20
	55-65	97%	99%	99%	99%	99%	98%	98%	20
	65-75	95%	98%	99%	99%	97%	93%	[a]	17
	≥75	89%	95%	99%	100%	[a]	[a]	[a]	9
Women	<55	97%	98%	99%	99%	100%	99%	95%	20
	55-65	95%	97%	99%	100%	97%	97%	93%	20
	65-75	94%	96%	98%	101%	98%	96%	[a]	17
	≥75	88%	96%	101%	97%	[a]	[a]	[a]	9

* Conditional on 1 month survival.

[a] Standard error of conditional survival proportion > 5%.
Relative survival, survival after MI compared to survival in the general population with the same age and gender.

Discussion

In this study of 14,434 MI patients we provide an overview of long-term prognoses according to age and sex, based on contemporary mortality rates. Our results demonstrate that the overall median life-expectancy after MI varies between 6 and more than 20 years, mainly depending on age at presentation. Our relative survival analyses show that survival in patients with a prior MI is only a few percent lower per year compared to the general population. Conditional survival analysis displays that survival after MI is especially decreased in the first year post MI and after 15 years follow-up. Information on long-term prognosis after MI is needed to guide medical decisions and might be of interest for patients because it affects their personal life choices.

Previous studies have determined temporal trends in mortality after MI by comparing groups of patients who were admitted during different calendar years.[8-11] These studies have demonstrated that mortality has fallen substantially during the past decades, most likely due to the progress that has been made in improvement of emergency medical response, development of treatments and improvement of secondary prevention after MI.[8, 12] In the present study, we further investigate this improved prognosis by a comparison with the general population and performing conditional survival analyses. Such estimates of (conditional) relative survival in patients with prior MI are scarce.[2]

Relative survival provides a measure of the excess mortality experienced by MI patients compared to the general population. Relative survival after MI remains favorable during up to 20 years follow-up. At 10 years of follow-up, for example, cumulative relative survival is about 90% indicating that 10-year survival in MI patients is 10% lower compared to the general population. This prognosis is encouraging and highlights the effectiveness of current treatment following MI. However, according to the guidelines, even a 10% survival difference in ten years assures that intense surveillance and secondary prevention remains warranted in these patients.[13]

In view of the comparison with the general population,[1] it might be noteworthy that the excess mortality is not only due to the index MI and therefore cannot be interpreted as mortality due to cardiac death. Mortality after MI could also be higher compared to the general population as a result of risk factors that that are associated with both MI and mortality, such as smoking (associated with MI) and death from lung cancer (associated with smoking).

Conditional one-year relative survival was relatively low directly following MI and decreased again slightly for patients who had already survived for some time (15 years). The relatively low survival directly following MI is due to a rather high in-hospital mortality.[14] The second decrease in survival in patients who had already survived for some time may partly be explained by the risk profile present in MI patients compared to the general population, or by late complications following MI such as death from heart failure. Still, since this risk profile, or such complications, did not cause such high mortality rates in the period from 1 to 15 years following MI, increased awareness with stringent secondary prevention for patients with a longstanding history of MI might be necessary.

Conditional one-year relative survival occasionally was 101% for older patients. Although absolute survival rates cannot be greater than 100%, relative survival rates can exceed 100%. This occurs if mortality in the general population is higher than mortality after MI. With conditional one-year relative survival we investigated relative survival in one-year intervals of follow-up. A survival exceeding 100% in such an interval could be explained by random variation or by selection of more healthy MI patients during follow-up.

Strengths and limitations

To our knowledge, this is the first paper investigating (conditional) relative survival in MI patients with follow-up data up to 20 years. Although the present study has unique strengths, some potential limitations should be mentioned. First, the present data are derived from a single center, which could result in a lower external validity. However, we think that this is unlikely to be the case given the uniform definition

and therapeutic modalities of MI. Second, the current report is based on MI patients who survived until hospital admission for their index event, therefore the survival estimates apply to hospitalized patients or patients with a history of MI only.

Conclusion

At present, MI patients have a substantial long-term survival. Compared to the general population survival after MI is only a few percent lower per year. Nevertheless, this survival difference remains an important target for treatment and secondary prevention. This applies even more to the first year after MI, and to those patients who survived more than 15 years after MI, because at these periods the relative survival difference is most pronounced. Insight into relative and conditional survival is useful for patients, who may use this information to plan their remaining life.

References

1. Smith AK, Williams BA, Lo B. Discussing overall prognosis with the very elderly. N Engl J Med 2011;365(23):2149-51.
2. Nelson CP, Lambert PC, Squire IB, Jones DR. Relative survival: what can cardiovascular disease learn from cancer? Eur Heart J 2008;29(7):941-7.
3. Janssen-Heijnen ML, Houterman S, Lemmens VE, Brenner H, Steyerberg EW, Coebergh JW. Prognosis for long-term survivors of cancer. Ann Oncol 2007;18(8):1408-13.
4. Nauta ST, Deckers JW, Akkerhuis KM, van Domburg RT. Short- and long-term mortality after myocardial infarction in patients with and without diabetes: changes from 1985 to 2008. Diabetes Care 2012;35(10):2043-7.
5. Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. Cancer 1996;78(9):2004-10.
6. Brenner H, Hakulinen T. Up-to-date cancer survival: period analysis and beyond. Int J Cancer 2009;124(6):1384-90.
7. Dickman PW. Estimating and modelling relative survival using SAS. In; 2004.
8. Fox KA, Steg PG, Eagle KA, Goodman SG, Anderson FA, Jr., Granger CB, Flather MD, Budaj A, Quill A, Gore JM. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. JAMA 2007;297(17):1892-900.
9. Nauta ST, Deckers JW, Akkerhuis KM, van Domburg RT. Age-dependent care and long-term (20year) mortality of 14,434 myocardial infarction patients: Changes from 1985 to 2008. Int J Cardiol 2012.
10. Nauta ST, Deckers JW, van Domburg RT, Akkerhuis KM. Sex-related trends in mortality in hospitalized men and women after myocardial infarction between 1985 and 2008: equal benefit for women and men. Circulation 2012;126(18):2184-9.
11. Coles AH, Fisher KA, Darling C, McManus D, Maitas O, Yarzebski J, Gore JM, Lessard D, Goldberg RJ. Recent trends in post-discharge mortality among patients with an initial acute myocardial infarction. Am J Cardiol 2012;110(8):1073-7.
12. Roe MT, Messenger JC, Weintraub WS, Cannon CP, Fonarow GC, Dai D, Chen AY, Klein LW, Masoudi FA, McKay C, Hewitt K, Brindis RG, Peterson ED, Rumsfeld JS. Treatments, trends, and outcomes of acute myocardial infarction and percutaneous coronary intervention. J Am Coll Cardiol 2010;56(4):254-63.

13. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvanne M, Scholte Op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F, Cooney MT, Bax J, Baumgartner H, Ceconi C, Dean V, Fagard R, Funck-Brentano C, Hasdai D, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Aboyans V, Ezquerra EA, Baigent C, Brotons C, Burell G, Ceriello A, De Sutter J, Deckers J, Del Prato S, Diener HC, Fitzsimons D, Fras Z, Hambrecht R, Jankowski P, Keil U, Kirby M, Larsen ML, Mancia G, Manolis AJ, McMurray J, Pajak A, Parkhomenko A, Rallidis L, Rigo F, Rocha E, Ruilope LM, van der Velde E, Vanuzzo D, Viigimaa M, Volpe M, Wiklund O, Wolpert C. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) * Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2012;33(13):1635-701.

14. Kostis WJ, Deng Y, Pantazopoulos JS, Moreyra AE, Kostis JB. Trends in mortality of acute myocardial infarction after discharge from the hospital. Circ Cardiovasc Qual Outcomes 2010;3(6):581-9.

Part IV

Traditional risk factors

Chapter 11

Risk factors for coronary heart disease and survival after myocardial infarction

Sjoerd T Nauta
Jaap W Deckers
Robert M van der Boon
K Martijn Akkerhuis
Ron T van Domburg

Eur J Prev Cardiol. 2012 Sep 13

Abstract

Objectives

Several risk factors for coronary heart disease (CHD) have been associated with improved in-hospital survival after myocardial infarction (MI). We aimed to confirm this paradox and assess whether it extends to long-term outcome. In addition, we investigated temporal mortality trends.

Methods

We examined the relation between the presence of 4 modifiable risk factors for CHD (hypertension, dyslipidemia, diabetes mellitus and smoking) and mortality in 14,434 consecutive patients admitted with MI to a coronary care unit from 1985 to 2008.

Results

Two-thirds of MI patients (n=10,003) had at least one risk factor for CHD on hospital admission. The presence of at least one compared to no CHD risk factors was associated with a favorable 30-day mortality rate (5% vs. 7%, adjusted odds ratio 0.72, 95%CI: 0.62-0.83). There was significant interaction between the presence of CHD risk factors and decade of hospitalization (p = 0.001). The adjusted 10-year mortality hazard ratio (HR) of at least one CHD risk factor compared to none, was 1.2 (95% CI: 1.0-1.4), 0.89 (0.65-1.2) and 0.89 (0.79-0.99) in 1985-1990, 1990-2000 and 2000-2008, respectively. Survival improved over time. Adjusted 10-year mortality fell (adjusted HR (2000-08 versus 1985-1990) 0.59 (95%CI 0.52-0.66) in patients with, and 0.76 (95% CI 0.65-0.89) in those without CHD risk factors).

Conclusions

The presence of at least one modifiable CHD risk factor was associated with improved outcome after MI. Patients with CHD risk factors benefited from more substantial mortality reductions during the past decades.

Keywords

Mortality, Coronary Heart Disease, STEMI, NSTEMI, Diabetes, Hyperlipidemia, Hypertension, Smoking, Long-term survival, Paradox.

Introduction

Hypertension, dyslipidemia, smoking and diabetes mellitus are traditional risk factors for coronary heart disease (CHD) in patients without established cardiovascular disease.[1,2] Contrary, two recent studies of patients with a myocardial infarction (MI) have shown the presence of these CHD risk factors to be associated with a significantly lower in-hospital mortality rate.[3,4] However, further confirmation of these findings is needed and the impact on long-term outcome has not been established yet.[5]

Since 1985, considerable progress has been made in the management of MI; clinical evidence has guided the introduction of thrombolytic therapy, primary percutaneous coronary intervention (PCI), tailored treatment according to individual risk and improved secondary prevention.[6-8] As a result, outcome after MI has improved substantially.[6-8] Previous studies have shown that these treatments are used more frequently in patients with at least one modifiable CHD risk factor (hypertension, dyslipidemia, diabetes mellitus and smoking).[3,4] As these treatments have increasingly been used in the past decades we also wondered whether the association between CHD risk factors and mortality changed between 1985 and 2008.

Therefore, The main goal of this research was to establish the association between the presence of modifiable CHD risk factors and 30-day, as well as long-term (20-year) mortality after MI. In addition, we also compared the relation between the presence of CHD risk factors and outcome according to decades of hospital admission (i.e. 1985-1990 vs. 1990-2000 vs. 2000-2008).

Methods

All consecutive patients aged >18 years with a first admission for ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI) to the Intensive Coronary Care Unit (ICCU) of the Thoraxcenter, Erasmus University Medical Center between June 1985 and December 2008 were included.[7]

The primary discharge diagnosis of STEMI was made in the presence of the following characteristics: chest pain or equivalent symptoms in combination with dynamic ECG changes consistent with MI and a typical serial rise (to at least three times the upper normal value) and fall in serum biochemical markers of cardiac necrosis such as creatine kinase-MB or troponin-T. Patients were diagnosed as STEMI in the presence of ST-segment elevation >0.1 mV in at least two contiguous peripheral leads, or >0.2 mV in at least two contiguous pre-cordial leads, and as NSTEMI otherwise.

Four modifiable CHD risk factors were recorded at hospitalization and included hypertension, dyslipidemia, diabetes and current smoking. Hypertension, dyslipidemia and diabetes were defined as previously diagnosed by a physician or receiving medication to lower blood pressure, cholesterol levels or glucose levels, respectively. Smoking was defined as current smoking. Assessment of these risk factors was based on patient/family self-report or previous medical records. Demographic characteristics (age, gender), cardiac history (previous MI, PCI or coronary artery bypass surgery (CABG)), family history of coronary heart disease (defined as one or more relatives, parent or sibling, with an MI diagnosed before the age of 60 years), anemia (Hemoglobin level <13.0 g/dl men, <12.0g/dl women), renal dysfunction (creatinine >150 µmol/l), invasive treatment modalities (thrombolysis and PCI) and medication at ICCU discharge were collected.

The study endpoint was all-cause mortality at 30 days and at 20 years. Survival date was assessed in 2010 through municipal Civil Registries which is updated regularly and therefore highly accurate in the Netherlands. Follow-up was available for 99% of all patients.

This project was carried out in accordance with current rules of ethics and legislature. The Ethical Committee of the Erasmus Medical Center waived the need for their approval because register-based studies do not require ethical approval according to Dutch law (entitled 'WMO').

Statistical Analysis

The patients were categorized depending on the presence or absence of CHD risk factors. Continuous variables were summarized as mean and standard deviation or median and interquartile range and Analysis of Variance (ANOVA) or Kruskal-Wallis test, respectively were used to calculate p-values. Categorical variables were summarized as percentages. Test for trend was performed using the number of CHD risk factors as a categorical measurement. Using Cox regression, age adjusted cumulative survival curves for the presence or absence of at least one CHD risk factor were constructed and examined using the log-rank test. The independent association between the presence of risk factors and mortality was examined using logistic regression for 30-day outcome and the Cox proportional hazards model for long-term (20-year) outcome. Multivariate adjustment was performed for age, gender, previous MI, previous CABG, family history of CHD, renal dysfunction, anemia, decade of admission and discharge diagnosis. Sensitivity analysis were performed in patients who died the first day after admission and those without prior coronary heart disease. We tested for interaction between the presence of CHD risk factors and 1) decade of admission or 2) discharge diagnosis. Because there was significant interaction between the presence of CHD risk factors and decade of admission, results are also presented for each decade of admission separately. Temporal trends were assessed by comparing decades of hospital admission, i.e. 1985 to 1990 vs. 1990 to 2000 vs. 2000 to 2008. Complete long-term (20-year) follow-up of patients admitted after 1990 is unavailable, therefore, we used 10-year outcomes when comparing decades of hospitalization. For these decades we also report the prevalence of modifiable risk factors. Results are reported as odds ratios (OR) –for 30-day mortality– and hazard ratios (HR) –for long-term mortality– and their respective 95% confidence intervals. All statistical tests were 2-tailed, and p-values were considered significant at <0.05. Analysis was performed using SPSS software version 17.0 (SPSS, Chicago, USA).

Table 1: Baseline characteristics and clinical presentation of patients hospitalized for MI according to absence, presence and number of coronary heart disease risk factors.

	No CHD risk factors	≥1 CHD risk factors	1 CHD risk factor	2 CHD risk factors	3 or 4 CHD risk factors	P for trend
No. of patients	4431 (31%)	10 003 (69%)	5652 (39%)	3134 (22%)	1217 (8%)	
Baseline						
Age, mean (SD)	64 (12)	61 (12)	61 (12)	61 (12)	60 (12)	<0.001
Gender (female), %	27%	28%	27%	29%	33%	<0.001
Family history of CHD, %	15%	31%	28%	33%	41%	<0.001
Cardiac history, %						
Previous MI	35%	32%	31%	34%	33%	0.27
Previous PCI	15%	14%	13%	15%	17%	0.12
Previous CABG	11%	9%	9%	10%	9%	0.10
CHD Risk factors, %						
Hypertension	0%	51%	32%	69%	94%	<0.001
Dyslipidemia	0%	40%	19%	57%	92%	<0.001
Diabetes	0%	20%	9%	24%	62%	<0.001
Current smoker	0%	47%	41%	50%	68%	<0.001
Comorbidity						
Renal dysfunction	9%	9%	8%	9%	12%	<0.001
Anemia	45%	40%	39%	41%	41%	<0.001
Discharge diagnosis, %						
STEMI	51%	46%	50%	40%	41%	<0.001
Reperfusion therapy*, %						
PCI	47%	56%	52%	59%	72%	<0.001
Thrombolytic therapy	26%	23%	25%	21%	15%	<0.001
Medication at ICCU, % discharge						
Statin**	62%	76%	74%	77%	81%	<0.001
Aspirin	62%	70%	66%	72%	79%	<0.001
Beta-blocker	52%	61%	59%	63%	66%	<0.001
ACE inhibitor or ARB	17%	21%	18%	22%	31%	<0.001
Ca-antagonist	24%	23%	23%	24%	18%	<0.01
Nitrates	13%	13%	13%	12%	11%	0.02
Diuretics	13%	13%	13%	12%	13%	0.19
Antiarrhythmics	5%	4%	4%	3%	4%	<0.01

CHD, coronary heart disease. CHD risk factors include: hypertension, diabetes mellitus, dyslipidemia, current smoking.

* STEMI patients only, n=6820.

** Only in patients admitted from 2000 to 2008, n= 7618.

Results

Prevalence of CHD risk factors

A total of 10 003 (69.3%) out of the 14 434 MI patients had at least one modifiable CHD risk factor (hypertension, dyslipidemia, diabetes or smoking). A total of 5652 (39.2%) patients had one, 3134 (21.7%) had two, and 1217 (8.4%) had three or four of these CHD risk factors. In the overall study population, hypertension was present in 35%, dyslipidemia in 28%, diabetes mellitus in 14%, while 32% were current smokers.

Patient characteristics and management

Patients with at least one CHD risk factor were younger, more often female, more often had a family history of CHD or renal dysfunction and less often had anemia or a discharge diagnosis of STEMI compared to patients with no CHD risk factors (p for trend < 0.001 for all). Patients with at least one CHD risk factor were significantly more likely to receive PCI for STEMI or medical therapy including statins, aspirin, β-blockers and ACE-inhibitors/angiotensin-receptor blockers compared to patients with no CHD risk factors (Table 1).

Mortality

At 30 days, 892 patients had died. Age-adjusted cumulative 30-day mortality was lower in patients with at least one CHD risk factor as opposed to no such risk factors (5% vs. 7%; Figure 1A; Age-adjusted OR 0.63, 95%CI: 0.55-0.73). Multivariate adjusted 30-day mortality was also lower (adjusted OR 0.72, 95%CI: 0.62-0.83) in patients with at least one CHD risk factor compared to patients with no CHD risk factor (Figure 2). The association between one or more risk factors and 30-day survival remained significant after exclusion of patients who died on the first day after admission (adjusted OR 0.77, 95%CI: 0.65-0.91). Furthermore, the association did not change after excluding all patients with a previous MI, PCI or CABG (adjusted OR 0.66, 95%CI: 0.55-0.81; Figure 2A).

With longer duration of follow-up, this paradox disappeared in the full cohort. At 20 years, a total of 5269 patients had died. Age-adjusted cumulative 20-year mortality was about equal in patients with at least one CHD risk factor (71% vs. 68%; age-

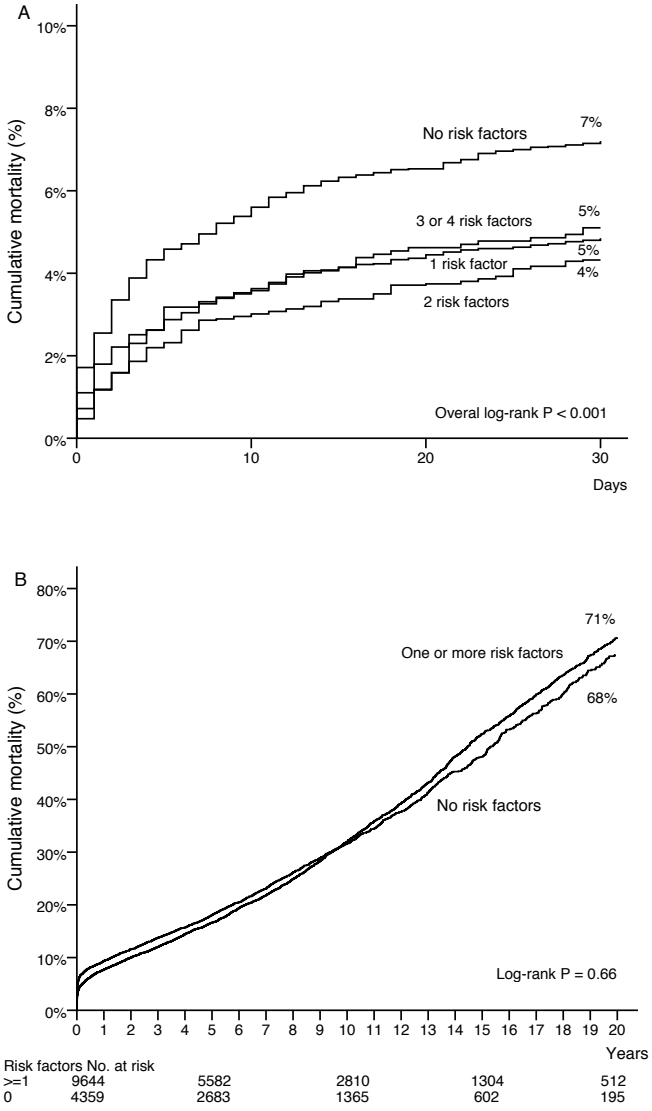

Figure 1: Age-adjusted short- (up) and long-term (bottom) mortality according to the absence or presence and number of coronary heart disease risk factors.

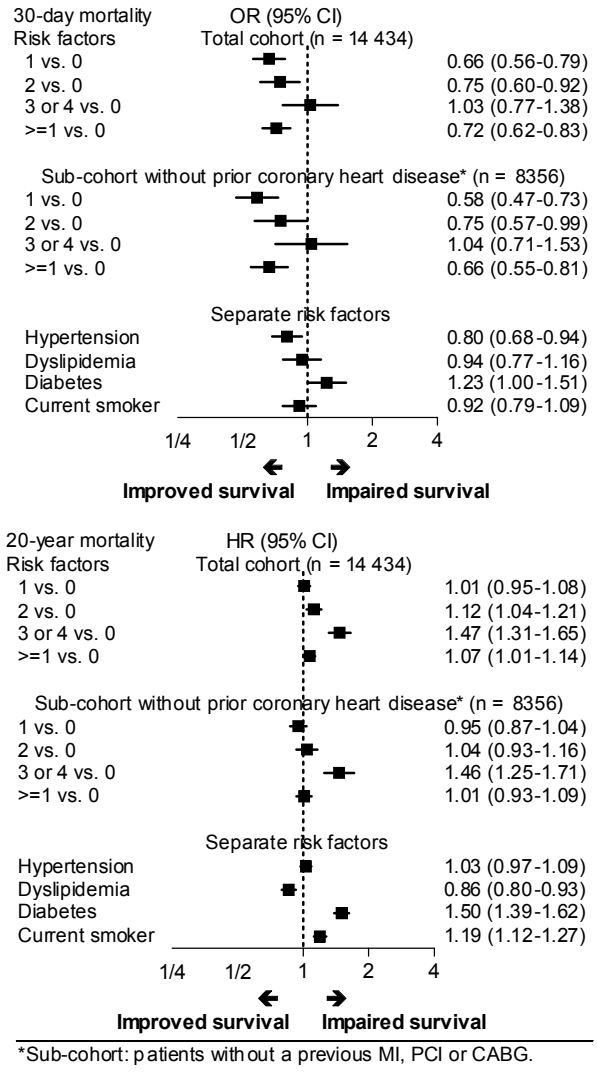

Figure 2: Adjusted short- (top) and long-term (bottom) mortality according to absence, presence and number of coronary heart disease risk factors in the total cohort and in a sub-cohort of patients without prior coronary heart disease.

adjusted OR 1.0, 95%CI: 0.94-1.1; Figure 1B). Multivariate adjusted 20-year mortality was higher (adjusted HR 1.1, 95%CI: 1.0-1.1) in patients with at least one CHD risk factor with a gradual increase in mortality as the number of risk factors increased (Figure 2). There was no significant interaction between presentation without CHD risk factors and diagnosis (STEMI or NSTEMI) (p = 0.27 for 30-day mortality and p = 0.31 for 20-year mortality).

Temporal trends

With time patients more often presented with dyslipidemia and diabetes and less often as a current smoker (Table 2). The inequality in prescription of medication and use of reperfusion therapy did not decrease over time.

There was significant interaction between the presence of CHD risk factors and decade of hospitalization (p = 0.025 for 30-day mortality). The 30-day mortality odds ratio (CI) of at least one CHD risk factor compared to none, was 1.1 (0.79-1.5), 0.63 (0.50-0.80) and 0.65 (0.51-0.82) in 1985-1990, 1990-2000 and 2000-2008, respectively. There was also significant interaction for long-term mortality (p = 0.001). The 10-year mortality hazard ratio (CI) of at least one CHD risk factor compared to none, was 1.2 (1.0-1.4), 0.89 (0.65-1.2) and 0.89 (0.79-0.99) in 1985-1990, 1990-2000 and 2000-2008, respectively.

Table 2: Changes in prevalence of modifiable risk factors over time.

	1985-1990	1990-2000	2000-2008	P for trend
No. of patients	2216 (15%)	4600 (32%)	7618 (53%)	
Risk factor				
Hypertension	35%	21%	32%	<0.001
Dyslipidemia	11%	22%	35%	<0.001
Diabetes	7.9%	11%	17%	<0.001
Current smoker	39%	31%	31%	<0.001
1 or more risk factors	69%	64%	73%	<0.001

In temporal trend analyses, mortality after MI was lower in the 1990s and 2000s compared to the 1980s (Figure 3). This improvement over time differed significantly between patients with no and those with at least one CHD risk factor. In patients with no CHD risk factor, adjusted 30-day mortality was 62% lower in the 2000s compared to the 1980s. In patients with at least one CHD risk factor adjusted 30-day mortality was 77% lower in the 2000s compared to the 1980s.

Long-term mortality in patients with no CHD risk factor was 24% lower in the 2000s compared to the 1980s. Long-term mortality in patients with at least one CHD risk factor was 41% lower in the 2000s compared to the 1980s (Figure 3).

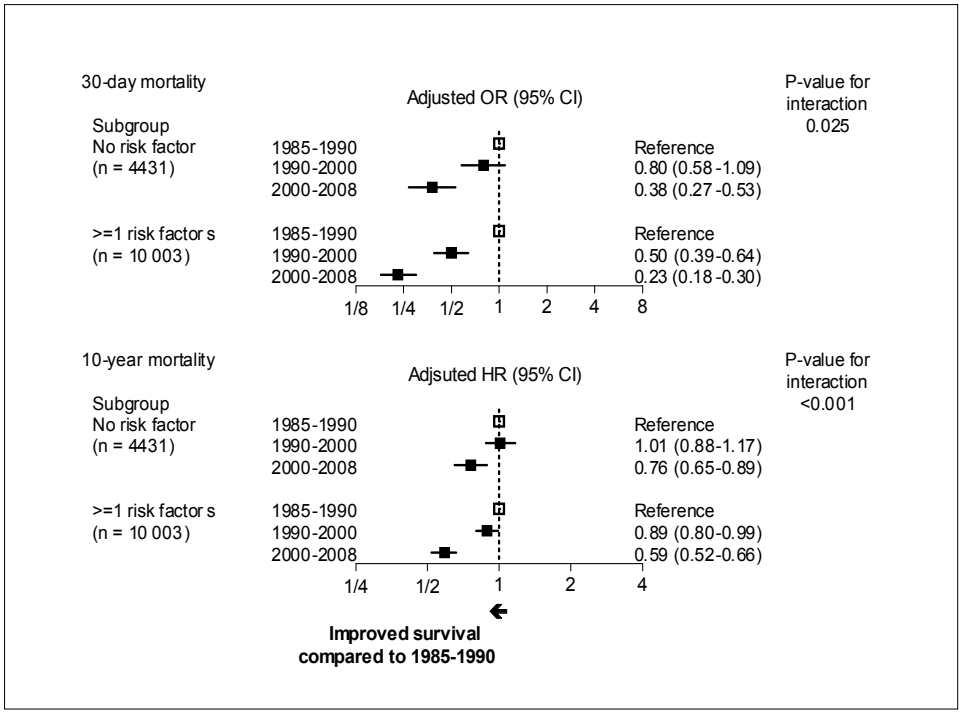

Figure 3: Temporal trends: decrease in adjusted mortality from 1985 to 2008 depending on the absence or presence of at least one coronary heart disease risk factor. Mortality in 1990-2000 and 2000-2008 is compared to 1985-1990.

Discussion

In the present study of 14 434 MI patients, we confirm the presence of a CHD risk factor paradox for short-term (30-day) outcome. MI patients with at least one compared to none modifiable CHD risk factor had a favorable unadjusted and adjusted short-term survival. With longer duration of follow-up, this paradox sustained for patients admitted in the 1990s and 2000s, but completely disappeared for those admitted in the 1980s. Improvement in outcome after MI during the last two decades was more pronounced for patients with CHD risk factors as compared to those without any risk factor.

The absence of CHD risk factors should not necessarily be viewed as a guarantee of a favorable prognosis. It could be that the management associated with the presence of CHD risk factors is causally related to better outcome. Patients with CHD risk factors might receive MI targeted therapy at an earlier time after first symptoms because they appear to be at higher risk. In previous studies, rapid initiation of aspirin, heparin, clopidogrel, GP IIb/IIIa inhibitors, ß-blockers and ACE-inhibitors and investigation by coronary angiogram at hospitalization for MI was reported to be more frequent in patients with at least one CHD risk factor.(ref 3,4) Also, patients with CHD risk factors might receive more adequate treatment. In our analysis, as well as in previous studies, treatment with PCI and CABG surgery was more frequent in patients with compared to those without CHD risk factors.[3, 4] In addition, in our study patients with CHD risk factors more often received evidence based medical care at ICCU discharge. This treatment discrepancy could result in relatively poor outcome in patients without CHD risk factors.

Some other potential explanations unlikely explain the relatively high mortality in patients without one compared to at least one CHD risk factor. Specifically, our findings were independent of mortality on the day of admission and prior coronary heart disease. In addition, according to our multivariate analysis confounding factors including older age and renal dysfunction did not cause the paradox. And previous studies show it is also not due to heart failure, presenting blood pressure, heart rate, body mass index, pre-hospital delay, infarct location and significance of coronary disease.[3, 4] Still, patients without CHD risk factors might have unmeasured risk factors

such as pre-diabetes, a high blood pressure or cholesterol level that did not reach the disease threshold, an unhealthy lifestyle and non-cardiovascular comorbidities.[9] Further studies should seek to gain more insight into the possible explanations of this CHD risk factor paradox.

Data from the CRUSADE Quality Improvements Initiative from 2001 to 2004, have shown that NSTEMI patients without documented CHD risk factors had a worse in-hospital survival.[4] Also, an NRMI-registry study (from 1994 to 2006) demonstrated an inverse relation between the number of CHD risk factors and in-hospital mortality in MI patients without prior cardiovascular disease.[3] The authors of these studies mention confounding from unknown risk factors and inequalities in the use of short-term treatment and use of cardiac procedures as most likely explanations, in line with our study results.[3, 4] Both these studies do not report outcome after 30-days.

Our study is unique in that it relates data on long-term mortality conditional on the presence and absence of CHD risk factors. In the overall cohort, adjusted 20-year mortality was 1.5-fold increased in patients with three or four CHD risk factors compared to none. Although this increase is statistically significant, it is rather small compared to the risk of MI associated with these CHD risk factors in the general population.[10, 11] However, in an ostensibly healthy population, persons with risk factors for CHD are compared to healthy individuals resulting in high relative risks.[2, 10] In an MI population, patients with CHD risk factors are compared to other patients who have developed an MI. Therefore, relative risks might substantially decrease towards the null (so-called “index event bias”).[12]

From our subgroup analyses it appears that patients without CHD risk factors admitted in the 1990s and 2000s also have impaired long-term mortality compared to those with CHD risk factors. Long-term mortality in patients with no CHD risk factors might be relatively high due to differences in prescription of or response to secondary prevention. Current treatment of CHD risk factors and secondary prevention is very effective and contributes to 50% of the observed cardiovascular mortality decline in the general population during the past 25 years.[13] Patients without CHD risk factors might less often receive secondary prevention or might benefit less in absolute terms. [1]

By comparing the 2000s with the 1980s we provide evidence that MI patients with one or more compared to no CHD risk factors benefit significantly more from improved short- and long-term outcome over time. These improvements in outcome are attributable to improvements in medical care.6-11 Increased awareness of the relatively high risk of patients without –compared to those with– CHD risk factors, and subsequent equal treatment might improve outcomes in these patients.

Limitations

Our study has several potential limitations. We combined patients with a STEMI and a NSTEMI in our analyses. However, we demonstrated that there is no significant interaction between discharge diagnosis and presence of risk factors and mortality. Thus, our results are applicable to both STEMI and NSTEMI patients. Our study is observational and its results may be limited by bias, unmeasured confounders, and residual confounding. Therefore, we cannot make causal inferences. In addition, data on comorbidity were quite limited. Last, ascertainment of risk factors was through medical record review at hospitalization and may have been incomplete. Still, we believe that our conclusion is robust.

Conclusion

We showed that the presence of at least one CHD risk factor yielded a favorable short-term survival after MI. With longer duration of follow-up, this association was sustained for MI patients admitted in the 1990s and the 2000s. Future studies should aim to seek for mechanisms and subsequent solutions to improve short-term outcome in patients without CHD risk factors.

References

1. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, De Backer G, Ebrahim S, Gjelsvik B, Herrmann-Lingen C, Hoes A, Humphries S, Knapton M, Perk J, Priori SG, Pyorala K, Reiner Z, Ruilope L, Sans-Menendez S, Op Reimer WS, Weissberg P, Wood D, Yarnell J, Zamorano JL, Walma E, Fitzgerald T, Cooney MT, Dudina A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Funck-Brentano C, Filippatos G, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Altiner A, Bonora E, Durrington PN, Fagard R, Giampaoli S, Hemingway H, Hakansson J, Kjeldsen SE, Larsen ML, Mancia G, Manolis AJ, Orth-Gomer K, Pedersen T, Rayner M, Ryden L, Sammut M, Schneiderman N, Stalenhoef AF, Tokgozoglu L, Wiklund O, Zampelas A. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur J Cardiovasc Prev Rehabil 2007;14 Suppl 2:E1-40.

2. 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(18):1837-47.

3. Canto JG, Kiefe CI, Rogers WJ, Peterson ED, Frederick PD, French WJ, Gibson CM, Pollack CV, Jr., Ornato JP, Zalenski RJ, Penney J, Tiefenbrunn AJ, Greenland P. Number of coronary heart disease risk factors and mortality in patients with first myocardial infarction. JAMA 2011;306(19):2120-7.

4. Roe MT, Halabi AR, Mehta RH, Chen AY, Newby LK, Harrington RA, Smith SC, Jr., Ohman EM, Gibler WB, Peterson ED. Documented traditional cardiovascular risk factors and mortality in non-ST-segment elevation myocardial infarction. Am Heart J 2007;153(4):507-14.

5. Nauta ST, Deckers JW, Akkerhuis KM, van Domburg RT. Age-dependent care and long-term (20year) mortality of 14,434 myocardial infarction patients: Changes from 1985 to 2008. Int J Cardiol 2012.

6. Simoons ML, Serruys PW, vd Brand M, Bar F, de Zwaan C, Res J, Verheugt FW, Krauss XH, Remme WJ, Vermeer F, et al. Improved survival after early thrombolysis in acute myocardial infarction. A randomised trial by the Interuniversity Cardiology Institute in The Netherlands. Lancet 1985;2(8455):578-82.

7. Nauta ST, Deckers JW, Akkerhuis M, Lenzen M, Simoons ML, van Domburg RT. Changes in Clinical Profile, Treatment, and Mortality in Patients Hospitalised for Acute Myocardial Infarction between 1985 and 2008. PLoS One 2011;6(11):e26917.

8. Jernberg T, Johanson P, Held C, Svennblad B, Lindback J, Wallentin L. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. JAMA 2011;305(16):1677-84.

9. Lazzeri C, Valente S, Chiostri M, Picariello C, Gensini GF. In-hospital peak glycemia and prognosis in STEMI patients without earlier known diabetes. Eur J Cardiovasc Prev Rehabil 2010;17(4):419-23.

10. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364(9438):937-52.

11. Yang ZJ, Liu J, Ge JP, Chen L, Zhao ZG, Yang WY. Prevalence of cardiovascular disease risk factor in the Chinese population: the 2007-2008 China National Diabetes and Metabolic Disorders Study. Eur Heart J 2012;33(2):213-20.

12. Dahabreh IJ, Kent DM. Index event bias as an explanation for the paradoxes of recurrence risk research. JAMA 2011;305(8):822-3.

13. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, Giles WH, Capewell S. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med 2007;356(23):2388-98.

Part V

Percutaneous coronary interventions

Chapter 12

Seven-year safety and efficacy of the unrestricted use of drug-eluting stents in saphenous vein bypass grafts

Sjoerd T Nauta
Nicolas M van Mieghem
Michael Magro
Jaap W Deckers
Cihan Simsek
Robert-Jan van Geuns
Wim J van der Giessen
Peter De Jaegere
Evelyn Regar
Ron T van Domburg
Patrick W Serruys

Catheter Cardiovasc Interv. 2012 May 1;79(6):912-8

Abstract

Objectives

The aim was to investigate the 7-year clinical outcomes of patients treated with either drug-eluting stents (DES) or bare-metal stents (BMS) for saphenous vein graft disease (SVG).

Background

Atherosclerotic disease in SVG has several peculiarities which make it not possible to extrapolate outcomes of the use of DES as compared to BMS, from outcomes observed in native coronary arteries. To date no long-term safety and efficacy results for DES in SVG have been published.

Methods

Between January, 2000 and December, 2005 a total of 250 consecutive patients with saphenous vein graft disease were sequentially treated with DES (either sirolimus- or paclitaxel-eluting stents) or with BMS. Yearly follow-up was performed.

Results

At 7¼ years, a total of 101 patients died (58 (46%) in the BMS group and 43 (42%) in the DES group, p-value= 0.4). There was no significant difference in the combined endpoint mortality or myocardial infarction. Cumulative target vessel revascularisation (TVR) was higher in the BMS group compared to the DES group (41% vs. 29% respectively; adjusted hazard ratio (HR) 0.63, 95% confidence interval (CI): 0.39 to 1.0). The cumulative incidence of major adverse cardiac events was 73% versus 68% in the BMS and DES groups respectively (adjusted HR 0.93, 95% CI: 0.67 to 1.3).

Conclusions

In the present study, the unrestricted use of DES for SVG lesions appeared safe and effective up to 7¼ years- and the use of DES resulted in a clinically relevant lower rate of TVR.

Introduction

Coronary artery bypass graft surgery (CABG) often involves saphenous vein graft (SVG) conduits.[1] However, the lifespan of SVG has proven to be limited – at 10 years, 50% of such grafts contain at least one significant stenosis.[2] Significant atherosclerotic disease of SVG, despite optimal medical therapy, may result in the recurrence of symptoms and a higher risk of major adverse cardiac events necessitating re-intervention.[1]

Given the high risk of redo-surgery,[3] and the availability of new technologies including embolic protection devices and dedicated catheters, PCI with bare-metal stents (BMS) has surpassed CABG as the treatment of first choice for treating saphenous vein graft disease.[4, 5] Still, the cumulative event rate after stent implantation remains high because of atherosclerotic disease progression and in-stent restenosis.[6, 7] Earlier the RRISC trial showed a catch-up in the repeat revascularization rates in patients treated with sirolimus-eluting stents (SES). Moreover, the authors reported significant increase in late mortality in patients treated with SES as compared to those treated with BMS.[8]

Atherosclerotic disease in SVG has several peculiarities – including the plaque composition and restenotic process[9-12] – that differ from native coronary arteries. Therefore, it is uncertain whether the beneficial effects of drug-eluting stents (DES) compared to BMS in native coronary arteries could be extrapolated to SVGs. The safety and efficacy for DES in SVG has been proven for clinical outcomes up to 3 years in multiple meta-analyses.[13-21] However, no study reports the long-term outcomes after DES in SVG.

We therefore set out to investigate the long-term safety and efficacy outcomes (up to 7 years) of a consecutive series of patients treated with BMS or DES for lesions in saphenous vein grafts.

Methods

Patient selection

Between January 1, 2000 and December 31, 2005 a total of 250 percutaneous coronary interventions were performed in our institution using BMS (n=128), SES (n=21) or paclitaxel-eluting stent (PES; n=101) in saphenous vein graft lesions. Patients who received previous brachy therapy (n=27) and patients who received no stent (n= 35) or a Symbiot™ Covered Stent (n = 2) are not included in this number.

All patients remained in their first original enrolled cohort during the follow-up period. The BMS subgroup contained all consecutive patients before April 16, 2002. The 16th of April our institution commenced the unrestricted use of drug-eluting stents as default strategy. Until January 2003 SES (Cypher®, Cordis Corp., Johnson & Johnson, Warren, NJ, USA) were used exclusively, whereas from February 2003 PES (TAXUS™, Express2™ or Liberté™, Boston Scientific, Natick, MA, USA) replaced the SES as the device of choice for every percutaneous coronary intervention -including vein graft interventions. This study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki.

All procedures were performed according to standard procedural guidelines and their details have been reported previously.[22] Every patient was pre-treated with aspirin and ≥300 mg clopidogrel. Angiographic success was defined as residual stenosis ≤30% by online quantitative coronary angiography in the presence of Thrombolysis In Myocardial Infarction flow grade 3. All patients were advised to maintain aspirin lifelong and clopidogrel for at least 1 month if BMS were used, for ≥3 months for patients with SES, and ≥6 months for patients with PES. Distal embolisation protection devices and peri-procedural glycoprotein IIb/IIIa inhibitors were used according to the operator's discretion.

Definitions and clinical endpoints

Definitions of baseline characteristics are according to the RESEARCH and T-SEARCH registry definitions, and have previously been described.[22, 23]

Safety end-points included all-cause mortality, the composite of all cause mortality/ myocardial infarction (MI) and stent thrombosis, whereas the efficacy end point consisted of target vessel revascularization (TVR). The combined endpoint major adverse cardiac event (MACE) was defined as a composite of all-cause mortality, any MI related or unrelated to TVR stenting and TVR.

MI was diagnosed by recurrent symptoms and/or new electrocardiographic changes in association with a concomitant rise and fall in creatinin kinase-MB mass or troponin-T/ troponin-I to ≥3 times the upper limit of normal. A TVR was defined as a percutaneous or surgical re-intervention driven by any lesion (≥50% of the luminal diameter) located in the index graft, in the presence of ischemic symptoms, or a positive functional ischemia study. Stent thrombosis was defined as angiographically defined thrombosis with Thrombolysis In Myocardial Infarction flow grade 0 or 1 or the presence of a flow limiting thrombus, accompanied by acute onset of ischemic symptoms at rest, similar to the ARC definite criteria.[22, 24]

Survival status was assessed through municipal civil registries. A prospectively developed questionnaire inquiring about patients' current health status, clinical events and medication use was sent to all living patients on a yearly basis. In case of an event, medical records, discharge summaries and, when necessary, angiographic films, were systematically reviewed. Cause of death was acquired via the Central Bureau of Statistics, The Hague, The Netherlands or by directly contacting the patients' General Physician.[22]

Statistical analysis

Continuous variables are presented as mean and standard deviation or as median and boundary of interquartile range, categorical variables as absolute numbers and percentage. Normality assumption was evaluated by the Kolmogorov-Smirnov test. Continuous variables were compared using Student's unpaired t-test or Mann-Whitney non-parametric test. Categorical variables were compared using chi-square statistics or Fischer's exact test, as appropriate.

The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method, and curves were compared using log-rank test. Observed unadjusted and adjusted measures of association were obtained by Cox regression models and presented as hazard ratios. Due to the total number of events we had to restrict the number of possible confounders entered into the model.[25] Separate Cox regression analyses were performed to identify independent predictors of adverse events using all clinical and procedural variables listed in Tables I and II. These independent predictors are shown in the results section and were entered into the Cox regression model to obtain the adjusted hazard ratios (HR) and 95% confidence intervals (CI). All statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, Illinois).

Results

Survival status was available for 98.4% of the BMS patients and 99.4% of the DES patients. Clinical follow-up consisted of 1 582 person-years. The baseline and procedural characteristics of patients in both groups are depicted in Table I. Overall both groups were very similar; however, patients in the DES group were less likely to have hyperlipidaemia or a family history of coronary artery disease. Further, procedural characteristics differed in terms of a higher frequency of three-vessel disease, a smaller average stent diameter and a longer total stented length in the DES group. The use of glycoprotein IIb /IIIa inhibitors decreased over time, from 41% in the BMS group to 21% in the DES group ($p = 0.001$). Whereas the duration of post-discharge clopidogrel increased from a median of three (IQR 2-6) in the BMS group to six months (IQR 6-6; $p < 0.001$) in the DES group. In univariate analysis, the prescribed duration of clopidogrel was not significantly related to TVR (p-value=0.15) or any of the other clinical outcomes. No differences in self-reported long-term medications were observed (Table II).

Event rates are depicted in Table III. At 7¼ years, a total of 101 patients died. Cause of death was cardiac in 66% in the BMS group and 70% in the DES group. Cumulative all-cause mortality was 46% versus 42% in the BMS and DES groups respectively (Figure 1). When adjusting for independent predictors there was no significant improvement in cumulative mortality. Independent predictors (p-value < 0.1) of both cardiac and all-cause mortality at 7¼ years were increasing age, diabetes mellitus, renal impairment, enrolment diagnosis, and the left anterior descending (LAD) as revascularization territory.

The cumulative incidence of the combined endpoint mortality or MI was 57% in the BMS group vs. 60% in the DES group (Figure 2). Independent predictors (p-value < 0.1) of mortality or MI at 7¼ years were diabetes mellitus, renal impairment, and enrolment diagnosis.

At 7¼ year, cumulative TVR was 41% in the BMS group as compared to 29% in the DES group (Figure 3). In the DES group TVR was reduced by 37% (adjusted HR 0.63, 95% CI: 0.39 to 1.0). Two separate TVRs in the BMS group and one TVR in the DES group that

were performed due to angiographic follow-up are not considered as an event. A total of six (5.0%) patients treated with BMS suffered from stent thrombosis occurring at a median of 220 days (IQR 163-1198) versus only one (0.8%) in the DES group occurring at 606 days. The only independent predictor (p-value < 0.1) of TVR at 7¼ years was previous MI.

Cumulative MACE in the BMS group was 73% versus 68% in the DES group (Figure 4). Independent predictors (p-value < 0.1) of MACE at 7¼ years were increasing age, enrolment diagnosis and, average stent diameter.

Table I: Baseline and procedural characteristics stratified according to stent type

	BMS (n = 128)	DES (n = 122)	P-value
Male, n (%)	102 (80%)	103 (84%)	0.33
Age, mean±SD	69±9.6	68±8.7	0.31
Cardiac history			
Previous MI	59 (46%)	61 (50%)	0.23
Previous PCI	34 (27%)	36 (30%)	0.77
Risk factors			
Diabetes mellitus	27 (21%)	38 (31%)	0.07
Hyperlipidaemia	57 (45%)	81 (66%)	0.001
Hypertension	55 (43%)	60 (49%)	0.33
Family history of CAD	22 (17%)	34 (28%)	0.043
Current smoker	21 (16%)	10 (8%)	0.049
Renal impairment	2 (2%)	6 (5%)	0.13
BMI	26 ±3.7	27 ±3.8	0.33
Enrolment diagnosis			**0.37**
Stable angina	42 (33%)	50 (41%)	
Unstable angina	68 (53%)	60 (50%)	
Acute MI	18 (14%)	10 (8%)	
Shock	0 (0%)	1 (1%)	

(continues)

Table I: Baseline and procedural characteristics stratified according to stent type (continued)

	BMS (n = 128)	DES (n = 122)	P-value
Procedural characteristics			
Revascularisation territory			
LAD	39 (49%)	37 (33%)	0.40
LCX	67 (53%)	54 (49%)	0.53
RCA	39 (31%)	38 (34%)	0.56
Native vessels treated			
LAD	14 (11%)	16 (13%)	0.70
LCX	13 (10%)	15 (12%)	0.43
RCA	16 (13%)	22 (18%)	0.38
LM	3 (2.3%)	2 (1.6%)	1.00
Disease complexity			
3 vessel disease	24 (19%)	44 (36%)	<0.01
Multiple grafts treated	4 (3.2%)	3 (2.6%)	1*
In stent restenosis	10 (8%)	10 (8%)	0.91
Number of stents per lesion	2 [1-2]†	2 [1-3]†	0.21
Total stent length, mm	26 [18-40]†	32 [18-57]†	0.02
Average stent diameter, mm	3.7±0.6	3.2±0.7	<0.001
Success rate			
Angiographic success	124 (97%)	117 (98%)	0.46
Number of lesions successfully treated	1 [1-2]†	1 [1-2]†	0.97
Distal protection device used	6 (4.7%)	2 (1.6%)	0.28
Glycoprotein IIb/IIIa inhibitors	53 (41%)	26 (21%)	<0.01

* P-value by Fisher's exact test.

† Data presented as median [interquartile range].

BMI, body mass index; BMS, bare-metal stent; CAD, coronary artery disease; DES, drug-eluting stent; IQR, interquartile range; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; SD, standard deviation.

Table II: Self-reported medical treatment at 3 year follow according to stent type

	BMS (n = 99)	DES (n = 99)	P-value
Alive at 3 year			
Aspirin	85 (86%)	81 (82%)	0.44
Anticoagulants	17 (17%)	22 (22%)	0.37
β-blockers	81 (82%)	83 (84%)	0.71
ACE inhibitors or AT1 antagonists	54 (55%)	56 (57%)	0.78
Diuretics	31 (31%)	30 (30%)	0.88
Statins	93 (94%)	93 (94%)	1.0

ACE, angiotensin converting enzyme; AT1, angiotensine II type 1 receptor; BMS, bare-metal stent; DES, drug-eluting stent.

Table III: Association between stent type used and event rates: at 30 days and at 7¼ years

	Number of events (Kaplan Meier estimate)		Observed HR (95% CI)	Adjusted HR (95% CI)
	BMS (n = 126)	DES (n = 121)	DES vs. BMS	DES vs. BMS
Events at 30 days after PCI				
Total mortality	7 (5.6%)	4 (3.3%)		
Cardiac mortality	6 (4.8%)	4 (3.3%)		
Mortality or myocardial infarction	10 (7.9%)	7 (5.8%)		
Target vessel revascularisation	4 (3.2%)	2 (1.7%)		
Major adverse cardiac events	14 (11%)	8 (6.6%)		
Events at 7¼ years after PCI				
Total mortality	58 (46%)	43 (42%)	0.84 (0.56-1.3)	0.90 (0.59-1.4)†
Cardiac mortality	38 (35%)	30 (33%)	0.90 (0.55-1.4)	0.93 (0.56-1.5)†
Mortality or myocardial infarction	72 (57%)	63 (60%)	1.0 (0.74-1.5)	0.97 (0.71-1.4)‡
Target vessel revascularisation	45 (41%)	28 (29%)	0.62 (0.38-0.99)*	0.63 (0.39-1.0)§
Major adverse cardiac events	92 (73%)	74 (68%)	0.81 (0.59-1.1)	0.93 (0.67-1.3)‖

The observed (unadjusted) and adjusted HR compares DES vs. BMS with BMS as the reference.

* p-value < 0.05.

†, ‡, §, ‖ adjusted for independent predictors of the outcome of interest as described in the results section.

HR, Hazard ratio; CI, confidence interval; BMS, bare-metal stent; DES, drug-eluting stent; BMI, body mass index, PCI, percutaneous coronary intervention.

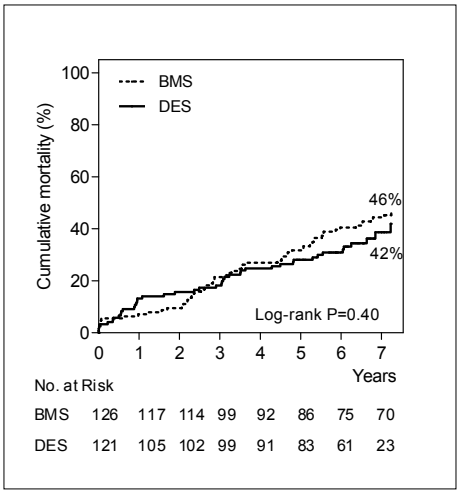

Figure 1: Kaplan Meier curve of cumulative mortality. BMS, bare-metal stent; DES, drug-eluting stent.

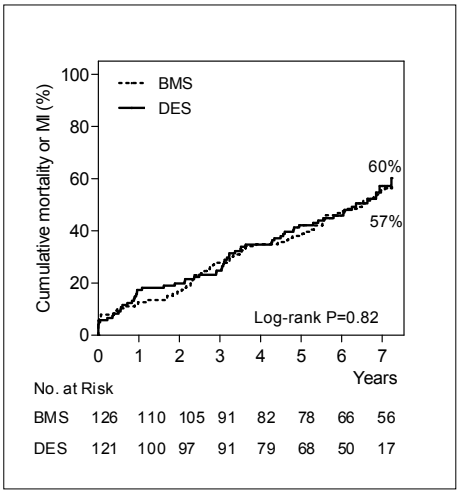

Figure 2: Kaplan Meier curve of cumulative mortality or MI. BMS, bare-metal stent; DES, drug-eluting stent; MI, myocardial infarction.

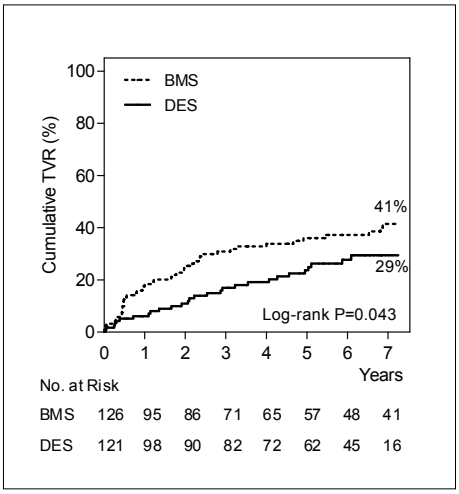

Figure 3: Kaplan Meier curve of cumulative TVR. BMS, bare-metal stent; DES, drug-eluting stent; TVR, target vessel revascularization.

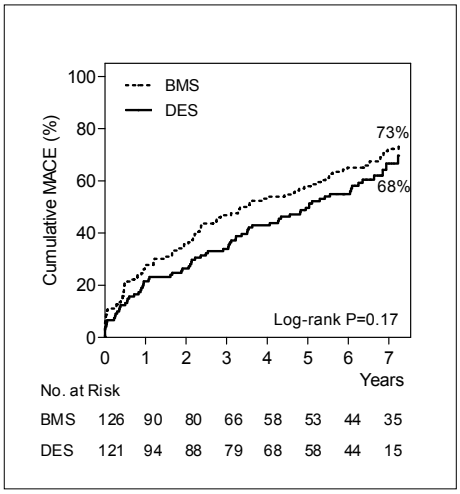

Figure 4: Kaplan Meier curve of cumulative MACE. BMS, bare-metal stent; DES, drug-eluting stent; MACE, major adverse cardiac event (combined endpoint of all-cause mortality, myocardial infarction, and target vessel revascularization).

Discussion

The present study shows that the unrestricted use of DES in SVG remains safe and effective as compared to BMS up to seven years of follow up, illustrated by similar mortality rates and clinically relevant lower rates of TVR in patients treated with DES. We have already reported the four-year follow up of DES vs. BMS in SVG.[23] At four years DES was considered safe and effective, illustrated by lower rates of TVR. These results have been validated by a meta-analysis of three randomized controlled trials –although the maximum follow-up duration in the three trials was 2.5 years.[17]

The treatment of SVG disease represents about 3-8% of the PCI cases in our centre. Atherosclerotic disease in SVG has several peculiarities which account for the poor outcome compared to native coronary arteries, including a different plaque composition, higher plaque burden, more friable material and frequent superimposed thrombus.[9,10] Further, the restenotic process in SVGs is different with several distinct phenomena including intimal hyperplasia, progression of atherosclerosis, local inflammatory reaction and thrombosis[12] whilst the major process in the coronaries is intimal hyperplasia.[11] Therefore, regarding clinical outcomes it is unlikely that the results in native coronary arteries –improved outcomes with use of DES– also hold for SVG.

The present study included a total of 250 'real world' consecutive patients treated for SVG disease. In terms of absolute reduction, at 7¼ years we find a reduction in TVR of 12%, which is identical to the absolute reduction in TVR at one year. The present study underscores the sustained clinical benefit with DES in SVG over BMS over 7¼ years. Further, the absolute risk reduction, representing the number needed to treat (NNT), is very comparable –if not equal- to studies in patients with single de novo lesions (12% absolute TVR reduction at 7¼ years in the present study, 16% at 5 year in the RAVEL study,[26] 11% at 5 year in the SIRIUS study,[27] and 10% at 5 year in the TAXUS study[28]). In the present study the overall event rates remain high as compared to event rates after native vessel stenting.[29] Overall morality at 7¼ years is 43%. The most likely explanation for the high event rates is the relatively high mean age, the high frequency of measured comorbidities and risk factors and the fact that all patients in the present study presented with an occlusion in a SVG.

To date, other large-scale registries have not yet reported long-term outcome (>3 years) in this specific patient subset.[18, 30, 31] Therefore the duration of the follow-up of the present study is probably the longer worldwide and the institution has unique reputation for long term follow-up.[32] Interestingly, the long term cumulative incidence of MACE of 73% in BMS patients at 7¼ years is identical to the cumulative incidence of MACE in Dutch patients at 5 years treated two decades ago with balloon angioplasty.[33] This suggests that the expected survival free of MACE increased with 2¼ years between patients treated for SVG lesions in 1985 and in 2002. Today, with the use of DES the estimated cumulative incidence of MACE further improved to 68% at 7¼ years.

Of note, the study population stems from an era when embolic protection devices were not yet fully established. Embolic protection devices were used in less than 5% of cases. Embolic protection devices have been shown to reduce MACE by up to 40%.[34] As such the use of embolic protection devices in SVG PCI is a class I level of recommendation B recommendation in the recent ESC/EACTS guidelines on myocardial revascularisation.[35] The implementation of embolic protection devices could have had a positive impact on absolute numbers of short and longer-term outcome in our study cohort.

A limitation of the present study is that the results are based on a nonrandomized patient population without completely identical groups. In the DES group, more complex patients were being treated with PCI compared to the BMS group. Although we statistically adjusted for clinical and procedural differences between both groups, it could be debated whether this is sufficient. Further, the results are based on a relatively small patient cohort and therefore may have lack of power. Large-scale randomized controlled trials with long-term follow up are advocated to prove the long-term benefit of DES over BMS in SVG.

Conclusions

In the present study, the use of DES for SVG lesions appeared safe and effective up to 7¼ years, and DES resulted in a clinically relevantly lower rate of TVR.

Potential conflict of interest

None.

References

1. Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, Hart JC, Herrmann HC, Hillis LD, Hutter AM, Jr., Lytle BW, Marlow RA, Nugent WC, Orszulak TA, Antman EM, Smith SC, Jr., Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Ornato JP. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation 2004;110(9):1168-76.

2. Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. J Am Coll Cardiol 1996;28(3):616-26.

3. Weintraub WS, Jones EL, Morris DC, King SB, 3rd, Guyton RA, Craver JM. Outcome of reoperative coronary bypass surgery versus coronary angioplasty after previous bypass surgery. Circulation 1997;95(4):868-77.

4. Baim DS. Percutaneous treatment of saphenous vein graft disease: the ongoing challenge. J Am Coll Cardiol 2003;42(8):1370-2.

5. Morrison DA, Sethi G, Sacks J, Henderson W, Grover F, Sedlis S, Esposito R, Ramanathan K, Weiman D, Saucedo J, Antakli T, Paramesh V, Pett S, Vernon S, Birjiniuk V, Welt F, Krucoff M, Wolfe W, Lucke JC, Mediratta S, Booth D, Barbiere C, Lewis D. Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: a multicenter, randomized trial. Investigators of the Department of Veterans Affairs Cooperative Study #385, the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). J Am Coll Cardiol 2001;38(1):143-9.

6. de Jaegere PP, van Domburg RT, Feyter PJ, Ruygrok PN, van der Giessen WJ, van den Brand MJ, Serruys PW. Long-term clinical outcome after stent implantation in saphenous vein grafts. J Am Coll Cardiol 1996;28(1):89-96.

7. Garg S, Serruys PW. Coronary stents: looking forward. J Am Coll Cardiol 2010;56(10 Suppl):S43-78.

8. Vermeersch P, Agostoni P, Verheye S, Van den Heuvel P, Convens C, Van den Branden F, Van Langenhove G. Increased late mortality after sirolimus-eluting stents versus bare-metal stents in diseased saphenous vein grafts: results from the randomized DELAYED RRISC Trial. J Am Coll Cardiol 2007;50(3):261-7.

9. Webb JG, Carere RG, Virmani R, Baim D, Teirstein PS, Whitlow P, McQueen C, Kolodgie FD, Buller E, Dodek A, Mancini GB, Oesterle S. Retrieval and analysis of particulate debris after saphenous vein graft intervention. J Am Coll Cardiol 1999;34(2):468-75.

10. Depre C, Havaux X, Wijns W. Pathology of restenosis in saphenous bypass grafts after long-term stent implantation. Am J Clin Pathol 1998;110(3):378-84.

11. Farb A, Sangiorgi G, Carter AJ, Walley VM, Edwards WD, Schwartz RS, Virmani R. Pathology of acute and chronic coronary stenting in humans. Circulation 1999;99(1):44-52.

12. van Beusekom HM, van der Giessen WJ, van Suylen R, Bos E, Bosman FT, Serruys PW. Histology after stenting of human saphenous vein bypass grafts: observations from surgically excised grafts 3 to 320 days after stent implantation. J Am Coll Cardiol 1993;21(1):45-54.

13. Lupi A, Navarese EP, Lazzero M, Sansa M, De Servi S, Serra A, Bongo AS, Buffon A. Drug-eluting stents vs. bare metal stents in saphenous vein graft disease. Insights from a meta-analysis of 7,090 patients. Circ J 2011;75(2):280-9.

14. Hakeem A, Helmy T, Munsif S, Bhatti S, Mazraeshahi R, Cilingiroglu M, Effat M, Leesar M, Arif I. Safety and efficacy of drug eluting stents compared with bare metal stents for saphenous vein graft interventions: A comprehensive meta-analysis of randomized trials and observational studies comprising 7,994 patients. Catheter Cardiovasc Interv 2010.

15. Joyal D, Filion KB, Eisenberg MJ. Effectiveness and safety of drug-eluting stents in vein grafts: a meta-analysis. Am Heart J 2010;159(2):159-169 e4.

16. Lee MS, Yang T, Kandzari DE, Tobis JM, Liao H, Mahmud E. Comparison by meta-analysis of drug-eluting stents and bare metal stents for saphenous vein graft intervention. Am J Cardiol 2010;105(8):1076-82.

17. Meier P, Brilakis ES, Corti R, Knapp G, Shishehbor MH, Gurm HS. Drug-eluting versus bare-metal stent for treatment of saphenous vein grafts: a meta-analysis. PLoS One 2010;5(6):e11040.

18. Testa L, Agostoni P, Vermeersch P, Biondi-Zoccai G, Van Gaal W, Bhindi R, Brilakis E, Latini RA, Laudisa ML, Pizzocri S, Lanotte S, Brambilla N, Banning A, Bedogni F. Drug eluting stents versus bare metal stents in the treatment of saphenous vein graft disease: a systematic review and meta-analysis. EuroIntervention 2010;6(4):527-36.

19. Sanchez-Recalde A, Jimenez Valero S, Moreno R, Barreales L, Lozano I, Galeote G, Martin Reyes R, Calvo L, Lopez-Sendon JL. Safety and efficacy of drug-eluting stents versus bare-metal stents in saphenous vein grafts lesions: a meta-analysis. EuroIntervention 2010;6(1):149-60.

20. Wiisanen ME, Abdel-Latif A, Mukherjee D, Ziada KM. Drug-Eluting Stents Versus Bare-Metal Stents in Saphenous Vein Graft Interventions: A Systematic Review and Meta-Analysis JACC Cardiovasc Interv 2010;3(12):1262-1273.

21. Mamas MA, Foley J, Nair S, Wiper A, Clarke B, El-Omar M, Fraser DG, Khattar R, Neyses L, Fath-Ordoubadi F. A Comparison of Drug-Eluting Stents versus Bare Metal Stents in Saphenous Vein Graft PCI Outcomes: A Meta-Analysis. J Interv Cardiol 2011.

22. Ong AT, Hoye A, Aoki J, van Mieghem CA, Rodriguez Granillo GA, Sonnenschein K, Regar E, McFadden EP, Sianos G, van der Giessen WJ, de Jaegere PP, de Feyter P, van Domburg RT, Serruys PW. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. J Am Coll Cardiol 2005;45(6):947-53.

23. van Twisk PH, Daemen J, Kukreja N, van Domburg RT, Serruys PW. Four-year safety and efficacy of the unrestricted use of sirolimus- and paclitaxel-eluting stents in coronary artery bypass grafts. EuroIntervention 2008;4(3):311-7.

24. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115(17):2344-51.

25. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. J Clin Epidemiol 1995;48(12):1503-10.

26. Morice MC, Serruys PW, Barragan P, Bode C, Van Es GA, Stoll HP, Snead D, Mauri L, Cutlip DE, Sousa E. Long-term clinical outcomes with sirolimus-eluting coronary stents: five-year results of the RAVEL trial. J Am Coll Cardiol 2007;50(14):1299-304.

27. Ellis SG, Stone GW, Cox DA, Hermiller J, O'Shaughnessy C, Mann T, Turco M, Caputo R, Bergin PJ, Bowman TS, Baim DS. Long-term safety and efficacy with paclitaxel-eluting stents: 5-year final results of the TAXUS IV clinical trial (TAXUS IV-SR: Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent). JACC Cardiovasc Interv 2009;2(12):1248-59.

28. Weisz G, Leon MB, Holmes DR, Jr., Kereiakes DJ, Popma JJ, Teirstein PS, Cohen SA, Wang H, Cutlip DE, Moses JW. Five-year follow-up after sirolimus-eluting stent implantation results of the SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) Trial. J Am Coll Cardiol 2009;53(17):1488-97.

29. Simsek C, Magro M, Boersma E, Onuma Y, Nauta ST, Gaspersz MP, van der Giessen WJ, van Domburg RT, Serruys PW, Thora IC. The Unrestricted Use of Sirolimus- and Paclitaxel-Eluting Stents Results in Better Clinical Outcomes During 6-Year Follow-Up Than Bare-Metal Stents An Analysis of the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) and T-SEARCH (Taxus Stent Evaluated At Rotterdam Cardiology Hospital) Registries. Jacc-Cardiovasc Inte 2010;3(10):1051-1058.

30. Tu JV, Bowen J, Chiu M, Ko DT, Austin PC, He Y, Hopkins R, Tarride JE, Blackhouse G, Lazzam C, Cohen EA, Goeree R. Effectiveness and safety of drug-eluting stents in Ontario. N Engl J Med 2007;357(14):1393-402.

31. James SK, Stenestrand U, Lindback J, Carlsson J, Schersten F, Nilsson T, Wallentin L, Lagerqvist B. Long-term safety and efficacy of drug-eluting versus bare-metal stents in Sweden. N Engl J Med 2009;360(19):1933-45.

32. van Domburg RT, Kappetein AP, Bogers AJ. The clinical outcome after coronary bypass surgery: a 30-year follow-up study. Eur Heart J 2009;30(4):453-8.

33. Plokker HW, Meester BH, Serruys PW. The Dutch experience in percutaneous transluminal angioplasty of narrowed saphenous veins used for aortocoronary arterial bypass. Am J Cardiol 1991;67(5):361-6.

34. Coolong A, Baim DS, Kuntz RE, O'Malley AJ, Marulkar S, Cutlip DE, Popma JJ, Mauri L. Saphenous vein graft stenting and major adverse cardiac events: a predictive model derived from a pooled analysis of 3958 patients. Circulation 2008;117(6):790-7.

35. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas PE, Widimsky P, Alfieri O, Dunning J, Elia S, Kappetein P, Lockowandt U, Sarris G, Vouhe P, von Segesser L, Agewall S, Aladashvili A, Alexopoulos D, Antunes MJ, Atalar E, Brutel de la Riviere A, Doganov A, Eha J, Fajadet J, Ferreira R, Garot J, Halcox J, Hasin Y, Janssens S, Kervinen K, Laufer G, Legrand V, Nashef SA, Neumann FJ, Niemela K, Nihoyannopoulos P, Noc M, Piek JJ, Pirk J, Rozenman Y, Sabate M, Starc R, Thielmann M, Wheatley DJ, Windecker S, Zembala M. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2010;31(20):2501-55.

Chapter 13

Weekend versus weekday mortality in ST-segment elevation acute myocardial infarction patients between 1985 and 2008

Sanne M Snelder
Sjoerd T Nauta
K Martijn Akkerhuis
Jaap W Deckers
Ron T van Domburg

Int J Cardiol. 2013 Sep 30;168(2):1576-7

Abstract

Appropriate well-timed medical interventions can reduce mortality from ST-segment elevation myocardial infarction (STEMI)[1]. STEMIs occur every day. However staffing tend to be lower on weekends. This may lead to a lower use of invasive cardiac procedures for patients admitted during weekends. Higher mortality rates for patients admitted during the weekends may be the consequence[2, 3].

Appropriate well-timed medical interventions can reduce mortality from ST-segment elevation myocardial infarction (STEMI)[1]. STEMIs occur every day. However staffing tend to be lower on weekends. This may lead to a lower use of invasive cardiac procedures for patients admitted during weekends. Higher mortality rates for patients admitted during the weekends may be the consequence[2, 3].

Recent reports that compared mortality rates among acute myocardial infarction patients who were admitted on weekends and those admitted on weekdays were inconsistent[3-7].

The aim of our study is to compare mortality rates among 6.820 STEMI patients admitted on weekends and on weekdays for three time intervals (1985-1990, 1990-2000 and 2000-2008).

All consecutive patients aged >18 years with a first admission for ST-segment elevation myocardial infarction (STEMI) to the Intensive Coronary Care Unit (ICCU), between June 1985 and December 2008 were included[8].

Trained physicians and nurses accustomed to the use of standardized case report forms collected the data. The primary independent variable was admission on weekends (Saturday or Sunday) versus weekdays (Monday to Friday). The study endpoint was all-cause mortality at 30 days, 5 years and at 10 years. Survival data was assessed through municipal Civil Registries which is updated regularly and therefore highly accurate in the Netherlands. The author(s) of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology[9].

Data for the period 1985-2008 were grouped into 3 intervals according to decade of hospitalization (1985-1990, 1990-2000, and 2000-2008). Separate analyses were performed for each interval.

Cumulative survival curves according to admission were constructed using the Kaplan–Meier method, and compared by the log-rank test. We examined the independent association between admission on weekdays or weekends and mortality

using logistic regression for 30-day outcome and the Cox proportional hazards model for long-term outcome. Adjustment was performed for age, sex, previous MI, previous PCI, previous CABG, hypertension, diabetes, hyperlipidemia, family history of coronary artery disease and smoking status. Results are reported as odds ratios (OR) –for 30-day mortality– and hazard ratios (HR) –for long-term mortality– and their respective 95% confidence intervals. All statistical tests were 2-tailed, and p-values were considered significant at <0.05. Analysis was performed using SPSS software version 20.0 (SPSS, Chicago, Ill).

Between June 1985 and December 2008 a total of 6,820 consecutive patients were admitted to the ICCU with a STEMI, of whom 2,053 (30%) were admitted on weekends.

Table 1 Baseline characteristics

	1985-1990			1990-2000			2000-2008		
	Weekday	Weekend	P	Weekday	Weekend	P	Weekday	Weekend	P
No. of patients	**698**	**249**		**1413**	**515**		**2656**	**1289**	
Baseline									
Age (years)	60±12	59±12	0.2	60±13	60±13	0.8	61±13	60±13	<0.001
Gender (male)	78 %	76 %	0.6	74 %	76 %	0.3	75 %	73 %	0.2
Cardiac History									
Previous MI*	37 %	31 %	0.1	25 %	23 %	0.4	28 %	26 %	0.1
Previous PCI†	5 %	4 %	0.4	7 %	6 %	0.3	17 %	16 %	0.4
Previous CABG‡	7 %	12 %	0.02	6 %	6 %	1.0	8 %	6 %	0.8
Risk factors									
Hypertension	33 %	37%	0.2	29%	27 %	0.4	34 %	31%	0.1
Diabetes	9 %	8 %	0.8	10 %	12 %	0.3	15 %	13 %	0.1
Hyperlipidemia	8 %	8 %	1.0	15 %	15 %	1.0	24 %	22 %	0.1
Family history	22 %	20 %	0.5	21 %	21 %	0.9	26 %	29 %	0.1
Current smoker	41 %	47 %	0.1	35 %	36 %	0.5	37 %	42 %	0.001
Renal dysfunction	12 %	10 %	0.6	12 %	11 %	0.5	6 %	5 %	0.2
Anemia	34 %	30 %	0.3	41 %	44 %	0.3	41 %	37 %	0.02

* Myocardial infarction
† Percutaneous coronary intervention
‡ Coronary artery bypass grafting

Baseline characteristics are presented in Table 1. With the exception of age between 2000 and 2008 (61±13 vs 60±13 p=<0.001), previous CABG 1985-1990 (7% vs. 12% p=0.02), current smoking 2000-2008 (37% vs. 42% p=0.001) and anemia 2000-2008 (37% vs. 41% p=0.02) no differences were found between the groups.

During the years studied there was an increase in the prevalence of baseline diabetes, hyperlipidemia, anemia and previous PCI. In contrast, there was a decrease in the prevalence of baseline smoking, previous CABG and renal dysfunction.

During the study period a total of 1,929 STEMI patients died of whom 543 patients were admitted during the weekends (28%). Compared to the period 1985-1990 both short and long term mortality of STEMI patients was substantially lower in the period 2000-2008.

Kaplan-Meier cumulate survival curves demonstrated no difference in 30-day en 10 year mortality for weekend versus weekday admission in all 3 intervals (figure 1). After adjustment for age and baseline characteristics there was a difference between the weekends and weekdays in favor of STEMI patients who were admitted on weekends between 1990 and 2000 (OR=0.70 95% CI 0.51-0.97). The adjusted 5-year and 10-year mortality showed no difference between the groups.

Previous studies demonstrated the 'Weekend effect". Patients admitted on weekends to the acute care hospitals had higher mortality rates than those on weekdays[5]. Staffing levels are lower on weekends, consequently fewer urgent procedures are performed[5, 10].

Kostis et al found a higher mortality among patients with acute myocardial infarction admitted on weekends[3]. They concluded that the worse prognosis for patients admitted on the weekends is mediated in part by the lower rate of invasive procedures. A study in South Korea confirmed that the higher mortality rates in the weekends were due to differences in the rate of performance of medical or invasive procedures[7].

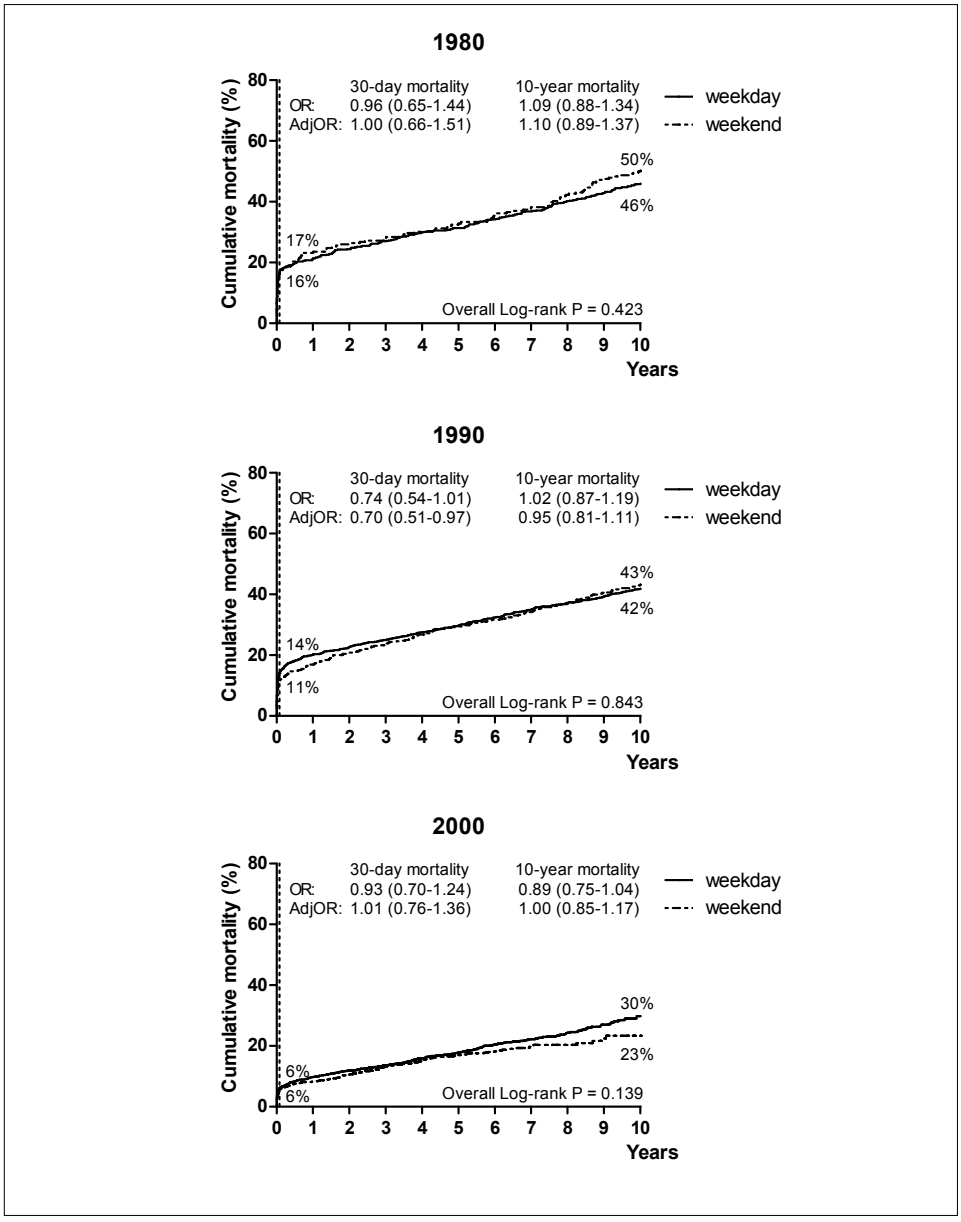

Figure 1: Kaplan Meier curves for 30 day and 10 year cumulative mortality. Unadjusted and adjusted odds ratios (OR and adjOR) for 30-day mortality and the unadjusted and adjusted hazard ratios (HR and adjHR) for 5-year and 10-year mortality and their respective 95% confidence intervals. With weekday used as reference group.

a) 1985-1990

b) 1990-2000

c) 2000-2008

In contrast our results showed that admission either on weekends or on weekdays did not influence both the 30-day mortality and the long-term mortality. This indicates high quality of care. Probably these findings are due to the proper availability of staff and the possibility to perform invasive procedures during the weekends.

Consistent with our results, three studies revealed no difference in mortality rates between weekend and weekday admissions for acute myocardial infarction patients. In a Japanese study Turin et al. found no difference in mortality (HR 1.07 95%CI 0.53–2.16)[4]. In Canada Bell et al. reported no difference in mortality (OR 1.03 95%CI 1.00–1.06) between 160,220 myocardial infarction patients admitted on weekends versus weekdays over a 10-year period. But they reported a lower rate of use of coronary angiography in the weekends[5, 11]. Another study from Japan Matsui et al. found no difference in mortality (6.6% vs 6.7%) even though they found a lower rate of stenting during the weekends[6]. These three studies compared respectively 28-day case mortality rates (Turin et al.), in hospital mortality (Bell et al.) and in-hospital, 30-day, and 1-year mortality rates (Matsui et al.). Our study not only compared short term mortality like these studies but also long term (5-year and 10-year) mortality.

Our study has important strengths. We analyzed all patients > 18 year admitted to our ICCU between 1985 and 2008 with STEMI, with no further in or exclusion criteria. We were not limited by a small study population, and our analyses cover an inclusion period of 24-years with follow-up data up to 10 years. A potential limitation is that the presented data are derived from a single center.

In conclusion, STEMI patients admitted during the weekends have similar short and long-term survival rates as patients admitted during weekdays.

References

1 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;109:1223-5.

2 Magid DJ, Wang Y, Herrin J, McNamara RL, Bradley EH, Curtis JP, et al. Relationship between time of day, day of week, timeliness of reperfusion, and in-hospital mortality for patients with acute ST-segment elevation myocardial infarction. JAMA. 2005;294:803-12.

3 Kostis WJ, Demissie K, Marcella SW, Shao YH, Wilson AC, Moreyra AE, et al. Weekend versus weekday admission and mortality from myocardial infarction. N Engl J Med. 2007;356:1099-109.

4 Turin TC, Kita Y, Rumana N, Sugihara H, Morita Y, Tomioka N, et al. Incidence, admission and case-fatality of acute myocardial infarction: weekend versus weekday in a Japanese population: 16-year results from Takashima AMI Registry (1988-2003). Eur J Epidemiol. 2009;24:93-100.

5 Bell CM, Redelmeier DA. Mortality among patients admitted to hospitals on weekends as compared with weekdays. N Engl J Med. 2001;345:663-8.

6 Matsui K, Kojima S, Sakamoto T, Ishihara M, Kimura K, Miyazaki S, et al. Weekend onset of acute myocardial infarction does not have a negative impact on outcome in Japan. Circ J. 2007;71:1841-4.

7 Hong JS, Kang HC, Lee SH. Comparison of case fatality rates for acute myocardial infarction in weekday vs weekend admissions in South Korea. Circ J. 2010;74:496-502.

8 Nauta ST, Deckers JW, Akkerhuis KM, van Domburg RT. Age-dependent care and long-term (20year) mortality of 14,434 myocardial infarction patients: Changes from 1985 to 2008. Int J Cardiol. 2012.

9 Coats AJ, Shewan LG. Statement on authorship and publishing ethics in the International Journal of Cardiology. Int J Cardiol. 2011;153:239-40.

10 Jneid H, Fonarow GC, Cannon CP, Palacios IF, Kilic T, Moukarbel GV, et al. Impact of time of presentation on the care and outcomes of acute myocardial infarction. Circulation. 2008;117:2502-9.

11 Bell CM, Redelmeier DA. Waiting for urgent procedures on the weekend among emergently hospitalized patients. Am J Med. 2004;117:175-81.

Chapter 14

Value of the SYNTAX score in patients treated by primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: the MI SYNTAXscore study

Michael Magro
Sjoerd T Nauta
Cihan Simsek
Yoshinobu Onuma
Scot Garg
Elco van der Heide
Willem J van der Giessen
Eric Boersma
Ron T van Domburg
Robert-Jan van Geuns
Patrick W Serruys

Am Heart J. 2011 Apr;161(4):771-81

Abstract

Aims

To evaluate the SYNTAX score (SXscore) calculated at two stages during a primary percutaneous intervention (PPCI), i.e., SXscore I (diagnostic), SXscore II (post wiring) and assesses its additional value to standard clinical risk scores in acute myocardial infarction.

Methods and Results

SXscores I and II were applied to 736 consecutive acute STEMI patients referred for PPCI between November 2006 and February 2008. SXscore changed significantly before - I =16 (IQR: 9.5-23) and after wiring- II =11 (IQR: 6-19), $p < 0.001$. Kaplan Meier methods were used to compare the primary end point MACE (composite of repeat MI, TVR and mortality) and secondary endpoint mortality at 1.5 years in tertiles of SXscore I and SXscore II. MACE was highest in the higher SXscore I tertile (11% vs.15% vs 23%, log rank <0.01), driven primarily by increased rate of mortality (9% vs. 11% vs. 17%, log rank = 0.02). MACE was also highest in SXscore II tertile, by a combination of increased mortality but also TVR (TVR rate :

2% vs. 3% vs. 9%, log rank <0.01). Predictive cox regression models for mortality and for MACE were significantly and similarly improved by addition of either SXscore I or SXscore II (HR 1.63, 95%CI 1.18-2.26, p <0.01 for MACE) with respective c-indices of 0.61 and 0.63 for MACE and 0.60 and 0.61 for mortality.

Conclusions

SXscore during PPCI is a useful tool that provides additional risk stratification to known risk factors of long term mortality and MACE in patients with STEMI.

Introduction

The SYNTAX score (SXscore)[1] is a tool that can be used to cumulatively quantify the extent of angiographic coronary artery disease. It has been developed from the Leaman score[2] and therefore takes into account not only the number of lesions, their location and characteristics but also their functional impact. In fact scoring of lesions is weighed according to the size of the perfused territory of the left ventricle. The SXscore has been shown to be a good predictor of adverse cardiovascular events including cardiac death, myocardial infarction and target lesion revascularisation in patients treated with percutaneous coronary intervention for complex disease[3-4].

Coronary angiographic characteristics at primary percutaneous intervention (PPCI) that are known to affect prognosis include culprit artery (left versus right), TIMI flow at presentation and the presence of multivessel disease especially chronic total occlusions[5-7]. The SXscore derived from the diagnostic phase of the PPCI can quantify these features. By consideration of whether the culprit lesion is occluded on presentation and accordingly scoring it as a total occlusion or otherwise, it can incorporate a numerical value that takes into account both the volume and degree of ischaemic left sided myocardium. The SXscore derived after wiring of the culprit lesion defines better the underlying culprit vessel anatomy in cases where this is obscured by the occlusion in the diagnostic phase.

The detailed anatomical and functional consideration of the SXscore may make it an attractive quantification tool for use as a prognostic indicator in patients presenting with ST elevation myocardial infarction (STEMI). To this end we set out to investigate the predictive value of the SXscore on long term outcomes in patients undergoing PPCI. The aims of our study are two-fold. First to calculate the SXscore derived at the two stages during a PPCI procedure and assess their predictive value for long term clinical outcome. Second we studied whether the SXscore is able to offer additional predictive value of long term clinical outcome when compared to the classical risk factors for survival and major adverse coronary events (MACE) in STEMI.

Methods

Between November 2006 and February 2008, 736 consecutive patients undergoing primary PCI for STEMI in our institution were screened for inclusion in the MI SYNTAXscore study. All patients in the referral area of the Thoraxcentre, Erasmus MC, Rotterdam that had symptoms of acute myocardial infarction (< 12 duration) were assessed clinically and by 12 lead ECG by paramedical personnel or peripheral hospital medical staff. Those who met criteria of acute myocardial infarction, were transported immediately to our centre for PPCI. Pre-treatment with aspirin, clopidogrel and heparin was administered pre-hospital. Urgent diagnostic angiography was followed by PPCI if appropriate. The procedure was performed using standard techniques. Drug eluting stents were implanted as first line choice of stents. Treatment of complications such as cardiogenic shock and cardiac arrest were performed according to guidelines.

Baseline clinical characteristics and procedural characteristics were prospectively recorded in a dedicated electronic database. For the purpose of this study, the only exclusion criteria were patients with previous coronary artery bypass grafting (CABG) in whom the SXscore could not be calculated. The SXscore for each patient was calculated by a team of two interventional cardiologists. All coronary lesions with a diameter stenosis ≥ 50%, in vessels ≥1.5 mm were scored using the SYNTAX score algorithm which is available on the website (www.syntaxscore.com). In case of disagreement with regards to the significance of a lesion quantitative coronary angiography was applied and the lesion included if it was ≥ 50 %. On agreement between the two cardiologists, the data was entered onto a dedicated software program. SYNTAX scoring was performed at 2 pre-defined stages of the index procedures:

SXscore I : Initial diagnostic angiogram. This takes into account the patency of the infarct related artery. Thus an infarct related artery (IRA) with a TIMI flow of 0 or 1 is scored as a total occlusion with thrombus.

SXscore II : After wiring/small balloon. If TIMI flow improves with these measures, this allows assessment of lesion severity as well as additional disease downstream. On the other hand, persistence of a TIMI 0/1 that does not allow adequate visualisation of the lesion is scored as in SXscore I. (total occlusion with thrombus)

The investigators calculating the SYNTAX score were blinded to the patients clinical characteristics. The scoring was done prospectively at each stage so that the investigators were blinded to the next stage film, to the procedural data and to the clinical outcomes. No change in scoring was allowed once a score was assigned.

Intra- and inter-observer variability

The first 100 consecutive films from the cohort were analysed by a third independent observer to obtain inter-observer variability and by the same team 8 weeks after the first scoring phase to obtain intra-observer variability. The investigators remained blinded to the results of the first analysis. This number of patients was selected based on our previous experience with the variability of the SYNTAX score.[8]

Follow-up

Survival data for all patients was obtained from the municipal registry. A health questionnaire was subsequently sent to all living patients with specific questions on readmission and major adverse cardiac events. For patients with an adverse event at another centre, medical records, discharge summaries and, when necessary, angiographic films, were systematically reviewed. General practitioners, referring cardiologists and patients were contacted as necessary for additional information. Events were adjudicated by two experienced interventional cardiologists according to the definitions below. Written informed consent was obtained from all patients.

Definitions

ST elevation myocardial infarction was diagnosed when patients had symptoms of an acute myocardial infarction lasting at least 30 minutes and accompanied by >1mm (0.1mV) ST elevation in two or more contiguous leads and later confirmed by a CK and CK-MB rise and/or troponin rise.

Thrombolysis in myocardial infarction (TIMI) flow grade and corrected TIMI frame count as well as myocardial blush grade (MBG) at the start and end of the procedure were determined from the angiographic films as previously described.[9-10] TLR was defined as any PCI of the index lesion and including the 5mm adjacent segments in either main vessel or sidebranch. Stent thrombosis was defined according to the Academic Research Consortium (ARC).[11]

Primary and secondary endpoints

The primary clinical end point was MACE at 1.5 years, defined as a composite of cardiac or non-cardiac death, repeat myocardial infarction (MI) and ischaemia driven target vessel revascularisation (TVR). Repeat MI in the acute post-PPCI phase was defined as clinical signs of re-infarction with recurrent or persistent symptoms and ST segment changes and requiring a repeat PPCI and/or a second peak in the CK-MB mass or troponin –T/troponin-I increase to ≥3 times the upper limit of normal not related to an interventional procedure and new pathological Q waves in 2 or more contiguous electrocardiograph leads. A repeat MI post discharge was defined as in the definitions section above. TVR was defined as revascularisation of any part of the index coronary artery. Secondary endpoints included separately, all cause mortality, repeat MI and TVR.

Statistical analysis

Normality assumption for continuous variables was evaluated by the Kolmogorov-Smirnov test. These are presented as mean±1SD or as median and interquartile range accordingly. Student's unpaired *t* test or Mann-Whitney non-parametric tests were used to evaluate differences in continuous variables. Categorical variables are presented as counts and percentages and differences in categorical variables between subgroups were evaluated with chi-square test or Fisher's exact test. The cohort was divided into three groups determined by SXscore tertiles. Levene's homogeneity-of-variance test was employed to test for equal variance. For those variables meeting the assumption of equal variance analysis of variance (ANOVA) was used to describe differences between the 3 groups. If the ANOVA assumptions were not met we used the Kruskal-Wallis One-Way Analysis of Variance.

Kaplan-Meier method was used to generate cumulative survival curves and curves of event free survival for the various predefined endpoints and the log rank test was used to assess the difference in survival between SXscore tertile groups. Independent variables from multivariable analysis were used to assess the significance of SXscore I and SXscore II and its contribution to improvement of the model with respect to the primary and secondary endpoints as measured by c-indices. To explore the applicability of the findings in our cohort to other STEMI populations, we also assessed the addition of the scores to the widely used TIMI risk score with variables

including age, diabetes, hypertension, systolic blood pressure, heart rate, Killip class, weight, anterior STEMI. On multivariate analysis we determined whether adding SXscore improved the model significantly. The omnibus test of model coefficients was used to assess the improvement of the model. Proportionality of hazards was tested graphically based on visual inspection of log–log survival curves, and by performing a formal test of proportionality based on Schoenfeld residuals for each variable in the model.[12] The performance of the multivariate model with the SXscore was studied with respect to calibration. Calibration refers to whether the model agrees with the observed probabilities; it was measured with the Hosmer-Lemeshow goodness-of-fit test.

The weighted Kappa value determined intra and interobserver variability. A Kappa value of > 0.0 to ≤ 0.2 was considered slight; > 0.2 to ≤ 0.4 fair; > 0.4 to ≤ 0.6 moderate; > 0.6 to ≤ 0.8 substantial; and > 0.8 to ≤ 1.0 almost perfect[8].

All statistical tests were 2-tailed, and p values were significant at <0.05. Analysis was performed using SPSS software version 17.0 (SPSS, Chicago, USA).

No extramural funding was used to support this work.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Results

From the intial 736 patients screened, 27 were excluded due to unavailability of a complete diagnostic coronary angiogram while 21 were excluded since they had prior CABG. Survival status and follow-up could not be obtained in 19 patients. Thus the final number of patients included in our analysis was 669 as shown in figure 1.

Among the 669 patients, 385 (58%) had significant disease in at least one vessel other than the IRA. The median SXscore I was 16 (IQR: 9.5-23). TIMI 0/1 flow in the IRA was present in 61% of patients. The median SXscore II was 11 (IQR: 6-19). Stent implantation was deemed appropriate and performed in 616 (92%) of patients.

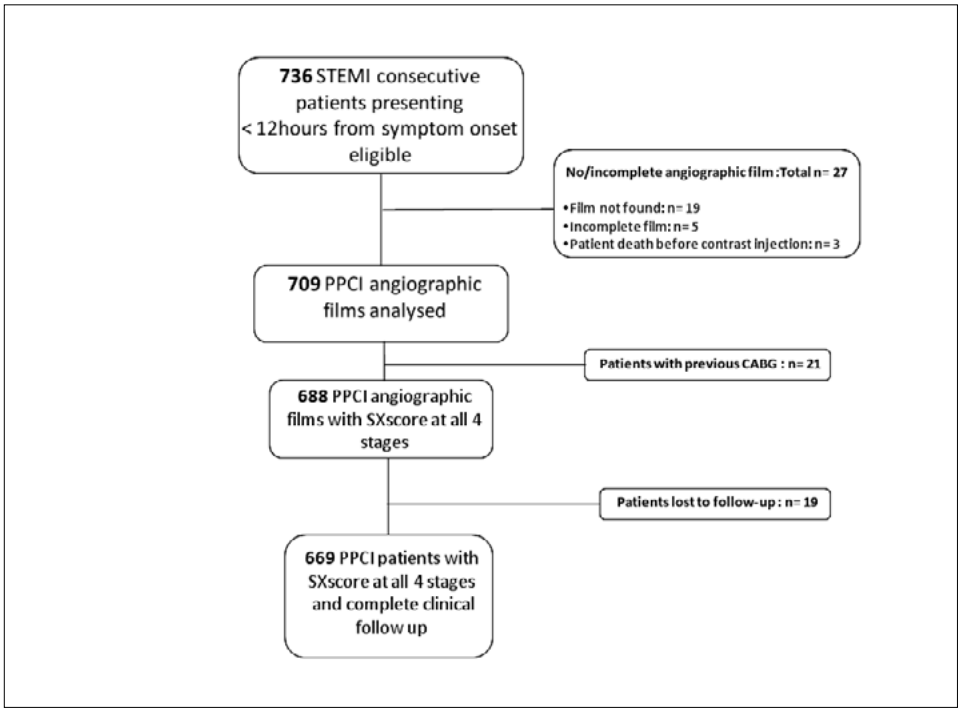

Figure 1: Flow chart of the MI SXscore study population.

There were significant differences between SXscore I and II, p < 0.001 as determined by the Kruskal Wallis test. This is illustrated in figure 2. The difference between the stages were more apparent on analysis of TIMI 1/0 presenting subgroup (fig. 2b) I 19 (IQR: 12-24.5) vs II 12 (IQR: 7-19), p <0.001.

The differences in basal clinical characteristics, angiographic characteristics, procedural characteristics and follow-up management according to three tertiles of SXscore I are shown in tables 1 and 2. Patients with higher SXscore I were older and more commonly had previous MI. These patients also presented with higher pulse rates, cardiogenic shock, anterior STEMI. The LAD was more commonly the culprit in the higher tertile while the RCA was more commonly the IRA in the lowest tertile. Stents implanted in the patients with higher scores were longer and more likely to involve bifurcations. Procedure failure with TIMI 0/1 flow, low MBG and high cTFC were more common in the highest tertile. Complete revascularisation within 3 months was more commonly achieved in patients with lower scores.

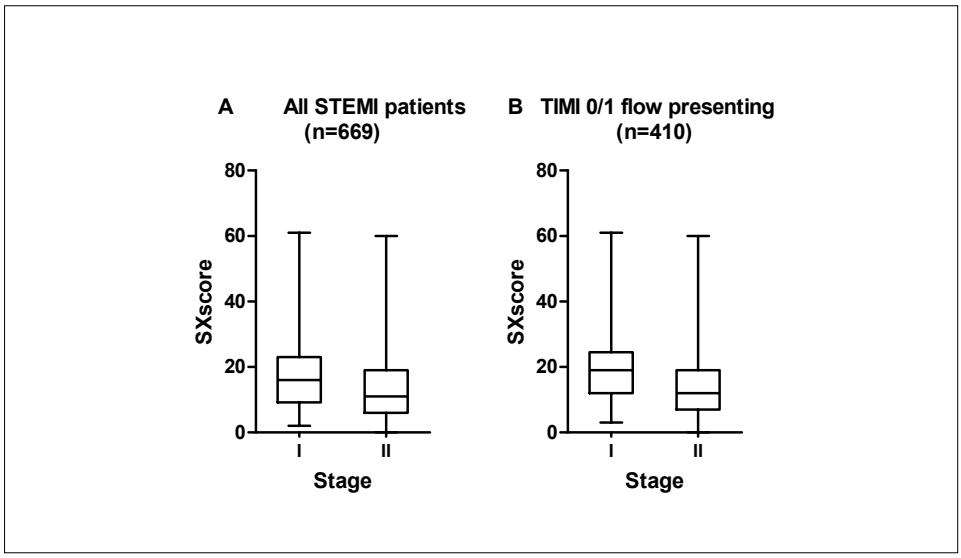

Figure 2: Box plots showing the SXscore at the 2 stages during PPCI; SXscore I obtained from the diagnostic stage and SXscore II obtained after wiring or after use of a small balloon. A, The SXscore changed significantly from I to II when tested with Kruskal-Wallis and subsequently Mann-Whitney tests. B, When patients with TIMI 0/1 only are considered, higher change from I (median 19) to II (median 12) is observed.

Table 1: Clinical characteristics of patients presenting with myocardial infarction according to SXscore I tertiles.

	SXscore I tertiles			p value*
	Lower (<10) n = 209	Intermediate (10-20) n = 241	Higher (>20) n = 219	
Baseline Characteristics				
Age, years	63±13	64±13	68±11	<0.01
Male	135(64%)	171 (71%)	163 (74%)	0.08
Diabetes	14 (8%)	21 (9%)	28 (13%)	0.09
Type I	9 (4%)	7 (3%)	12 (6%)	0.39
Type II	5 (2%)	15 (6%	17 (8%)	0.04
Hypertension	61 (29%)	87(36%)	76 (35%)	0.27
Hypercholesterolaemia	40 (19%)	51 (21%)	49 (22%)	0.71
Smokers				
Current	100 (48%)	105 (44%)	75 (34%)	0.01
Ex-	31 (15%)	29 (12%)	31 (14%)	0.66
Renal failure	3 (1%)	7 (3%)	8 (4%)	0.35
Family history of CAD	79 (38%)	73 (30%)	58 (27%)	0.04
Body Mass Index, Kg/m^2	27±4	27±4	27±4	0.74
Previous Myocardial Infarction	12 (6%)	33 (14%)	40 (18%)	< 0.01
Previous PCI	19 (9%)	23 (10%)	22 (10%)	0.95
Clinical presentation				
Symptom onset to balloon time > 90 mins.	168 (87%)	179 (83%)	174 (87%)	0.38
Out of hospital cardiac arrest	8 (4%)	10 (4%)	13 (6%)	0.53
Pulse rate, bpm	78±17	77±17	81±18	0.04
Blood pressure, mmHg				
Systolic	123±26	126±27	122±27	0.29
Diastolic	75±13	76±15	74±17	0.45
Cardiogenic Shock	11 (5%)	15 (6%)	29 (13%)	< 0.01
Killip class 2-4	11 (5%)	19 (8%)	22 (10%)	0.18

Data is expressed in numbers and (percentages), mean ± 1 standard deviation. Percentages are rounded. PCI = Percutaneous coronary intervention; * p value calculated using ANOVA for continuous variables or Kruskal Wallis test for non parametric variables and Chi-Square test for categorical variables.

Table 2: Angiographic characteristics, procedural characteristics and management of patients with a cute myocardial infarction according to SXscore I tertiles.

	SXscore I tertiles			
	Lower (<10) n = 209	Intermediate (10-20) n = 241	Higher (>20) n = 219	p value*
Angiographic Characteristics Pre-procedural				
Anterior STEMI	70 (34%)	128 (53%)	106 (48%)	< 0.01
Infarct Related Artery				
Left Main	0 (0%)	1 (0.4%)	4 (2%)	0.12
Left anterior descending	63 (30%)	115 (48%)	102 (47%)	< 0.01
Left Circumflex	39 (19%)	42 (17%)	28 (13%)	0.21
Right Coronary	106 (51%)	83 (34%)	86 (39%)	< 0.01
TIMI 0/1 in IRA	73 (35%)	169 (71%)	168 (77%)	< 0.01
Stent thrombosis (cause)	4 (2%)	13 (5%)	8 (4%)	0.15
Diseased vessels incl. IRA				
1-vessel disease	158 (76%)	95 (39%)	28 (13%)	< 0.01
2-vessel disease	40 (19%)	103 (43%)	63 (29%)	< 0.01
3-vessel disease ¶	10 (5%)	43 (18%)	128 (58%)	< 0.01
Left main disease	4 (2%)	3 (1%)	35 (16%)	< 0.01
Chronic Total Occlusion	2 (1%)	3 (1%)	41 (19%)	< 0.01
Procedural characteristics				
Stent Implantation	196 (94%)	225 (93%)	195 (89%)	0.10
Total Stent length, mm	26 (18-36)	28 (23-46)	32 (23-51)	< 0.01
Stent diameter, mm	3.3 ± 0.5	3.1 ± 0.5	3.2 ± 0.5	0.02
Bifurcation treatment in IRA	20 (10%)	55 (23%)	48 (22%)	< 0.01
Thrombectomy	37 (18%)	45 (19%)	42 (19%)	0.92
GP IIb/IIIa Inhibitors	46 (22%)	52 (22%)	49 (22%)	0.98
Inotropic agents	10 (5%)	9 (4%)	12 (6%)	0.67
Intra Aortic Balloon Pump	8 (4%)	13 (5%)	24 (11%)	0.01
Multivessel stenting	15 (7%)	26 (11%)	28 (13%)	0.16
Angiographic characteristics Post-procedural				
TIMI 0/1	3 (1%)	7 (3%)	18 (8%)	< 0.01
Corrected TIMI frame count at end procedure, fps	24 (16-36)	24 (18-35)	28 (20-44)	0.05 §
Myocardial Blush Grade 0/1	1 (1%)	5 (2%)	16 (7%)	< 0.01
Follow - up treatment				
Complete revascularisation within 3 months (PCI n=331, CABG n= 4)	180 (86%)	119 (49%)	36 (16%)	< 0.01
Medication at 1 year				
Aspirin	182 (87%)	200 (83%)	191 (87%)	0.60
Clopidogrel	203 (97%)	231 (96%)	203 (93%)	0.13
B-Blocker	192 (92%)	209 (87%)	188 (86%)	0.41
ACE-inhibitors	117 (56%)	157 (65%)	166 (69%)	0.20
Statins	178 (86%)	219 (91%)	204 (93%)	0.45

Data is expressed in numbers and (percentages), mean ± 1 standard deviation or median and (interquartile range); Percentages are rounded. STEMI = ST elevation myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction; GP = Glycoprotein; PCI = Percutaneous coronary intervention; CABG = Coronary artery bypass graft; IRA = infarct related artery;

* p value calculated using ANOVA for continuous variables and Chi-Square test for categorical variables.

¶ includes cases with left main disease plus one vessel disease.

§ p value by Kruskal Wallis test.

Similarly, for Sxscore II (tables 3 and 4), significantly higher scores were observed in patients with a previous myocardial infarction and those presenting with cardiogenic shock. Patients with higher scores were more likely to have longer stents implanted, more bifurcation treatment and multivessel stenting during the index procedure. Procedure failure with final TIMI flow 0/1 and impaired myocardial perfusion as determined by myocardial blush grade was more common in the tertiles with the higher scores. Whereas complete revascularisation within 3 months was achieved in 88% of patients in the lower tertiles, that in the highest tertile was low at 12.6%.

Table 3: Clinical characteristics of patients presenting with myocardial infarction according to SXscore II tertiles.

	Lower (<9) n = 238	Intermediate (9-17) n = 208	Higher (>17) n = 223	p value*
Baseline Characteristics				
Age, years	62±12	66±13	68±11	0.10
Male	157 (66%)	145 (70%)	167 (75%)	0.10
Diabetes				
Type I	9 (4%)	5 (2%)	14 (6%)	0.12
Type II	8 (3%)	10 (5%)	19 (9%)	0.46
Hypertension	74 (31%)	70 (34%)	80 (36%)	0.55
Hypercholesterolaemia	51 (21%)	36 (17%)	53 (24%)	0.25
Smoker				
Current	117 (52%)	90 (44%)	73 (35%)	< 0.01
Ex-	31 (13%)	27 (13%)	33 (16%)	0.82
Renal failure	3 (1%)	5 (2%)	10 (5%)	0.10
Family history of CAD	93 (39%)	63 (30%)	54 (24%)	< 0.01
Body Mass Index, Kg/m2	27±4	27±4	27±4	0.51
Previous Myocardial Infarction	14 (6%)	27 (13%)	44 (20%)	< 0.01
Previous PCI	24 (10%)	19 (9%)	21 (9%)	0.94
Clinical presentation				
Symptom onset to balloon time > 90 mins.	189 (86%)	161 (85%)	171 (86%)	0.98
Out of hospital cardiac arrest	8 (3%)	7 (3%)	16 (7%)	0.09
Pulse rate, bpm	77±17	78±17	81±19	0.09
Blood pressure, mmHg				
Systolic	126±26	122±27	122±27	0.87
Diastolic	76±13	74±17	74±15	0.25
Cardiogenic Shock	13 (6%)	14 (7%)	28 (13%)	0.01
Killip class 2-4	11 (5%)	14 (7%)	27 (12%)	0.01

Data is expressed in numbers and (percentages), mean ± 1 standard deviation. Percentages are rounded. PCI = Percutaneous coronary intervention;

* p value calculated using ANOVA for continuous variables or Kruskal Wallis test for non parametric variables and Chi-Square test for categorical variables.

Table 4: Angiographic characteristics, procedural characteristics and management of patients with acute myocardial infarction according to SXscore II tertiles.

	SXscore II tertiles			
	Lower (<9) n = 238	Intermediate (9-17) n = 208	Higher (>17) n = 223	p value *
Angiographic Characteristics Pre-procedural				
Anterior STEMI	85 (36%)	119 (57%)	100 (45%)	< 0.01
Infarct Related Artery				
Left Main	2 (1%)	0 (0%)	3 (1.3%)	0.26
Left anterior descending	75 (32%)	111 (53%)	94 (42%)	< 0.01
Left Circumflex	45 (19%)	27 (13%)	37 (17%)	0.23
Right Coronary	116 (48%)	70 (34%)	89 (40%)	< 0.01
TIMI 0/1 in IRA	136 (57%)	130 (63%)	144 (65%)	0.26
Stent thrombosis (cause)	5 (2%)	13 (6%)	7 (3%)	0.06
Diseased vessels incl. IRA				
1-vessel disease	189 (79%)	76 (37%)	16 (4%)	< 0.01
2-vessel disease	42 (18%)	96 (46%)	68 (31%)	< 0.01
3-vessel disease ¶	6 (3%)	36 (17%)	139 (62%)	< 0.01
Left main disease	5 (2%)	1 (1%)	36 (16%)	< 0.01
Chronic Total Occlusion	3 (1%)	3 (1%)	40 (18%)	< 0.01
Procedural characteristics				
Stent Implantation	218 (92%)	198 (95%)	200 (90%)	0.10
Total Stent length, mm	24 (18-32)	28 (23-51)	32 (23-51)	< 0.01
Stent diameter, mm	3.3 ± 0.5	3.2 ± 0.5	3.3 ± 0.5	0.09
Bifurcation treatment in IRA	17 (7%)	47 (23%)	59 (27%)	< 0.01
Thrombectomy	52 (22%)	37 (18%)	35 (16%)	0.22
GP IIb/IIIa Inhibitors	56 (24%)	46 (22%)	45 (20%)	0.69
Inotropic agents	8 (3%)	8 (4%)	15 (5%)	0.19
Intra Aortic Balloon Pump	9 (4%)	11 (5%)	25 (11%)	< 0.01
Multivessel stenting	11 (5%)	25 (12%)	33 (15%)	< 0.01
Angiographic characteristics Post-procedural				
TIMI 0/1	3 (1%)	6 (3%)	19 (9%)	< 0.01
Corrected TIMI frame count at end procedure, fps	26 (18-32)	32 (21-36)	28 (20-33)	0.02§
Myocardial Blush Grade 0/1	1 (1%)	5 (2%)	16 (7%)	< 0.01
Follow - up treatment				
Complete revascularisation within 3 months (PCI n=331, CABG n= 4)	210 (88%)	97 (47%)	28 (13%)	< 0.01
Medication at 1 year				
Aspirin	200 (84%)	177 (85%)	198 (89%)	0.60
Clopidogrel	228 (96%)	202 (97%)	205 (92%)	0.03
B-Blocker	212 (89%)	185 (89%)	194 (87%)	0.85
ACE-inhibitors	150 (63%)	123 (59%)	154 (69%)	0.44
Statins	207 (87%)	183 (88%)	210 (94%)	0.33

Data is expressed in numbers and (percentages), mean ± 1 standard deviation or median and (interquartile range); Percentages are rounded. STEMI = ST elevation myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction; GP = Glycoprotein; PCI = Percutaneous coronary intervention; CABG = Coronary artery bypass graft; IRA = infarct related artery;

* p value calculated using ANOVA for continuous variables and Chi-Square test for categorical variables.

¶ includes cases with left main disease plus one vessel disease.

§ p value by Kruskal Wallis test.

Long term clinical outcome

All patients had follow-up to 1.5 years. Mortality rate was 12.1%, TVR 4.6, MI 2.2% and cumulative MACE 16.4%. Angiographically defined stent thrombosis (ST) occurred in 1.2%. Kaplan Meier curves for survival, repeat myocardial infarction, target vessel revascularisation, according to the tertiles of SXscore I are shown in figure 3. Log rank test shows that the differences in mortality was significant between the highest and

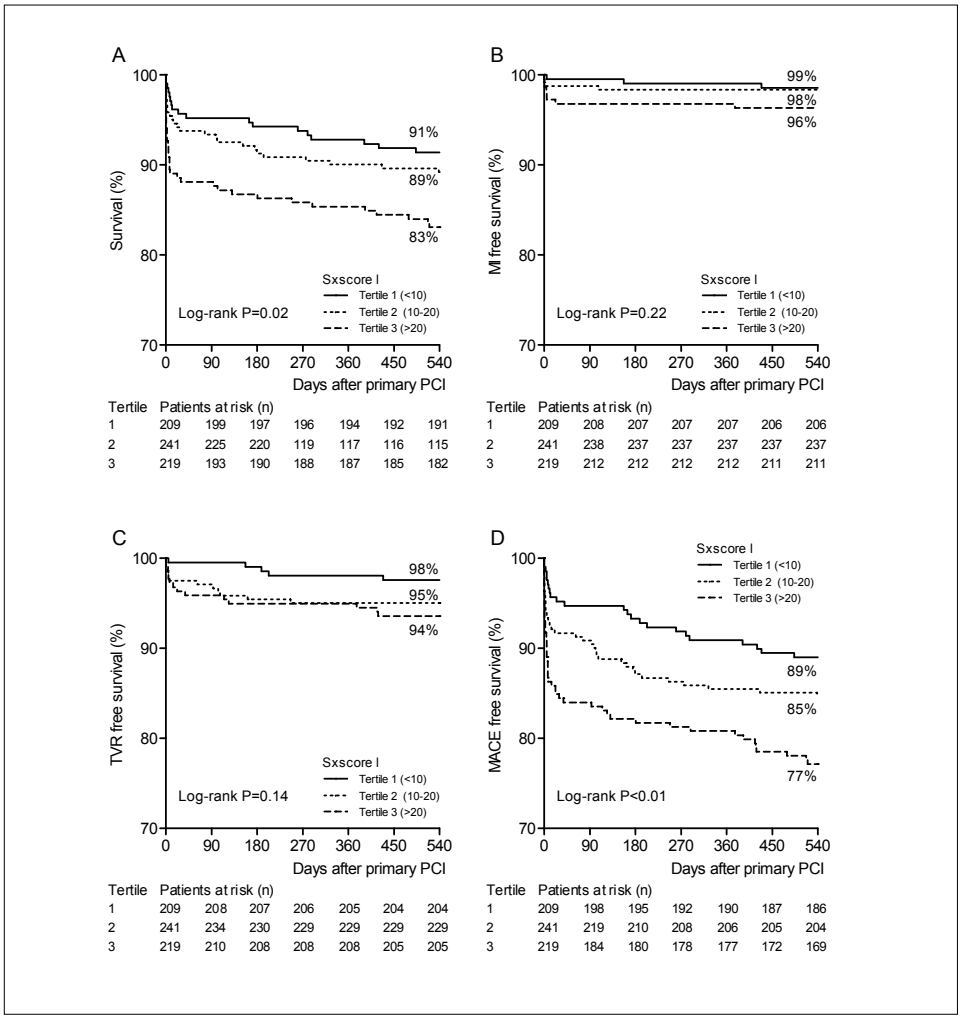

Figure 3: Kaplan-Meier event-free survival curves and their log-rank tests for patients presenting with STEMI and categorized in tertiles of the SXscore I. A, 1.5-year mortality. B, Repeat MI. C, TVR. D, MACE.

lower 2 tertiles. There was no statistically significant differences between tertiles for repeat MI and TVR so that the difference in MACE between tertiles was primarily driven by difference in mortality. Stent thrombosis, although numerically higher in the highest tertile was not statistically different (1% vs. 0.4% vs. 2.3%; log rank 0.17) Figure 4 shows the Kaplan Meier curves for SXscore II. Log rank test shows difference in mortality (9% vs. 11% vs. 17%, log rank = 0.02) and TVR (2% vs. 3% vs. 9%, log rank

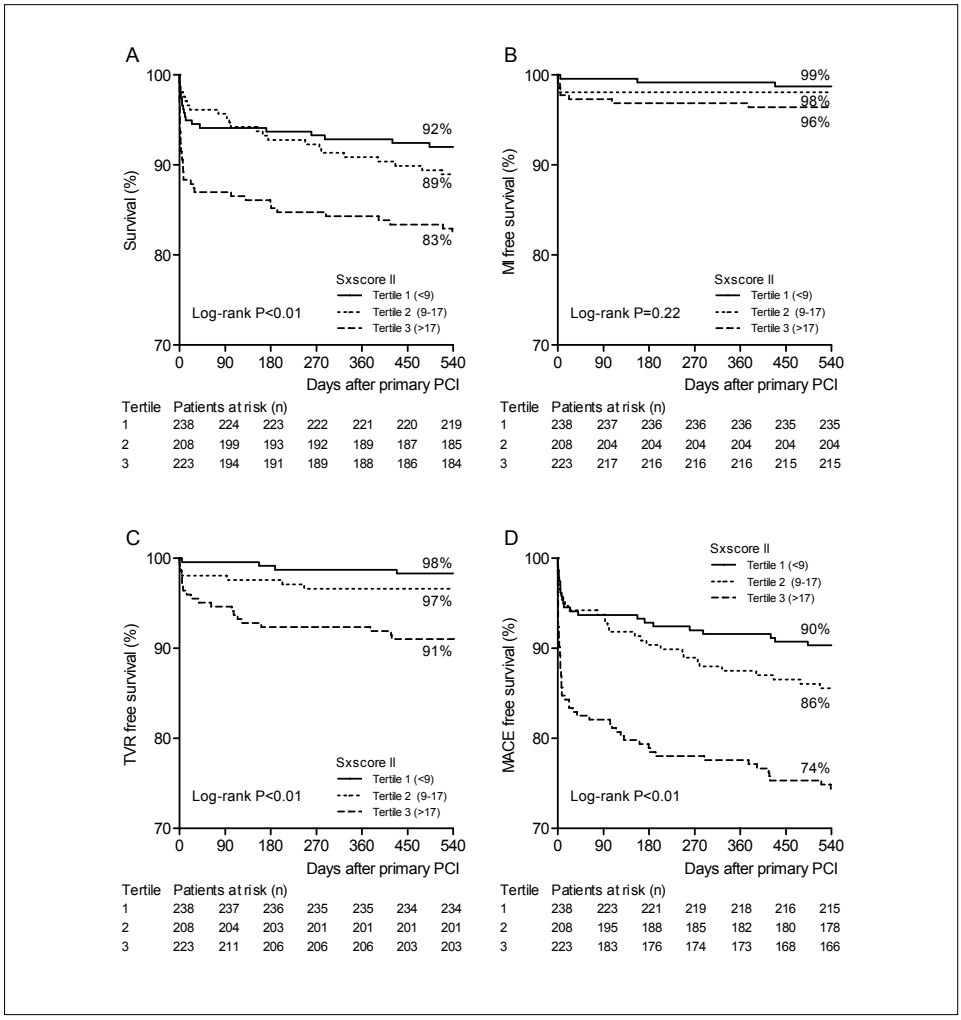

Figure 4: Kaplan-Meier event-free survival curves and their log-rank tests for patients presenting with STEMI and categorized in tertiles of the SXscore II. A, 1.5-year mortality. B, Repeat MI. C, TVR. D, MACE.

<0.01) between the higher and lower tertiles but not between the intermediate and lower tertiles. There was no difference in repeat myocardial infarction. The difference in MACE between the highest and lower tertiles is determined mostly by differences in mortality, followed by TVR. Angiographic ST was higher in the highest tertile (0.8% vs. 1% vs. 1.8% vs. log rank 0.60).

A cox regression model with independent variables from our data was significantly improved in discrimination for both mortality and MACE when SXscore I or Sxscore II were added to the model. The c-indices for SXscore I were 0.60 and 0.61 for mortality and MACE respectively while c-indices for SXscore II were 0.61 and 0.63 for mortality and MACE respectively. Similarly, when only TIMI risk score variables for STEMI were introduced in the model, SXscore showed a significant improvement. (table 5). In fact, adding either SXscore I or Sxscore II to the TIMI risk score model improved the prediction of MACE (p value = < 0.01), and mortality (p value = < 0.04). Hazards ratio for mortality with a 20 point increase in the SXscore in a combined model adjusted for TIMI risk variables was 1.52 (1.03 - 2.23), p = 0.04 and 1.51 (1.03 – 2.21), p = 0.03 for SXscore I and II respectively. For MACE, hazards were 1.63 (1.17 – 2.27), p < 0.01 for SXscore I and 1.63 (1.18 – 2.26), p <0.01 for SXscore II respectively.

Table 5: Hazard ratios from multivariate analysis of TIMI risk score and SXscore with value of model improvement for mortality and MACE.

Endpoint	Mortality		MACE	
Risk Score	**HR (95%CI)**	**p value**	**HR (95%CI)**	**p value**
TIMI score	1.41 (1.29 - 1.55)	< 0.01	1.32 (1.22 - 1.43)	< 0.01
Model Improvement by adding SXscore I to TIMI	0.04*		< 0.01*	
SXscore I	1.52 (1.03 - 2.23)	0.04	1.63 (1.17 – 2.27)	0.04
TIMI score	1.42 (1.29 – 1.55)	< 0.01	1.32 (1.22 – 1.43)	< 0.01
Model Improvement by adding SXscore II to TIMI	0.04*		< 0.01*	
SXscore II	1.51 (1.03 – 2.21)	0.03	1.63 (1.18 – 2.26)	< 0.01

MACE= major adverse cardiac events; HR= hazard ratios; CI= confidence intervals;
TIMI= thrombolysis in myocardial infarction risk score;

* by omnibus test of model coefficients

Interobserver and intraobserver variability

Interobserver variability as measured by the weighted Kappa statistic was moderate (0.56 for both SXscores I and II). Intraobserver variability was substantial with values of 0.70 and 0.77 SX scores I and II respectively.

Discussion

The SYNTAX score (SXscore), originally designed for quantifying stable coronary artery disease, can be usefully employed in a STEMI population with disease in the native coronary arteries as demonstrated in our study. The extent of coronary artery disease and the successful intervention as determined by angiography at each stage during a PPCI and as graded by SXscores I and II is associated with the rate of mortality and major adverse cardiac events both at 1.5 years follow-up. Both SXscores are independent predictors of mortality and MACE adding incremental value to the TIMI risk score in STEMI patients treated with PPCI. This therefore adds to the well established risk factors of mortality as previously described in the major trials that studied the STEMI population.[13-15] Additionally, the score can be utilised by clinicians, interventional cardiologists and cardiac surgeons to better assess and quantify the risk of complications and tailor management strategies accordingly. This is the first study that reports the prognostic value of the SXscore, calculated purposely and exclusively for STEMI patients at two stages with the methodology described. Moreover since more than 99% of our cohort were treated with drug eluting stents in the setting of myocardial infarction, the study results are the first to show applicability of the SXscore in a 'real world' population with STEMI, treated almost exclusively with DES.

Risk scores in STEMI

The predictive power of clinical parameters derived from independent risk factors from the major reperfusion in acute coronary syndrome studies including the Thrombolysis In Myocardial Infarction (TIMI) trials, Global Registry of Acute Coronary Events (GRACE), Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) is considerable.[14-15] Angiographic

characteristics that have additional independent prognostic significance include the infarct related artery (IRA), patency of the IRA, presence of 3 vessel disease and chronic total occlusions. This present study highlights the importance of more detailed characterisation of coronary artery disease in patients undergoing PPCI. In this present era of treatment of IRA lesions with stent implantation whenever possible, information about the lesion complexity is useful for prediction of future events which include revascularisation of the target vessel, stent thrombosis and repeat myocardial infarction in the territory of the index IRA. In fact 1.5 year TVR rates are considerably higher in patients in the higher SXscore II tertile. The higher disease complexity, the lower PCI success rate as well as the need for longer, more overlapping stents, bifurcation treatment are likely contributing factors for the increased need of revascularisation in this patient subgroup.

Functional consideration of the SXscore

By consideration of the flow to the left ventricle at the site of the lesion, a functional aspect has been added to the score. Thus for a right dominant coronary artery system, the right coronary artery (RCA) supplies approximately 16% of the flow to the left ventricle whereas the left coronary artery supplies 84%. In a left dominant system, the LAD supplies 66% and the left circumflex artery 33% of the flow to the left ventricle. Appropriately, the SXscore assigns 1 to the RCA lesions, 1.5 to the LCx and 3.5 to the LAD in consideration of function alone. In STEMI, a larger left ventricular infarct size can be anticipated when the culprit lesion is in the LAD. The level at which the occlusion occurs is also given weight in the score so that more proximal lesions which supply a larger myocardial territory, carry higher scores. Moreover SXscore I assigns a higher value to IRA's which have TIMI 1/0 flow on diagnostic angiography during PPCI. Thus further points are added and may be appropriate as the extent of myocardial damage is known to be higher in patients presenting with closed versus patent IRAs. This functional combination is a plausible reason for the better early separation of the survival curves between all three tertiles of SXscore I when compared to SXscore II as illustrated in figure 3 and figure 4 respectively.

Lesion complexity consideration

Angiographic characterisation of the culprit lesion is possible in the majority of patients presenting with acute STEMI. Patients with a patent IRA with TIMI 2 or higher flow can have characterisation outright from the diagnostic angiography unless the thrombus burden is high. In patients presenting with an occluded IRA with TIMI 1/0 flow, wiring or use of a small balloon can increase the flow to reveal the underlying lesion anatomy. SXscore II in these patients is lower than SXscore I since the increase in flow reduces the 5 points added in the latter for total occlusion. Patients in whom TIMI 0/1 flow persists after wiring may have higher intracoronary pressures from larger infarct sizes and possibly higher thrombus burden which is associated with a poorer prognosis.[16] In addition, higher SXscores are assigned to patients with complex lesions with points added for trifurcations, bifurcations, ostial stenosis, severe tortuosity, lesion length >20mm, heavy calcification, thrombus and diffuse disease or small vessels.[1] Although these features are historically and in our study more prevalent in patients who already have a poorer prognosis based on their high clinical risk factors alone (age, diabetes, smokers) SXscore can still give additional prognostic information. The better characterisation of the underlying disease anatomy in the SXscore II may be a major reason for the better prognostic impact on MACE in the long term.

Multivessel disease, STEMI and the SXscore

That patients with multivessel coronary artery disease have worse outcome when compared to single vessel disease in myocardial infarction has been reported since the pharmacological reperfusion era.[17] In the PPCI era, these patients have been shown to achieve less ST segment recovery, a sign of myocardial reperfusion in a substudy of the CADILLAC trial.[6] In this substudy, 1 year mortality and MACE rates also differed between patients with single-, double-, and triple-vessel disease and presence of the latter was the strongest amoung classical candidate predictors of outcome. The concomitant presence of a chronic total occlusion (CTO) in a vessel other than the IRA has been shown to be a considerably more important risk factor than presence of multivessel disease alone in a study by van der Schaaf et al.[7] In the present study, the mortality rate was highest in the highest tertile of SXscore which predominantly

included patients with 3 vessel disease and the largest number of CTOs. With the additional information about the nature of the lesions in multivessel disease subjects, the SXscore may be a better predictor than mere numeration of the vessels involved.

Implications for clinical practice

In patients undergoing PPCI for acute STEMI, quantification of the presence, severity and complexity of coronary vessel disease by the SXscore is a useful tool in determining short term and long term outcome independently of any other clinical and angiographic and procedural characteristics. Patients in the higher tertiles are at high risk and may need more intensive supportive and interventional management to improve their event free survival.

Implications for PCI trials

In 'all comer' revascularisation trials that include patients with a spectrum of coronary disease and patients treated for acute STEMI, the SXscore seems a useful tool in addition to the classical risk factors that ensures comparison of equal coronary disease anatomy between the cohorts being investigated.

Limitations

Although data was acquired prospectively the study has a retrospective design and is in fact a registry analysis and therefore suffers from limitations. Data on enzymatic or other imaging-derived infarct size quantification was not available in all patients. Also myocardial blush grade, ST segment resolution as markers of reperfusion could not be determined in all patients and we used cTFC instead. These could not be incorporated in the models and whether these would be better predictors than the SXscore remains unexplored.

Conclusion

The SXscore derived from angiography after during PPCI predicts long term mortality and MACE in patients with STEMI. The score is relatively easy to obtain and has a moderate reproducibility, making it a clinically useful tool.

Acknowledgements

We would like to thank all the interventional cardiologists who performed the procedures during the study period; P. de Jaegere, P. de Feyter, H.J. Duckers, E. Regar, M. van der Ent, A. Dirkali, A.G. de Vries, A.L. Gaster, C. van Mieghem, G. Sianos, S. Ramcharitar, N. Kukreja; the cardiac catheterisation staff of the Thoraxcenter, Erasmus MC and the staff of hospitals in Rotterdam – Havenziekenhuis, Maasstad Ziekenhuis, Sint Franciscus Gasthius, Ruwaard van Putten Ziekenhuis, Vlietland Ziekenhuis, IJsselland Ziekenhuis – and Albert Schweizer Ziekenhuis, Dordrecht The Netherlands, who collaborated in the data collection process.

None of the authors report any conflict of interest.

References

1. Sianos G, Morel MA, Kappetein AP, *et al.* The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;**1**(2):219-27.

2. Leaman DM, Brower RW, Meester GT, *et al.* Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. Circulation 1981;**63**(2):285-99.

3. Valgimigli M, Serruys PW, Tsuchida K, *et al.* Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. Am J Cardiol 2007;**99**(8):1072-81.

4. Capodanno D, Di Salvo ME, Cincotta G, *et al.* Usefulness of the SYNTAX score for predicting clinical outcome after percutaneous coronary intervention of unprotected left main coronary artery disease. Circ Cardiovasc Interv 2009;**2**(4):302-8.

5. Morrow DA, Antman EM, Parsons L, *et al.* Application of the TIMI risk score for ST-elevation MI in the National Registry of Myocardial Infarction 3. JAMA 2001;**286**(11):1356-9.

6. Sorajja P, Gersh BJ, Cox DA, *et al.* Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. Eur Heart J 2007;**28**(14):1709-16.

7. van der Schaaf RJ, Vis MM, Sjauw KD, *et al.* Impact of multivessel coronary disease on long-term mortality in patients with ST-elevation myocardial infarction is due to the presence of a chronic total occlusion. Am J Cardiol 2006;**98**(9):1165-9.

8. Garg S, Girasis C, Sarno G, *et al.* The SYNTAX score revisited: A reassessment of the SYNTAX score reproducibility. Catheter Cardiovasc Interv 2009.

9. Gibson CM, Schomig A. Coronary and myocardial angiography: angiographic assessment of both epicardial and myocardial perfusion. Circulation 2004;**109**(25):3096-105.

10. van 't Hof AW, Liem A, Suryapranata H, *et al.* Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. Circulation 1998;**97**(23):2302-6.

11. Cutlip DE, Windecker S, Mehran R, *et al.* Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;**115**(17):2344-51.

12. Kleinbaum DG. Survival Analysis: A Self-Learning Text In. Second ed. New York: Springer-Verlag; 2005

13. Morrow DA, Antman EM, Charlesworth A, *et al.* TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation 2000;**102**(17):2031-7.

14. Halkin A, Singh M, Nikolsky E, *et al.* Prediction of mortality after primary percutaneous coronary intervention for acute myocardial infarction: the CADILLAC risk score. J Am Coll Cardiol 2005;**45**(9):1397-405.

15. Yan AT, Yan RT, Tan M, *et al.* In-hospital revascularization and one-year outcome of acute coronary syndrome patients stratified by the GRACE risk score. Am J Cardiol 2005;**96**(7):913-6.

16. Sianos G, Papafaklis MI, Daemen J, *et al.* Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. J Am Coll Cardiol 2007;**50**(7):573-83.

17. Sanz G, Castaner A, Betriu A, *et al.* Determinants of prognosis in survivors of myocardial

Chapter 15

Usefulness of the SYNTAX score to predict "no reflow" in patients treated with primary percutaneous coronary intervention for ST-segment elevation myocardial infarction

Michael Magro
Sjoerd T Nauta
Cihan Simsek
Eric Boersma
Elco van der Heide
Evelyn Regar
Ron T van Domburg
Felix Zijlstra
Patrick W Serruys
Robert-Jan van Geuns

Am J Cardiol. 2012 Mar 1;109(5):601-6.

Abstract

The no-reflow phenomenon has been shown to have a significant effect on clinical outcome in patients with acute ST segment elevation myocardial infarction (STEMI). Angiographic features incorporated in the SYNTAXscore (SXscore) obtained on a diagnostic angiogram during primary percutaneous coronary intervention (PPCI) may be associated with the occurrence of myocardial no-reflow. The study aimed to assess the ability of the SXscore to predict no-reflow during PPCI. The SXscore was applied to 669 consecutive patients presenting with acute ST elevation myocardial infarction between November 2006 and February 2008. Angiographic analysis of the PPCI procedure was used to determine no-reflow. The median SXscore was 16 (9.5-23). No-reflow occurred in 77 (12%) patients. On univariate logistic regression analysis the SXscore showed strong association with odds ratio (OR) of 1.42, 95% CI (1.16-1.76), $p < 0.001$ for every 10 units increase in the score. On multivariate logistic regression in a model including clinical variables, SXscore was an independent predictor on no-reflow: (OR); 1.29 95%CI 1.02-1.63), $p < 0.001$. Classification and regression tree analysis identified SXscore of > 21 as best cut off with patients having a double risk of no-reflow as compared to those with SXscore ≤ 21. (events 9% vs.18%, p value 0.006). In conclusion, the SXscore obtained in the diagnostic phase of PPCI for acute STEMI can identify patients at risk of developing no-reflow. Periprocedural pharmacological or mechanical preventive measures of no-reflow may in the future be directed at those at higher risk as identified by the SXscore.

Keywords

ST segment elevation myocardial infarction, Primary percutaneous coronary intervention, SYNTAX score, myocardial no-reflow.

Introduction

Myocardial no reflow diagnosed angiographically during primary percutaneous coronary intervention (PPCI) is associated with a increased incidence of clinical events and a poor survival rate following an acute ST segment elevation myocardial infarction (STEMI).[1] The no-reflow phenomenon is in fact established as a good surrogate of adverse cardiovascular events in patients treated for STEMI.[2] Patients at a high risk of no-reflow include older subjects, those with previous coronary artery bypass surgery, those presenting with a higher Killip class and a longer ischaemic time. Angiographic characteristics of STEMI patients with a high risk of subsequent no-reflow include patency of the infarct related artery, saphenous graft as culprit vessel and multivessel disease. A high thrombus burden as assessed angiographically is also known to be associated with a higher risk of developing the no-reflow phenomenon.[3]

Such angiographic characteristics can be quantified by the SYNTAX score (SXscore).[4] The latter, obtained on the diagnostic angiogram during PPCI incorporates information including the patency of the infarct related artery, the area of myocardium at risk, supplied by the culprit vessel at the level of occlusion, as well as information on the complexity of the lesion and extent and severity of coronary artery disease.[5] Patients with high SXscores are at increased risk of adverse events including mortality and the prognostic value has been shown to be independent and additive to other risk variables incorporated in risk scores such as the TIMI and PAMI scores.[4, 6-8] The mechanisms that relate a high SXscore to adverse cardiovascular events is unclear and may in part be mediated by a higher risk of failure to achieve an adequate myocardial reperfusion during PPCI.

We hypothesized that with its additional angiographic characterization of patients presenting for PPCI, the SXscore can stratify patients at risk of developing myocardial no-reflow.

Methods

Between November 2006 and February 2008, 736 consecutive patients undergoing primary PCI for STEMI in our institution were screened for inclusion in the MI SXscore study.[4] All patients in the referral area of the Thoraxcentre, Erasmus MC, Rotterdam that had symptoms of acute myocardial infarction (< 12 duration) were assessed clinically and by 12 lead ECG by paramedical personnel or peripheral hospital medical staff. Pre-treatment with aspirin, clopidogrel and heparin was administered pre-hospital. Urgent diagnostic angiography was followed by PPCI with standard techniques. Drug eluting stents were implanted as first line choice of stents. Treatment of complications such as cardiogenic shock and cardiac arrest were performed according to guidelines.

The SXscore was calculated as previously described.[4] Patients with previous coronary artery bypass grafting (CABG) in whom the SXscore could not be calculated were excluded from the study. All coronary lesions with a diameter stenosis ≥ 50%, in vessels ≥1.5 mm were scored using the SXscore algorithm which is available on the website (www.syntaxscore.com). The SXscore for each patient was calculated by a team of two interventional cardiologists. In case of disagreement with regards to the significance of a lesion quantitative coronary angiography was applied and the lesion included if it was ≥ 50%. On agreement between the two cardiologists, the data was entered into a dedicated software program.

The investigators calculating the SXscore were blinded to the patient's clinical characteristics. The scoring was done prospectively at each stage so that the investigators were blinded to the next stage film, to the procedural data and to the clinical outcomes. No change in scoring was allowed once a score was assigned.

Thrombolysis In Myocardial Infarction (TIMI) flow and corrected TIMI frame count were assessed as previously reported[9]. Myocardial blush grade was assigned as described by van 't Hof et al.[10] Angiographic epicardial artery no-reflow was defined as an acute temporary or persistent reduction in coronary flow (TIMI 0/1) in the absence of dissection, thrombus, spasm or high grade residual stenosis at the target lesion. Slow flow was recorded if there was a temporary reduction from TIMI flow

grade 3 to 2. Distal embolisation was defined as visible downstream movement of a contrast filling-defect from the site of the culprit lesion. Distal occlusion was defined as a distal filling defect with an abrupt 'cutoff' in one of the peripheral coronary artery branches of the infarct-related vessel distal to the site of angioplasty.

Survival data for all patients was obtained from the municipal registry. A health questionnaire was subsequently sent to all living patients with specific questions on readmission and major adverse cardiac events. For patients with an adverse event at another centre, medical records, discharge summaries and, when necessary, angiographic films, were systematically reviewed. General practitioners, referring cardiologists and patients were contacted as necessary for additional information. Events were adjudicated by two experienced interventional cardiologists according to the definitions below. *ST segment elevation myocardial infarction* was diagnosed when patients had symptoms of an acute myocardial infarction lasting at least 30 minutes and accompanied by >1mm (0.1mV) ST elevation in two or more contiguous leads and later confirmed by a creatinine kinase (CK) and CK-MB rise and /or troponin rise. *Target vessel revascularisation* was defined as any PCI of the index infarct-related artery. *Major adverse cardiac events* (MACE) was defined as a composite of death, repeat myocardial infarction and target vessel revascularisation.

The no-reflow phenomenon was defined by at least one of the following: final TIMI flow grade <3; final myocardial blush grade <2; temporary epicardial coronary no-reflow; distal coronary occlusion; and a final corrected TIMI frame count of >100 frames per second.[9]

Continuous variables are expressed as mean and standard deviation or as median and interquartile range while categorical variables are presented as absolute numbers and percentage. Normality assumption was evaluated by the Kolmogorov-Smirnov test. Continuous variables were compared using Student's unpaired t-test or Mann-Whitney non-parametric test. Categorical variables were compared using chi-square statistics or Fischer's exact test, as appropriate.

Observed unadjusted and adjusted measures of association were obtained by logistic regression models and presented as odds ratios (OR) and 95% confidence

intervals (CI). Separate logistic regression analyses were performed to identify independent predictors of no-reflow using all clinical variables. These univariate predictors were entered into a second logistic regression model to obtain the adjusted OR. The multivariate model consisted of SXscore and the clinical variables; age, sex, out of hospital arrest, Killip class, cardiogenic shock, pulse rate, and blood pressure.

Classification and regression tree analysis was performed to determine the best SXscore value cut-off that stratifies patients at high versus low risk of developing no-reflow.To assesswhich of the angiographic characteristics best impact the association of SXscore and no-reflow, a separate logistic regression analysis in a multivariate model with the angiographic variables infarct-related artery, TIMI flow pre-wiring, thrombus grade post-wire, number of vessels diseased, chronic total occlusion and bifurcation was performed.

Also, the cumulative incidence of adverse events according to the presence of no-reflow was estimated according to the Kaplan-Meier method, and curves were compared using the log-rank test. A value of <0.05 was used to indicate statistical significance unless declared otherwise. All statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, Illinois).

Results

From the initial 736 patients screened, 27 were excluded due to unavailability of a complete diagnostic coronary angiogram while 21 were excluded since they had prior CABG. Survival status and follow-up could not be obtained in 19 patients. Thus the final number of patients included in our analysis was 669. The median SXscore was 16 (9.5-23). Differences in the baseline clinical characteristics in patients with low and high SXscores are shown in table 1. Patients with a higher SXscore (≥16) were more commonly older, male, more often had type 2 diabetes and were more likely to be

Table 1: Baseline and presenting characteristics of patients with acute myocardial infarction according to low or high MI SYNTAX score.

	Lower (<16) n = 332	Higher (≥16) n = 337	p value*
Age, years	63±13	67±12	<0.01
Male	221 (67%)	248 (74%)	0.047
Diabetes	22 (7%)	41 (12%)	0.014
Type I	11 (3%)	17 (5%)	0.26
Type II	12 (4%)	25 (7%)	0.03
Hypertension	101 (30%)	123 (37%)	0.096
Hypercholesterolaemia	64 (19%)	76 (23%)	0.30
Smoker			
Current	155 (47%)	125 (37%)	0.012
Ex-	46 (14%)	45 (13%)	0.036
Renal failure	4 (1%)	14 (4%)	0.018
Family history of CAD	121 (36%)	89 (26%)	<0.01
Body Mass Index, Kg/m^2	27±4	27±4	0.74
Previous Myocardial Infarction	25 (8%)	60 (18%)	< 0.01
Previous PCI	30 (9%)	34 (10%)	0.64
Symptom onset to balloon time > 90 mins.	257 (84%)	264 (87%)	0.27
Out of hospital cardiac arrest	13 (4%)	18 (5%)	0.38
Pulse rate, bpm	77±16	80±19	0.037
Blood pressure, mmHg			
Systolic	124±26	123±27	0.29
Diastolic	75±14	75±16	0.45
Cardiogenic Shock	19 (6%)	36 (11%)	0.02
Killip class 2-4	18 (5%)	34 (10%)	0.024

Data is expressed in numbers and (percentages), mean ± 1 standard deviation. Percentages are rounded. PCI = Percutaneous coronary intervention;

* p value calculated using ANOVA for continuous variables or Kruskal Wallis test for non parametric variables and Chi-Square test for categorical variables.

Table 2: Angiographic characteristics, procedural characteristics and management of patients with acute myocardial infarction with low and high MI SYNTAX score.

	Lower (<16) n = 332	Higher (≥16) n = 337	p value*
Anterior STEMI	127 (38%)	177 (53%)	<0.001
Infarct Related Artery			
Left Main	6 (2%)	36 (11%)	<0.01
Left anterior descending	111 (34%)	169 (50%)	<0.01
Left Circumflex	63 (19%)	46 (14%)	0.06
Right Coronary	156 (47%)	119 (35%)	<0.01
TIMI 0/1 in IRA	157 (48%)	253 (75%)	<0.01
Stent thrombosis (cause)	12 (4%)	13 (4%)	0.86
Diseased vessels incl. IRA			
1-vessel disease	222 (67%)	59 (18%)	<0.01
2-vessel disease	91 (27%)	115 (34%)	0.06
3-vessel disease¶	18 (5%)	163 (48%)	<0.01
Left main disease	6 (2%)	36 (11%)	<0.01
Chronic Total Occlusion	4 (1%)	42 (13%)	<0.01
Stent Implantation	311 (94%)	305 (91%)	0.096
Total Stent length, mm	28 (18-40)	30 (23-51)	<0.01
Stent diameter, mm	3.0±0.5	3.0±0.5	0.83
Bifurcation treatment in IRA	47 (14%)	76 (23%)	<0.01
Thrombectomy	62 (19%)	62 (19%)	0.93
GP IIb/IIIa Inhibitors	73 (22%)	74 (22%)	0.99
Inotropic agents	14 (4%)	17 (5%)	0.61
Intra Aortic Balloon Pump	15 (5%)	30 (9%)	0.024
Multivessel stenting	26 (8%)	43 (13%)	0.036
TIMI 0/1	7 (2%)	21 (6%)	<0.01
Corrected TIMI frame count at end, fps	24 (16-36)	26 (18-40)	0.052
Myocardial Blush Grade 0/1	3 (1%)	19 (6%)	<0.01

Data is expressed in numbers and (percentages), mean ± 1 standard deviation or median and (interquartile range); Percentages are rounded. STEMI = ST elevation myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction; GP = Glycoprotein; PCI = Percutaneous coronary intervention; IRA = infarct related artery;

* p value calculated using ANOVA for continuous variables and Chi-Square test for categorical variables.

¶ includes cases with left main disease plus one vessel disease.

§ p value by Kruskal Wallis test.

current smokers. A history of previous myocardial infarction was also more common in the higher SXscore patients. Patients presenting in the acute phase with a higher pulse rate, cardiogenic shock and higher Killip class more often had a higher SXscore.

Table 2 shows the differences in angiographic and procedural characteristics between patients with low and high SXscores. The left main stem and the left anterior descending coronary artery were more commonly the culprit vessels in patients with high SXscore whereas the left circumflex coronary artery and the right coronary artery were more commonly the IRA in low SXscore patients. Furthermore, the IRA more often had poor antegrade flow (TIMI 0/1) in patients with a high SXscore. Multivessel disease, chronic total occlusions and bifurcations were more often present in patients with higher scores. In fact multivessel stenting and bifurcation stenting were more often performed in these patients. These patients also had a higher total stent length implanted during the index PPCI. There was no difference in the procedural use of thrombectomy devices or GP IIb/IIIa inhibitors between the two groups. The use of an intra-aortic balloon pump was necessary in double the patients with SXscore of 16 or higher when compared to those with score below 16.

The no-reflow phenomenon occurred in 77 (12%) of patients included in the analysis. The components used to define the composite endpoint are shown in table 3. On univariate logistic regression analysis, the SXscore showed a strong association with no-reflow, unadjusted odds ratio (OR) of 1.42, 95% CI (1.16-1.76), $p < 0.001$ for every 10 unit increase in the score. The other univariate predictors of no-reflow were age, sex, out of hospital arrest, Killip class, shock, pulse rate and blood pressure. After adjusting for these predictors in multivariate logistic regression, the SXscore was an independent predictor of no-reflow: adjusted (OR); 1.29 95%CI 1.02-1.63), $p <0.001$ per 10 unit increase in the score. (table 4)

Classification and regression tree analysis identified SXscore of > 21 as best cut off with patients having a double risk of no-reflow as compared to those with SXscore ≤ 21. (events 9% vs.18%, p value 0.006)

Table 3: Differences in angiographically detected complications between patients presenting with a low versus a high MI SYNTAX score.

Angiographic complication	Lower (<16) n = 332	Higher (≥16) n = 337	p value*
Dissection	17 (5%)	12 (4%)	0.322
Perforation	6 (2%)	4 (1%)	0.51
Distal Embolisation	16 (5%)	15 (5%)	0.82
Slow Flow	7 (2%)	14 (4%)	0.13
Angiographic no reflow	6 (2%)	11 (3%)	0.23
TIMI 0/1 final	7 (2%)	21 (6%)	<0.001
Corrected TIMI frame count >100 fps	5 (2%)	24 (7%)	<0.001
Myocardial Blush Grade 0/1	3 (1%)	19 (6%)	<0.001
Composite No-reflow	29 (9%)	48 (14%)	0.026

Data is expressed in numbers and (percentages).Percentages are rounded.

Table 4: Predictors of myocardial no-reflow on multivariate analysis in model with clinical characteristics and MI SXscore.

Predictors	Odds ratio (95% CI)	p value
MI SXscore	1.29 CI (1.02 – 1.63)	<0.001
Age	1.23 (0.99-1.54)	0.058
Pulse rate	1.02 (1.01-1.03)	0.012

Table 5: Angiographic predictors of no-reflow.

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Infarct related artery				
Left Main Stem	3.46 (1.69-7.08)	0.001	2.42 (0.96-6.09)	0.060
Left anterior descending	1.50 (0.93-2.41)	0.098	1.37 (0.80-2.35)	0.25
Left circumflex	0.41 (0.17-0.95)	0.037	0.56 (0.22-1.43)	0.22
Right coronary	0.96 (0.59-1.56)	0.86		
Number of vessels with significant disease				
2-vessel	0.71 (0.41-1.23)	0.218	-	-
3-vessel	1.54 (0.94-1.54)	0.094	1.18 (0.63-2.22)	0.60
Chronic Total Occlusion	1.99 (0.92-4.29)	0.081	1.03 (0.40-2.65)	0.95
Bifurcation at IRA	0.80 (0.42-1.53)	0.497	-	-
TIMI flow pre-wiring	0.66 (0.53-0.82)	<0.001	0.71 (0.56-090)	0.004
Thrombus grade post-wire	1.73 (1.43-2.10)	<0.001	1.60 (1.32-1.95)	<0.001

Assessment of the relation of angiographic characteristics and no-reflow are summarized in table 5. Angiographic characteristics that were independent predictors of no-reflow on multivariate analysis included left main stem involvement, TIMI flow grade on presentation as well as thrombus grade after wiring.

The Kaplan Meier curves in figure 1 and figure 2 show the increased mortality rate (31% vs. 10%, p <0.001) and MACE (35% vs. 14%, p <0.001) at 18 months in patients who developed no-reflow respectively.

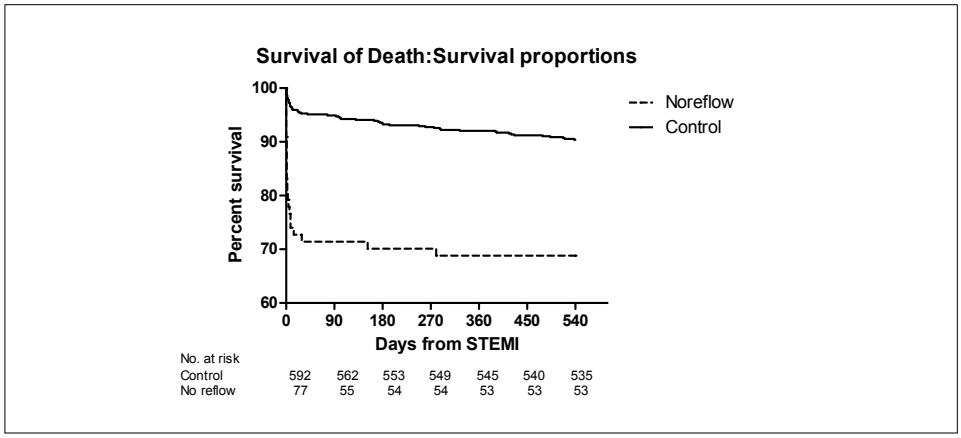

Figure 1: Kaplan Meier curves with the survival in patients with and without no-reflow (control). At 18 months follow-up, mortality rate was 31 % vs. 10%, Log rank p < 0.001.

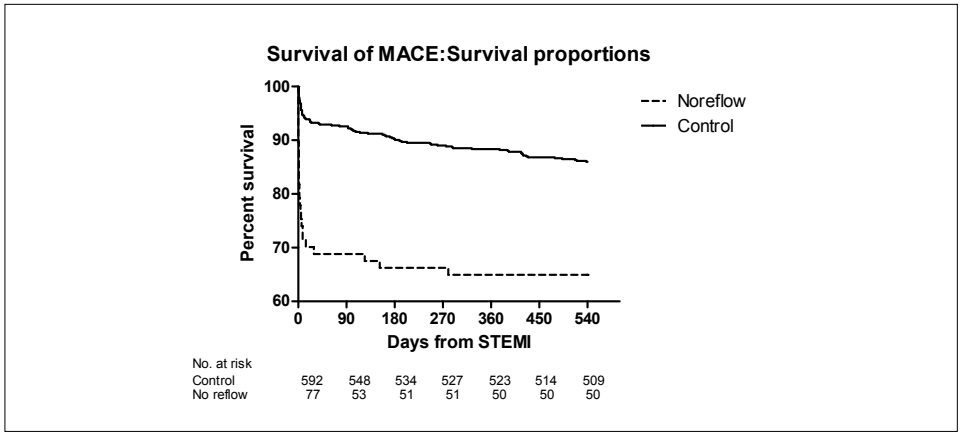

Figure 2: Kaplan Meier curves with the MACE (major adverse cardiac events including death, repeat myocardial infarction and target vessel revascularisation) free survival in patients with and without no-reflow. At 18 months follow-up MACE rate was 35% vs. 14%, Log rank p <0.001.

Discussion

The SXscore is an independent predictor of myocardial no-reflow in patients with ST segment elevation myocardial infarction. A SXscore of >21 carries a double risk of developing no-reflow. Myocardial no-reflow carries a poor prognosis with an increased mortality rate. Thus intra-procedural measures that can prevent this phenomenon would be especially beneficial in patients at high risk as can be identified by the SXscore.

In this study no-reflow was identified by changes in the TIMI flow in the epicardial artery which directly affect myocardial perfusion as well as more direct imaging of myocardial perfusion as measured by the myocardial blush grade. TIMI flow grade is a crude but accurate indicator for myocardial reperfusion if this is suboptimal i.e. <3. The corrected TIMI frame count adds more sensitivity for categorizing no-reflow for patients in whom TIMI flow is ≥2 is achieved. A cut-off of 100fps has been chosen based on data from previous studies.[9]

One of the major components of the SXscore that enhances its predictive value on the eventual achievement of microvascular perfusion is the patency or otherwise of the infarct related artery. An occluded infarct related artery (IRA) has been shown to be associated with a worse, postprocedural myocardial perfusion (TMPG 3: 54.9% vs. 18.7%, p<0.0001). Patency of the IRA often signifies earlier spontaneous reperfusion which reduces the actual ischaemic time. As a result infarction size is limited and an improvement in left ventricular ejection fraction (LVEF) is higher in such patients, that is reflected in an improved 1-year outcome.[11] The SXscore adds 5 points if the IRA has TIMI 0/1 flow reflecting the importance of IRA patency on both no-reflow and short and long term mortality. A poor antegrade flow is also often associated with a higher thrombus load and this in turn has been associated with both slow flow and the no-reflow phenomenon.[12] Embolisation of atherothrombotic material has been implicated as an important pathophysiological mechanism leading to poor microvascular perfusion. Anti-thrombitc, thrombolytic or thrombus aspiration have all been shown to reduce the incidence of the no-reflow phenomenon.[13-15] Given the associated risks associated with these adjunctive therapeutic measures such as bleeding and cerebrovascular accidents, identification and limitation of use to patients who may benefit most from these treatments is desirable.

The difference in the myocardial area at risk is also an important component of the SXscore and the different weighting given to the coronary arteries does influence the occurrence of no-reflow. While infarction in the left circumflex artery is less likely to result in detectable no-reflow, that in the proximal left coronary artery, especially the left main stem, carries a x 3.5 risk of no-reflow.

In the present study, the presence of a chronic total occlusion (CTO) and three vessel disease have a non-significant trend of association with no-reflow. While the lack of statistical significance can be attributed to lack of power, the incorporation of these parameters in the SXscore ensure appropriate consideration of these parameters in the risk stratification of no-reflow. On the other hand CTO and multi-vessel disease are not as important as TIMI flow and location of occlusion. No reflow as an angiographic marker of myocardial perfusion focuses on the territory at risk which although as expected is affected mostly by the characteristics pertinent to the infarct related artery, can be affected by the presence and extent of disease elsewhere. Diffuse disease often signifies impaired microcirculatory resistance index.[16] Moreover, collateral circulation to the microvascular bed which is considered to be protective would be poorly developed or insufficient if the contributing artery is also diseased.

Although observers scoring the SXscore were blinded to the next step angiographic film and changes to the score were not allowed after film review, bias of scoring no-reflow in patients with high SXscores may still have affected our observations. However the post hoc analytic nature of the study derived from the MI SXscore study database guarantees to a limited extent the validity of our findings. The relation of the SXscore and the outcome is unlikely to have been influenced by operator dependent choice of treatment. In fact in our study patients with higher scores were not treated differently especially with regards to stenting, thrombectomy devices or GP IIb/IIIa inhibitors. In determining no-reflow we chose to use only angiographic parameters. ST resolution as another measure of no-reflow was not available in all patients. Moreover we could not determine the effect of the SXscore and the occurrence of no-reflow on final infarct size since neither enzymatic infarct size nor infarct size by non-invasive imaging modalities were available in all patients.

References

1. Ndrepepa G, Tiroch K, Fusaro M, Keta D, Seyfarth M, Byrne RA, Pache J, Alger P, Mehilli J, Schomig A, Kastrati A. 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. J Am Coll Cardiol 2010;55(21):2383-9.

2. Magro M, Serruys PW. Acute coronary syndromes: No-reflow--an ominous sign of cardiac dysfunction. Nat Rev Cardiol 2010;7(9):480-2.

3. Iwakura K, Ito H, Kawano S, Shintani Y, Yamamoto K, Kato A, Ikushima M, Tanaka K, Kitakaze M, Hori M, Higashino Y, Fujii K. Predictive factors for development of the no-reflow phenomenon in patients with reperfused anterior wall acute myocardial infarction. J Am Coll Cardiol 2001;38(2):472-7.

4. Magro M, Nauta S, Simsek C, Onuma Y, Garg S, van der Heide E, van der Giessen WJ, Boersma E, van Domburg RT, van Geuns RJ, Serruys PW. Value of the SYNTAX score in patients treated by primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: The MI SYNTAXscore study. Am Heart J 2011;161(4):771-81.

5. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1(2):219-27.

6. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, Giugliano RP, McCabe CH, Braunwald E. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation 2000;102(17):2031-7.

7. Halkin A, Singh M, Nikolsky E, Grines CL, Tcheng JE, Garcia E, Cox DA, Turco M, Stuckey TD, Na Y, Lansky AJ, Gersh BJ, O'Neill WW, Mehran R, Stone GW. Prediction of mortality after primary percutaneous coronary intervention for acute myocardial infarction: the CADILLAC risk score. J Am Coll Cardiol 2005;45(9):1397-405.

8. Garg S, Sarno G, Serruys PW, Rodriguez AE, Bolognese L, Anselmi M, De Cesare N, Colangelo S, Moreno R, Gambetti S, Monti M, Bristot L, Bressers M, Garcia-Garcia HM, Parrinello G, Campo G, Valgimigli M. Prediction of 1-year clinical outcomes using the SYNTAX score in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a substudy of the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Acute Myocardial Infarction) and MULTISTRATEGY (Multicenter Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction Study) trials. JACC Cardiovasc Interv 2011;4(1):66-75.

9. Gibson CM, Cannon CP, Murphy SA, Marble SJ, Barron HV, Braunwald E. Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. Circulation 2002;105(16):1909-13.

10. van 't Hof AW, Liem A, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. Circulation 1998;97(23):2302-6.

11. Dudek D, Rakowski T, El Massri N, Sorysz D, Zalewski J, Legutko J, Dziewierz A, Rzeszutko L, Zmudka K, Piwowarska W, De Luca G, Kaluza GL, Janion M, Dubiel JS. Patency of infarct related artery after pharmacological reperfusion during transfer to primary percutaneous coronary intervention influences left ventricular function and one-year clinical outcome. Int J Cardiol 2008;124(3):326-31.

12. Yip HK, Chen MC, Chang HW, Hang CL, Hsieh YK, Fang CY, Wu CJ. Angiographic morphologic features of infarct-related arteries and timely reperfusion in acute myocardial infarction: predictors of slow-flow and no-reflow phenomenon. Chest 2002;122(4):1322-32.

13. Svilaas T, Vlaar PJ, van der Horst IC, Diercks GF, de Smet BJ, van den Heuvel AF, Anthonio RL, Jessurun GA, Tan ES, Suurmeijer AJ, Zijlstra F. Thrombus aspiration during primary percutaneous coronary intervention. N Engl J Med 2008;358(6):557-67.

14. Sezer M, Oflaz H, Goren T, Okcular I, Umman B, Nisanci Y, Bilge AK, Sanli Y, Meric M, Umman S. Intracoronary streptokinase after primary percutaneous coronary intervention. N Engl J Med 2007;356(18):1823-34.

15. Gu YL, Kampinga MA, Wieringa WG, Fokkema ML, Nijsten MW, Hillege HL, van den Heuvel AF, Tan ES, Pundziute G, van der Werf R, Hoseyni Guyomi S, van der Horst IC, Zijlstra F, de Smet BJ. Intracoronary versus intravenous administration of abciximab in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention with thrombus aspiration: the comparison of intracoronary versus intravenous abciximab administration during emergency reperfusion of ST-segment elevation myocardial infarction (CICERO) trial. Circulation 2010;122(25):2709-17.

16. Fearon WF, Shah M, Ng M, Brinton T, Wilson A, Tremmel JA, Schnittger I, Lee DP, Vagelos RH, Fitzgerald PJ, Yock PG, Yeung AC. Predictive value of the index of microcirculatory resistance in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2008;51(5):560-5.

Chapter 16

The new European Society of Cardiology guidelines on myocardial revascularisation: an appraisal

Sjoerd T Nauta
Marcia Gaspersz
Jaap W DeckersW

Heart. 2012 Jan;98(1):11-4

Abstract

The latest Eropean Society of Cardiology (ESC) guidelines on myocardial revascularisation are reviewed. The nearly 300 recommendations make it almost impossible to apply them in their totality. We would propose 20 to 30 recommendations per guideline based on sound clinical evidence. Also, the scope of the current guideline is very wide, since it includes topics already incorporated in other guidelines, such as strategies for pre-intervention diagnosis and imaging as well as on secondary prevention. Some recommendations in the new guideline are sensible and will not be disputed. In particular, the encouragement of a balanced multidisciplinary decision process (the "Heart Team") is welcome.

Although coronary revascularization in unstable high risk patients is well accepted, this is less the case for the low risk patient with chest pain. This issue is controversial and a balanced discussion of the pros and cons of percutaneous coronary intervention (PCI) is missing. Despite convincing evidence indicating lack of benefit of PCI for chronic total occlusion, this procedure is not discouraged.

Lastly, most committee members were interventional cardiologists or cardiac surgeons. Guideline committees should be representative of the whole group of professionals, since the interpretation of the evidence by specialists may be biased. There may be a role for procedure oriented guidelines but, in that case, the items at issue should remain confined to matters directly related to technical aspects of the procedure.

Guidelines describe the current state of the art by formulating the current evidence base and recommendations for their application in clinical practice. On the basis of this premise, we reviewed the latest ESC guideline, those on myocardial revascularization. [1] The new document is a follow-up on the percutaneous coronary intervention (PCI) guideline from 2005, which has previously been discussed in this Journal.[2,3] The current document is a joint effort by interventional cardiologist as well as cardiovascular surgeons, and thus considers both percutaneous and surgical revascularization modalities. As a consequence, a "Heart Team," a more formal multidisciplinary team approach to coronary revascularization, is advocated. As such, the new approach goes a long way into establishing a sound basis for clinical decision making for patients with coronary insufficiency, and we – and others before us – have no doubt that it will fulfil that purpose.[4] Nevertheless, some topics covered in the guideline require clarification. In this review, we comment on those topics with the aim of improving future versions of such documents.

Specific issues

Scope of the guideline

The new guideline, which comprises 13 sections, provides recommendations for percutaneous as well as surgical revascularizations. In reality however, it goes further. For instance, the various strategies for pre-intervention diagnosis and imaging are included as well (chapter 5). A useful chapter without doubt, but we question the appropriateness of including this issue in this procedure oriented document. This is relevant since the worth of diagnostic tests has previously been described in the ESC guideline on Stable Angina.[5] Similarly, chapter 13 of the current guideline provides recommendations for secondary prevention. That subject has been covered extensively in the guideline on CVD Prevention.[6] The reader is thus left with the question where these topics are covered in future versions of these guidelines; and if the recommendations are different, which ones are to be followed. The scope of the current new guideline is thus too wide.

Number and levels of recommendations

The new guideline is quite lengthy but, with 52 pages, not extraordinarily so. However, its nearly 300 recommendations (table 1) make it almost impossible to apply them in their totality.[7]

We are of the opinion that I A ("strongly recommended") and III A ("strongly discouraged") recommendations should be issued only in the context of relevant changes in clinical outcomes resulting from performing (or withholding) specific interventions that were rigorously scrutinized and tested, preferably in randomized clinical trials. Unfortunately, this view was not taken by the current committee, with a very large number of recommendations based on "expert opinion" as a result. Leaving out such assessments would not only go a long a way in strengthening the value of the recommendations based on sound clinical evidence but, in addition, would make it much easier to apply the guideline in clinical practice. We also believe that some of the current recommendations are not appropriate or incorrect. For instance, the stratification scores used to estimate peri-procedural intervention risks (chapter 4, table 3) have been given specific recommendations. However, we are unaware of any studies that have shown that actual patient outcome will improve as a result of the

Table 1: Summary of recommendations in the new ESC guideline on coronary revascularization

Class *	Level †	No of recommendations per level	No of recommendations per class
I	A	53	
I	B	48	144
I	C	43	
IIa	A	8	
IIa	B	38	59
IIa	C	13	
IIb	A	3	
IIb	B	18	39
IIb	C	18	
III	A	12	
III	B	23	45
III	C	10	

* Class of recommendation

† Level of evidence

use of such scores and levels of recommendations are thus not applicable. The same is true for many other recommendations. For instance, the recommendations depicted in table 7 (chapter 5), which compares the value of different imaging techniques in (sub) groups of patients, are not based on studies in which these techniques were directly compared with each other.

Still, most recommendations in the new guideline are quite sound and will not lead to much controversy. For instance, mechanical, percutaneous coronary intervention of the infarct related vessel as early as possible in ST segment elevation MI, the preference for surgical revascularization intervention in case of multi-vessel disease, poor left ventricular function or diabetes, appropriate risk stratification and revascularization in patients in unstable clinical conditions, as well as physiologic assessment of the importance of intermediate coronary lesions prior to intervention, all seem very appropriate and sound. In particular, the encouragement of a balanced multidisciplinary decision process ("Heart Team") is a very welcome addition, which was given appropriate credit in a recent editorial by Taggart et al in this Journal.[4]

PCI in stable angina and chronic total occlusion

Although in suitable high risk patients coronary revascularization in unstable clinical conditions is generally well accepted, this is not true for low risk patients with stable chest pain. This is a controversial issue and, given the large number of procedures performed for this indication, not without reason. This topic is covered in chapter 6, and the reader would expect a concise but objective textual review of this subject. This section is, however, quite short and does not provide such an evaluation. However, from review of tables 8 and 9 in that chapter, it becomes clear that the authors do recommend PCI for this indication, with a (noteworthy) class IC (expert opinion) indication for 1 or 2 vessel disease not involving the proximal left anterior descending (LAD). Although the lack of references given for this recommendation is in line with the given C, the results of the randomized trials performed in these patients do not support this recommendation (see below). The table gives a IIa B recommendation for PCI when the proximal LAD is involved. This recommendation is based on two meta-analyses and two other studies comparing coronary artery bypass grafting (CABG) with PCI and are therefore not applicable. In fact, all but two references in this

table compare the results of PCI with surgical revascularization, and therefore do not address the issue of medical therapy versus PCI.

We realize that an objective assessment of the appropriateness of PCI in stable angina is not easy and confounded by specific issues. Observational data showing superiority of revascularization over medical treatment are not helpful because of significant treatment bias[8] and -unfortunately - the actual evidence base is quite small.

A summary of all randomized controlled clinical trials studies comparing PCI with medical therapy for stable angina is given in table 2 and figure 1. This analysis differs from previous analyses because we have excluded trials performed in the early nineties.[9-13] In that era, medical treatment was more or less placebo: for instance, statins and ACE inhibitors - currently considered standard medical treatment - were not available or not used. In addition, we excluded trials that investigated early post MI patients.[14-18] Overall, the combined results of these trials provide limited evidence for the superiority of PCI over medical therapy in stable chest pain syndromes. Of course, we acknowledge that some of these trials have come under criticism, and that patients switched from medical treatment to PCI (or CABG) (typically in about 25%). On the other hand, all subjects considered in these trials qualified for intervention on the basis of their specific coronary anatomy and were therefore quite selected.

Table 2: Characteristics of randomized clinical trials comparing PCI with medical treatment

Trial	Year of Most Recent Publication	Enrolment Period	Total No. of Patients	Nonprotocol Revascularizations in Medical Group (%)	Follow-up Length (Months)	Statin use at baseline (%)
AVERT[20]	1999	1995–1996	341	12	20	22
Bech et al.[21]	2001	NR	181	7	24	37
RITA 2[22]	2003	1992–1996	1,018	35	84	13
TIME[23]	2004	1996–2000	301	42	48	23
Hambrecht et al.[24]	2004	1997–2001	101	6	12	75
MASS II[25]	2006	1995–2000	408	24	60	NR
COURAGE[26]	2007	1991–2004	2,287	31	54	88
Nishigaki et al.[27]	2008	2002-2004	384	37	26	47

NR: not reported

This is different from the practical situation in which the patient with chest pain but with unknown coronary anatomy is contemplated. In the latter situation, eligibility for revascularization (and PCI) is uncertain, and a considerable number of

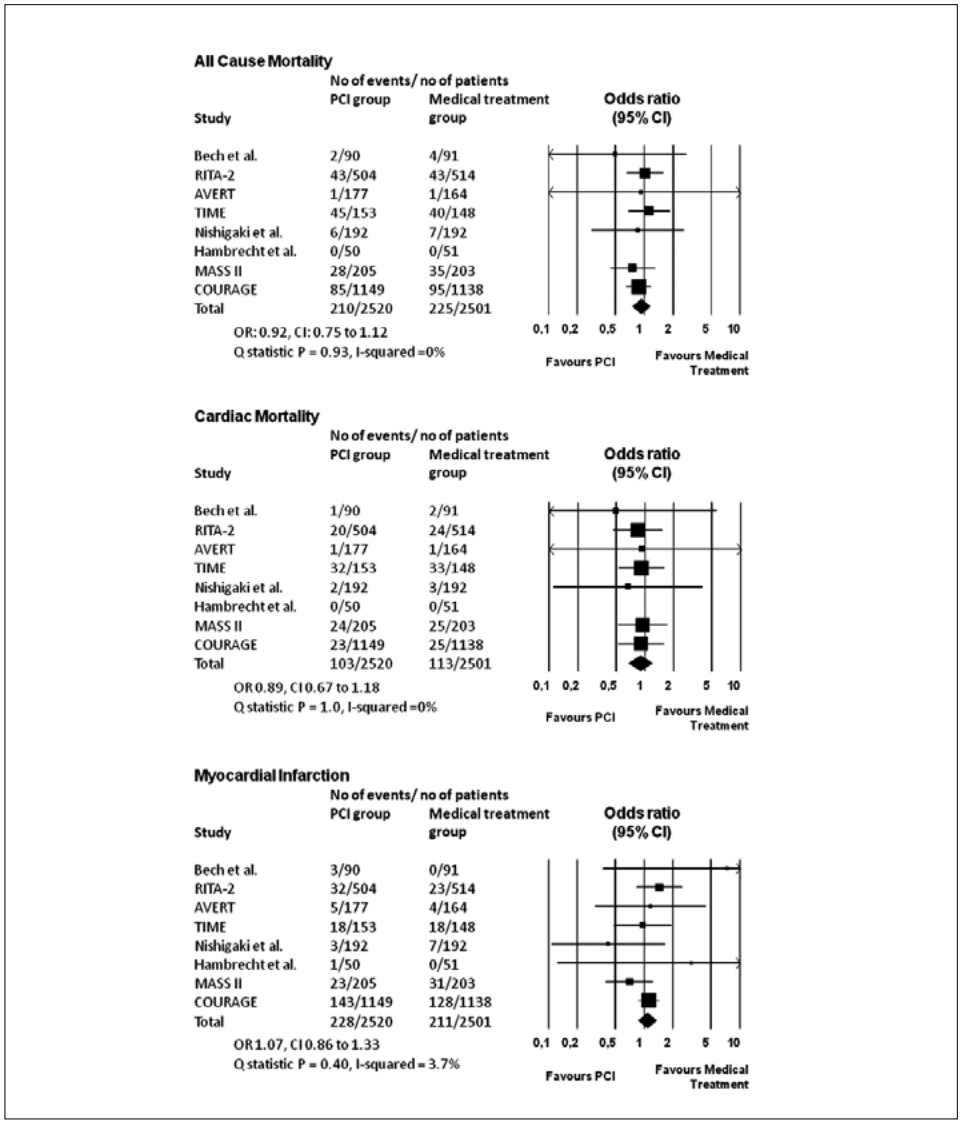

Figure 1. PCI versus medical treatment in stable angina.
For each trial we calculated the summary odds ratios and 95% confidence intervals for the clinical outcomes. We pooled studies using random effects models [28]

such patients will not be eligible for such a procedure because of anatomic or other circumstances. For instance, in the ICTUS trial, which investigated the possible benefit of revascularization in subjects with unstable angina, less than 60% of the patients scheduled to undergo intervention actually qualified for subsequent revascularization.[8] Thus, in the depicted trials, the true effectiveness of PCI in clinical practice may well have been exaggerated, and one could argue that, given their specific eligibility criteria, the randomized trials overestimated the true worth of PCI. Against this background, a balanced discussion of the pro and cons of PCI in this setting would have been helpful in the guideline. It is unreasonable to base a positive recommendation for PCI on the basis of results obtained in a subgroup of a subgroup of the (overall negative) COURAGE trial: an "evidence base" of 100 patients does not meet the criteria to justify millions of costly invasive procedures of uncertain clinical benefit.[8,19] A strategy of initial medical treatment is certainly the preferable option for the low risk patient with stable angina or in someone in whom the presence of obstructive coronary artery disease has just been established during diagnostic coronary angiography.

It is also noteworthy that, despite two negative randomized trials that specifically addressed this topic, the performance of percutaneous intervention for chronic total occlusion is not discouraged. Instead, an "experienced" intervention team is called to order, perhaps suggesting that the care was sub-standard in the trials that investigated this very issue.

General issues

Format of the guideline and composition of the writing committee

The current format of the guideline differs significantly from the previous version, and this makes it difficult to assess why, and on the basis of which information, the current recommendations have changed from those issued in the earlier document. We recommend that future versions of the guideline should be based upon and, where necessary, expand on previous versions.

Specific to this guideline, we have noted that the majority of the current committee members (and reviewers) were interventional cardiologists or cardiac surgeons. By contrast, other guideline development groups (such as NICE) also include other stakeholders such as primary care physicians, nurses, health economists, epidemiologists, cardiac radiologists, patient members and pharmacists (Timmis A. et al. Stable Angina: full guideline. 2011. www.nice.org.uk (accessed Aug 2011)). Guideline committees should be representative of the whole group of professionals and stakeholders, since it is likely that the interpretation of the evidence by specialists will be biased. There may be some role or place for procedure oriented guidelines but, in that case, the items at issue should remain confined to matters directly related to technical aspects of the actual procedure.

Regarding the number of recommendations, we think that 20 to 30 sound recommendations would be a reasonable number per guideline and, in view of our earlier comments and given the low number of recommendations based upon high quality clinical data; this should not be too difficult. A summary of our recommendations is given in box 1, and we hope that these will be helpful in developing future versions of the current as well as upcoming guidelines.

Box 1: Summary of our comments and suggestions

- Medical *treatment should be the initial management of the patient with stable chest pain. Strong recommendation, high quality data (Class IA)*
- *Percutaneous opening of a chronic total coronary occlusion is not recommended. High quality data (Class IIIA)*
- *The composition of the guideline committee must be representative of the profession at large*
- *The number of recommendations per guideline should be limited (e.g. between 20 and 30), and be based on sound (high quality) clinical evidence*
- *As a rule, recommendations based on opinion are not very useful and should be avoided. This pertains to most class II recommendations*
- *The scope of the guideline must not be too wide*
- *New versions of guidelines must build on and expand on previous versions, and relevant changes in recommenda*tions must be addressed specifically.

Disclosure

JWD was member of the ESC Committee on Practice Guidelines from 2002 to 2006, and was the review coordinator of the (previous) PCI guideline.

References

1. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas PE, Widimsky P, Kolh P, Alfieri O, Dunning J, Elia S, Kappetein P, Lockowandt U, Sarris G, Vouhe P, Kearney P, von Segesser L, Agewall S, Aladashvili A, Alexopoulos D, Antunes MJ, Atalar E, Brutel de la Riviere A, Doganov A, Eha J, Fajadet J, Ferreira R, Garot J, Halcox J, Hasin Y, Janssens S, Kervinen K, Laufer G, Legrand V, Nashef SA, Neumann FJ, Niemela K, Nihoyannopoulos P, Noc M, Piek JJ, Pirk J, Rozenman Y, Sabate M, Starc R, Thielmann M, Wheatley DJ, Windecker S, Zembala M. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J;31(20):2501-55.

2. Fox KA. COURAGE to change practice? Revascularisation in patients with stable coronary artery disease. Heart 2009;95(9):689-92.

3. Curzen NP. Is there evidence for prognostic benefit following PCI in stable patients? COURAGE and its implications: an interventionalist's view. Heart 2010;96(2):103-5.

4. Taggart DP, Boyle R, de Belder MA, Fox KA. The 2010 ESC/EACTS guidelines on myocardial revascularisation. Heart 2011;97(6):445-6.

5. Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, Daly C, De Backer G, Hjemdahl P, Lopez-Sendon J, Marco J, Morais J, Pepper J, Sechtem U, Simoons M, Thygesen K, Priori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Osterspey A, Tamargo J, Zamorano JL. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006;27(11):1341-81.

6. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, De Backer G, Ebrahim S, Gjelsvik B, Herrmann-Lingen C, Hoes A, Humphries S, Knapton M, Perk J, Priori SG, Pyorala K, Reiner Z, Ruilope L, Sans-Menendez S, Scholte op Reimer W, Weissberg P, Wood D, Yarnell J, Zamorano JL, Walma E, Fitzgerald T, Cooney MT, Dudina A. European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). Eur Heart J 2007;28(19):2375-414.

7. Tricoci P, Allen JM, Kramer JM, Califf RM, Smith SC, Jr. Scientific evidence underlying the ACC/AHA clinical practice guidelines. JAMA 2009;301(8):831-41.

8. Hirsch A, Windhausen F, Tijssen JG, Oude Ophuis AJ, van der Giessen WJ, van der Zee PM, Cornel JH, Verheugt FW, de Winter RJ. Diverging associations of an intended early invasive strategy compared with actual revascularization, and outcome in patients with non-ST-segment elevation acute coronary syndrome: the problem of treatment selection bias. Eur Heart J 2009;30(6):645-54.

9. Davies RF, Goldberg AD, Forman S, Pepine CJ, Knatterud GL, Geller N, Sopko G, Pratt C, Deanfield J, Conti CR. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. Circulation 1997;95(8):2037-43.

10. Folland ED, Hartigan PM, Parisi AF. Percutaneous transluminal coronary angioplasty versus medical therapy for stable angina pectoris: outcomes for patients with double-vessel versus single-vessel coronary artery disease in a Veterans Affairs Cooperative randomized trial. Veterans Affairs ACME InvestigatorS. J Am Coll Cardiol 1997;29(7):1505-11.

11. Hueb WA, Soares PR, Almeida De Oliveira S, Arie S, Cardoso RH, Wajsbrot DB, Cesar LA, Jatene AD, Ramires JA. Five-year follow-op of the medicine, angioplasty, or surgery study (MASS): A prospective, randomized trial of medical therapy, balloon angioplasty, or bypass surgery for single proximal left anterior descending coronary artery stenosis. Circulation 1999;100(19 Suppl):II107-13.

12. Schomig A, Mehilli J, de Waha A, Seyfarth M, Pache J, Kastrati A. A meta-analysis of 17 randomized trials of a percutaneous coronary intervention-based strategy in patients with stable coronary artery disease. J Am Coll Cardiol 2008;52(11):894-904.

13. Sievers N, Hamm CW, Herzner A, Kuck KH. Medical therapy versus PTCA: a prospective, randomized trial in patients with asymptomatic coronary single-vessel disease (abstr). Circulation 1993(88 (Suppl I)):p. I297.

14. Dakik HA, Kleiman NS, Farmer JA, He ZX, Wendt JA, Pratt CM, Verani MS, Mahmarian JJ. Intensive medical therapy versus coronary angioplasty for suppression of myocardial ischemia in survivors of acute myocardial infarction: a prospective, randomized pilot study. Circulation 1998;98(19):2017-23.

15. Erne P, Schoenenberger AW, Burckhardt D, Zuber M, Kiowski W, Buser PT, Dubach P, Resink TJ, Pfisterer M. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: the SWISSI II randomized controlled trial. Jama 2007;297(18):1985-91.

16. Madsen JK, Nielsen TT, Grande P, Eriksen UH, Saunamaki K, Thayssen P, Kassis E, Rasmussen K, Haunso S, Haghfelt T, Fritz-Hansen P, Hjelms E, Paulsen PK, Alstrup P, Arendrup H, Niebuhr-Jorgensen U, Andersen LI. Revascularization compared to medical treatment in patients with silent vs. symptomatic residual ischemia after thrombolyzed myocardial infarction--the DANAMI study. Cardiology 2007;108(4):243-51.

17. Mahmarian JJ, Dakik HA, Filipchuk NG, Shaw LJ, Iskander SS, Ruddy TD, Keng F, Henzlova MJ, Allam A, Moye LA, Pratt CM. An initial strategy of intensive medical therapy is comparable to that of coronary revascularization for suppression of scintigraphic ischemia in high-risk but stable survivors of acute myocardial infarction. J Am Coll Cardiol 2006;48(12):2458-67.

18. Zeymer U, Uebis R, Vogt A, Glunz HG, Vohringer HF, Harmjanz D, Neuhaus KL. Randomized comparison of percutaneous transluminal coronary angioplasty and medical therapy in stable survivors of acute myocardial infarction with single vessel disease: a study of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausarzte. Circulation 2003;108(11):1324-8.

19. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation 2008;117(10):1283-91.

20. Pitt B, Waters D, Brown WV, van Boven AJ, Schwartz L, Title LM, Eisenberg D, Shurzinske L, McCormick LS. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. N Engl J Med 1999;341(2):70-6.

21. Bech GJ, De Bruyne B, Pijls NH, de Muinck ED, Hoorntje JC, Escaned J, Stella PR, Boersma E, Bartunek J, Koolen JJ, Wijns W. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. Circulation 2001;103(24):2928-34.

22. Henderson RA, Pocock SJ, Clayton TC, Knight R, Fox KA, Julian DG, Chamberlain DA. Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. J Am Coll Cardiol 2003;42(7):1161-70.

23. Pfisterer M. Long-term outcome in elderly patients with chronic angina managed invasively versus by optimized medical therapy: four-year follow-up of the randomized Trial of Invasive versus Medical therapy in Elderly patients (TIME). Circulation 2004;110(10):1213-8.

24. Hambrecht R, Walther C, Mobius-Winkler S, Gielen S, Linke A, Conradi K, Erbs S, Kluge R, Kendziorra K, Sabri O, Sick P, Schuler G. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. Circulation 2004;109(11):1371-8.

25. Soares PR, Hueb WA, Lemos PA, Lopes N, Martinez EE, Cesar LA, Oliveira SA, Ramires JA. Coronary revascularization (surgical or percutaneous) decreases mortality after the first year in diabetic subjects but not in nondiabetic subjects with multivessel disease: an analysis from the Medicine, Angioplasty, or Surgery Study (MASS II). Circulation 2006;114(1 Suppl):I420-4.

26. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356(15):1503-16.

27. Nishigaki K, Yamazaki T, Kitabatake A, Yamaguchi T, Kanmatsuse K, Kodama I, Takekoshi N, Tomoike H, Hori M, Matsuzaki M, Takeshita A, Shimbo T, Fujiwara H. Percutaneous coronary intervention plus medical therapy reduces the incidence of acute coronary syndrome more effectively than initial medical therapy only among patients with low-risk coronary artery disease a randomized, comparative, multicenter study. JACC Cardiovasc Interv 2008;1(5):469-79.

28. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177-88.

Chapter 17

ESC-EACTS guidelines: myocardial revascularization

Jaap W Deckers
Sharif Khatibi
Yongzhao Feng
Sjoerd T Nauta

Hospital Cardiology Europe. 2012;1:9-11

Abstract

Current recommendations on myocardial revascularisation advocate coronary artery bypass grafting (CABG) in case of early cardiogenic shock and primary percutaneous coronary intervention (PCI) in all other ST-segment elevation myocardial infarction (STEMI) cases. In non-STEMI (NSTEMI), risk stratification is essential because benefit of revascularisation is strongest in high risk patients. In NSTEMI, unstable and stable angina, coronary artery disease distribution and severity dictate the mode of intervention, PCI or CABG. Observational and trial data support CABG in multi-vessel or left main disease.

Myocardial revascularisation by either percutaneous coronary intervention (PCI) (a percutaneous procedure first clinically applied in 1977) and coronary artery bypass grafting (CABG) (a surgical procedure originally developed in the 1960s) both fulfill an important role in the treatment of the more severe forms of coronary artery disease and its acute manifestations. Still, differences between the two revascularisation strategies are important and should be acknowledged.

With CABG, venous and/or arterial bypass grafts are placed on the epicardial mid-coronary vessel beyond the obstructive culprit lesion and, as such, provide extra sources of blood and nutrients to the distal myocardium. The nature of the surgical procedure implies that the additional distal flow through the graft (and distal coronary artery) can impede the regular, normal flow through the coronary vessel from its native origin. The consequence of this 'steal' phenomenon is that, with time, the original native vessel proximal to the bypass may become completely occluded. A second surgical procedure (redo) can be technically challenging for this reason. In addition, venous bypass grafts may become stenotic and obstructed when the ongoing systemic atherosclerotic process has not been brought under control. Fortunately, arterial bypass grafts, such as the internal mammary arteries, remain patent for much longer periods of time and these are therefore preferentially employed in the past two decades.

Box 1: Multidisciplinary decision-making (Heart Team)

The creation of a so-called 'Heart Team' serves the purpose of a balanced multi-disciplinary decisionmaking process. Complex cases should be reviewed by the Heart Team to determine which type of intervention (PCI or CABG) is best, and to document the consensus reached. If there is no urgency, patients should also be allotted sufficient time to arrive at an informed decision. For the very same reasons, a so-called ad hoc PCI, a percutaneous intervention that immediately follows the diagnostic coronary angiogram, is not encouraged.

PCI aims to restore the normal conductance capacity of the native vasculature by mechanical removal of a localised obstruction lesion. The coronary stent that almost always is left behind maintains patency and tries to limit the occurrence of restenosis. This process, caused by local inflammatory response, is nowadays counteracted by stent or balloon covered drugs (drug-eluting stents) that prevent the proliferation of cells involved in this reaction. Compared with surgical revascularisation, PCI can be repeated quite often, at least in theory. Given the specific characteristics of both revascularization techniques, PCI would seem the method of choice for single vessel disease, whereas CABG should be more suited for complex, multiple vessel or left main stem disease. Although both techniques thus seem to be complimentary, a considerable group of patients will qualify for either one of these therapeutic modalities and many clinical conditions, stable or unstable, can be treated with a choice of available but quite different therapeutic options, including PCI, surgical revascularisation or even medical treatment. In theory, most coronary lesions are amenable to PCI, but technological feasibility is only one component of the decision-making process. Other elements include clinical presentation, severity of angina, response to medical therapy, and extent of coronary artery disease, usually assessed with coronary angiography and/or computer tomography. Both revascularisation methods carry their specific procedure-related risks. Therefore, the balance between the short-term convenience of the less invasive PCI procedure against the durability of the more invasive surgical approach must be weighted carefully, both by physicians but also by the (well-informed) patients.

Against this background, it is fortunate that, at the European Society for Cardiology meetings in Stockholm in 2010, the new joint European Society of Cardiology and European Association for Cardiothoracic Surgery guidelines on myocardial revascularisation have been issued.[1] This completely new set of guidelines followed the 2006 PCI guidelines, and formalised the multidisciplinary approach to coronary intervention. The make-up of the writing committee, which mainly consisted of interventional cardiologists and cardiac surgeons, reflected this new collaborative effort, and the resulting document has rightfully received acclaim.[2,3]

By its nature, myocardial revascularisation provides best results in the presence of ischaemia. Cardiac conditions that qualify for myocardial revascularization are, in order of procedure effectiveness: ST-segment elevation myocardial infarction (STEMI); non-ST-segment elevation myocardial infarction (NSTEMI); unstable angina, and (chronic) stable angina. The most pertinent recommendations from the new revascularisation guidelines will be presented in the following sections.

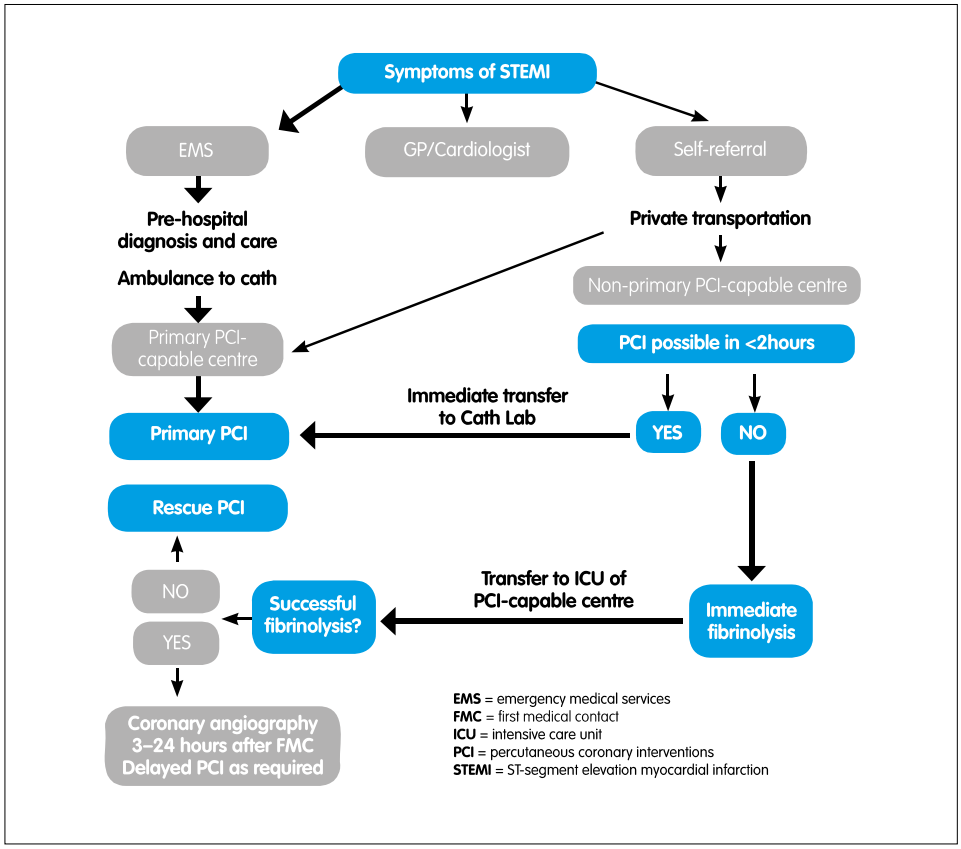

Figure 1: Organisation of ST-segment elevation myocardial infarction (STEMI) patient pathway describing pre and in-hospital management and reperfusion strategies within the 12 hours of first medical contact (see Ref 1).

Revascularisation in STEMI

Without doubt, acute coronary revascularisation with primary PCI is an extremely effective intervention in the setting of STEMI, the result of a sudden thrombotic coronary occlusion. The PCI reperfusion modality carries not only less risk of bleeding than thrombolytic treatment, but will also lead to more effective restoration of vessel patency, less re-occlusion, improved residual function, and better clinical outcome including better survival. However, in order to achieve its full potential, time delays must be avoided, and a system of care network should be established around each cardiac intervention centre to make sure that this is indeed the case. The currently recommended treatment and decision algorithm is presented in Figure 1. Of course, pre-hospital triage that includes a 12-lead ECG should be an integral element of such a scheme. The delay between first medical contact and injection of contrast material into the coronary artery must be less than 90 minutes. It goes without saying that this requirement calls for considerable organisational efforts, not only during the normal working hours, but also during the off hours and on weekends. Because a primary PCI is technically more demanding than an elective procedure, and given the strong inverse volume–outcome relationship in high-risk and emergency PCI procedures, primary PCI operators should perform at least two PCI procedures per week in an institution with an annual volume over 400 elective and 40 primary PCI procedures.

Given the nature of the pathophysiology of STEMI, the culprit lesion will be proximally located in one of the three large epicardial coronary arteries, and should almost always be amenable to PCI. Emergency CABG will be necessary in case a very large myocardial area is at risk, for instance in patients who present early in cardiogenic shock and/or are found to have complete obstruction (of dissection) of the left main stem. Emergency coronary bypass surgery will also be necessary then it proves to be impossible to reach the culprit vessel by percutaneous technique. In practice, this will rarely be the case. When severe three-vessel or left main stem disease is found to be present following primary PCI and CABG is deemed necessary, the operation can often be delayed until the patient has reached a more stable clinical condition, for example, between three and seven days following hospitalisation.

Box 2: Risk scores

Risk assessment is an important aspect of contemporary clinical practice and, in the framework of challenging invasive procedures with (small but not negligible) risk of complications, of considerable importance. Different models are available to assess the risk associated with PCI or CABG, although it has not yet been established whether the actual use of such models in clinical practice will improve outcome in an individual patient. Still, it is generally agreed that such prediction models provide useful guidance in the often difficult decision-making process of myocardial revascularisation.

EuroSCORE: Independent predictor of major adverse events in PCI and CABG: the score can be used to determine the risk of revascularisation associated with both procedures.

SYNTAX score: Independent predictor of adverse events in PCI. Has a role in identifying those patients at highest risk of adverse events with PCI.

GRACE score: Developed in patients with NSTEMI and the preferred risk classification scheme in these patients.

National Cardiovascular Database Registry risk score (NCDR): This score has been validated in patients undergoing PCI only.

Society of Thoracic Surgeons (STS) score: Relatively simple score that considers age, left ventricular ejection fraction and renal function. Applicable only in CABG.

According to the current recommendations, administration of fibrinolytic therapy must be restricted to those instances in which PCI cannot be performed within two hours of the first contact between patient and the medical system (in the first 12 hours following symptom onset). This can still be the case in some mountainous or rural areas.

Key points

- *Percutaneous coronary intervention (PCI) would seem the method of choice for single vessel disease, whereas CABG should be more suited for complex, multiple vessel or left main stem disease.*
- *The creation of a so-called 'Heart Team' serves the purpose of a balanced multidisciplinary decision-making process for the patient who qualifies for either one of these treatment options.*
- *In order of procedure effectiveness, myocardial revascularisation is most effective in ST-elevation myocardial infarction (STEMI), non-STEMI, unstable angina, and (chronic) stable angina pectoris.*
- *In patients with mild-to-moderate angina, an initially cautious approach to coronary revascularisation is reasonable: watchful waiting seems appropriate.*
- *In case PCI of coronary lesions of moderate severity is considered, a functional assessment of the stenosis, the determination of coronary flow reserve, is recommended.*

The recommended medical treatment in STEMI is straightforward: dual antiplatelet therapy must be initiated as early as possible and preferably prior to hospitalisation, unless there is serious risk of bleeding. Pain relief (with 4–8mg morphine) is usually necessary. Anticoagulation must be given immediately following hospitalisation. Aditional platelet inhibition with (intravenous) IIa/IIIb inhibitors is needed when restoration of coronary flow after PCI remains incomplete. Oral administration of beta-blockers is next, and ACE inhibitors and statins will be given subsequently. In the early phase of the hospitalisation, elevated blood pressure can be treated with high doses of (intravenous) nitrates.

Revascularisation in NSTEMI and unstable angina

NSTEMI is the most frequent manifestation of acute coronary syndromes and represents the largest group of patients undergoing myocardial revascularisation. In contrast to STEMI, NSTEMI usually occurs in elderly subjects, often in those with previously diagnosed atherosclerotic heart disease. By definition, the diagnosis of NSTEMI is made in the presence of myocardial necrosis. Unstable angina, the third member of the acute coronary syndrome family, is diagnosed in the presence of myocardial ischaemia at rest without evidence of myocardial damage. However, the extremely high sensitivity of the current generation of myocardial biomarkers, specifically the high sensitive troponin, makes it increasingly difficult to establish the diagnosis of unstable angina since elevated levels of these markers will be present in almost all instances of true 'angina at rest'. In clinical practice therefore, the difference between unstable angina and NSTEMI has become somewhat blurred and, for all practical purposes, the approach to both syndromes has been combined under this heading.

Patients with NSTEMI or unstable angina constitute a heterogeneous group with a variable prognosis. Most, but not all, randomised clinical trials performed in the setting of NSTEMI have shown beneficial effects of an early invasive strategy. However, the interpretation of their findings is hampered by the relatively frequent switches (cross-over) from one treatment allocation to the alternative and/ or the inability to perform revascularization for technical reasons (complex anatomy or normal findings) in the intervention arm. In other words, the contrast between the two treatment arms in many studies has usually been modest. In most trials, the rate of intervention was approximately 60–70%, with PCI by far being the most frequently performed revascularisation technique.

A substantial benefit with an early invasive strategy has only been proven in patients at high risk, and early risk stratification is therefore essential. To this end, the guidelines recommend the GRACE score (www.outcomes-umassmed.org/grace) as the preferred risk classification scheme. Not surprisingly, factors associated with increased risk in NSTEMI and unstable angina include haemodynamic instability, advanced age, ST segment depression, renal dysfunction, diabetes and previous

revascularisation. Patients at low risk can be managed medically, unless severe ischaemia is found to be present with subsequent non-invasive testing.

The issue of timing and type (PCI or CABG) of revascularisation also remains a matter of debate. The guidelines advocate coronary angiography to be performed within 24 hours in patients with elevated (>140 units) GRACE score. Otherwise, a time window of 72 hours is considered appropriate. No prospective trial has addressed the selection of mode of intervention: as in stable angina (see below), this should be based on the severity and distribution of the coronary abnormalities. The SYNTAX risk score has been advocated for this purpose, and CABG is then the preferred revascularization option when the score has a value that exceeds a value of about 30 units.

The medical regimen in NSTEMI is not unlike that of STEMI and includes platelet inhibition, intensive use of anticoagulant drugs and medication to lower myocardial oxygen need (heart rate and blood pressure reducing agents).

Stable angina pectoris

Depending on its symptomatic, functional, and anatomical complexity, stable angina pectoris can be treated by medical treatment or with myocardial revascularisation using PCI or CABG. The main indications for intervention are persistence of angina symptoms, despite extensive medical therapy and/or severe ischaemia during low levels of exercise. In all fairness, the evidence base for performing PCI or CABG in stable angina is quite limited. Randomised clinical trials that compared PCI with medical treatment have shown ambiguous results. Mortality seems unaffected although, at least in the short-term, PCI may be associated with better symptomatic relief. Observational data support the use of CABG in symptomatic subjects with multivessel and/ or left main disease. In clinical practice, an initially cautious approach to percutaneous or surgical coronary intervention seems reasonable in patients with mild-tomoderate angina and, certainly in the early phases of the disease, an approach of watchful waiting might be most appropriate. In case PCI of coronary lesions of moderate severity is considered, a functional assessment of the impact of the stenosis on coronary flow, the assessment of coronary flow reserve, is recommended.

References

1. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. Eur Heart J 2010;31(20):2501-55.

2. Taggart DP, Boyle R, de Belder MA, Fox KA. The 2010 ESC/EACTS guidelines on myocardial revascularisation. Heart 2011;97(6):445-6.

3. Nauta ST, Gaspersz M, Deckers JW. The new European Society of Cardiology guidelines on myocardial revascularisation: an appraisal. Heart 2012;98(1):11-4.

Part VI

Methodology

Chapter 18

Choosing an appropriate control group for an observational study design

Sjoerd T Nauta
Ron T van Domburg

Pharmacoepidemiol Drug Saf. 2012 Mar;21(3):341

Abstract

No abstract is available for this article.

To the Editor

Recently Haukka *et al*[1] investigated the association of statin use with all-cause and disease specific mortality utilizing nationwide databases in Finland. We feel that the interpretation of these results is difficult, and that a more appropriate study design might have improved the study.

In their large study, all persons in Finland who had purchased at least one statin prescription between 1997 and 2005 were compared to a control group matched for age, sex and place of residence from the general population. We think that the authors have chosen the wrong control group. Statins are predominantly prescribed in patients with coronary heart disease.[2] Thus, as secondary prevention. However, the control group of the present study includes predominantly patients without coronary heart disease. In our opinion, these two groups are by definition incomparable.

The study by Haukka et al concludes that due to the pronounced baseline differences a bias is likely, and it was therefore not possible to draw conclusions from this comparison.[1] Given their access to rich data, it seems that the authors could have chosen a more dedicated comparison group. Previously, observational studies that compared statin users with otherwise similar non-users demonstrated that it is possible to obtain reliable results.[3-4]

References

1. Haukka J, Niskanen L, Partonen T, Lonnqvist J, Tiihonen J. Statin usage and all-cause and disease-specific mortality in a nationwide study. Pharmacoepidemiol Drug Saf. Sep 29 2011.

2. Helin-Salmivaara A, Lavikainen P, Korhonen MJ, et al. Long-term persistence with statin therapy: a nationwide register study in Finland. Clin Ther. 2008;30 Pt 2:2228-2240.

3. Weiner MG, Xie D, Tannen RL. Replication of the Scandinavian Simvastatin Survival Study using a primary care medical record database prompted exploration of a new method to address unmeasured confounding. Pharmacoepidemiol Drug Saf. Jul 2008;17:661-670.

4. Hippisley-Cox J, Coupland C. Effect of statins on the mortality of patients with ischaemic heart disease: population based cohort study with nested case-control analysis. Heart. Jun 2006;92:752-758

Chapter 19

Tools & Techniques: Analysis of clustered data in interventional cardiology – current practice and methodological advice

Hester Lingsma
Sjoerd T Nauta
Nikki van Leeuwen
Gerard Borsboom
Nico Bruining
Ewout Steyerberg

EuroIntervention. 2013 May 20;9(1):162-4

Background

Clustered data are common in the field of interventional cardiology. Often multiple lesions are examined within the same patient and intravascular imaging modalities, such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT), result in multiple measurements from the same vessel segment. Multiple observations from one patient are likely to be correlated, which has implications for the statistical approach used to analyze the data.

The approach in the statistical analysis should be based on the study objective. If we study the effect of medication versus no medication, the level of analysis should be the patient. If we study the effect of stent implantation, the level of analysis could be the stented segment. One patient can have multiple stented segments and these are likely to be correlated. Ignoring this correlation in the analysis leads to too strong statistical inference. Specifically, misleadingly small standard errors (and thus p-values and confidence intervals) will be found because all observations are considered as independent observations. This wrongly inflates statistical power. Thus, analyses of data that include multiple observations per patient require some form of adjustment to account for the correlation between observations. This is common knowledge in the statistical literature (see for example Molenberghs[1]), however, clustered data are often analyzed without taking the within-cluster correlation into account in the medical literature[2].

The aim of this paper is to review the current analytical approach to clustered data in the field of interventional cardiology, and to present and illustrate statistical methods that take into account possible correlation within clusters. We provide syntax for different statistical packages to allow researchers to apply these methods.

Current practice

We conducted a systematic review to gain insight in the current statistical approaches to clustered data in the field of interventional cardiology. We focused on studies on optical coherence tomography (OCT), since this technique results in large numbers of observations per patient. We conducted a PubMed literature search, for original studies published between January 1, 2012 and December 31, 2012, in six important (interventional) cardiology journals: Circulation, Circulation cardiovascular interventions, EuroIntervention, European Heart Journal, Journal of the American College of Cardiology (JACC) and JACC cardiovascular interventions. A search with "optical coherence tomography" yielded 25 potentially eligible studies which were reviewed by two independent reviewers. In case of disagreement a third reviewer was consulted. Case-reports, reviews and editorials were excluded, leaving 17 studies (Appendix 1), all reporting data derived from multiple observations per patient. In 15 (88%) of the 17 studies inferences made from these multiple observations per patients were reported. Of those 15 studies, only 5 (33%) took the clustered nature of the data clearly into account in the statistical analysis. In 3 (20%) studies it was not clear whether the clustering was taken into account. In 7 (46%) studies it was clear that the clustering within patients was not taken into account. In these studies t-tests were mostly conducted, which assume that all observations are independent.

Methods to analyze clustered data

We illustrate the use of different statistical methods with data from a study that evaluated late recoil of a novel bioabsorbable everolimus-eluting coronary scaffold (BVS)[3]. The study consisted of 16 patients, who were treated with elective BVS implantation. All patients underwent an IVUS examination post-procedure and at 6 months of follow-up. A total of 484 paired cross-sectional areas (CSAs) were acquired, on average over 30 per patient. Late absolute stent recoil was defined as stent area at post-procedure minus stent area at follow-up. In each CSA, plaque morphology was assessed qualitatively and classified as calcific, fibronecrotic, or fibrocellular plaque.

In these data we address two research questions with different methods in line with the reviewed literature.

Research question 1: What is the stent recoil in this population? We can hereto provide a mean with a 95% confidence interval (CI).

Research question 2: What is the difference in stent recoil between the three different plaque types? We can hereto provide differences between plaque types with 95% CI.

Method 1: Independent observations

The simplest method is to analyze the data at CSA level, without taking into account the clustering within patients. Formally this approach assumes that each observation is statistically independent, i.e. that there is no correlation between different CSAs from the same patient. We calculate mean absolute recoil and 95% confidence interval (95% CI) based on all 484 CSAs. Alternatively the mean and 95% CI can be obtained from a linear regression model without any covariates. In this model only the intercept is estimated which equals the mean recoil. To estimate the differences between plaque types, a linear regression model with plaque type as a categorical covariate can be fitted. The linear models estimate unconditional effects, i.e. the average difference between plaque types in the population.

Method 2: Clustered observations

In contrast to the first approach, we can take the correlations between recoil values within patients into account. We can thereto use a linear multilevel model, also called random effect, mixed, or hierarchical model. The multilevel model contains two levels: patient and CSA. Patient is included in the model as a random effect, which allows estimation of patient specific recoil values. The estimated intercept equals the mean recoil, with clustering taken into account.

To estimate the differences between plaque types we used a linear multilevel model with a random intercept for patient and plaque type as a categorical covariate.

The interpretation of the differences between plaque types is somewhat different than in method 1. In method 1, we estimate differences within and across patients, while in method 2, we strictly estimate differences within patients.

Method 3: Patient level

Another approach simply averages the recoil values per patient. These means are saved. In a second step, the means are averaged to obtain an overall mean over all observations.

Results

All three methods estimated a similar mean absolute recoil of about 0.65 to 0.66 mm^2 (Table 1). As expected, the 95% confidence interval of the absolute recoil was smallest (-0.80; -0.49) when all CSAs were analyzed as independent observations and largest (-1.32; -0.01) when the CSAs were first summarized per patient. When the CSAs were analyzed as clustered observations with a multilevel model, the 95% CI was -1.27 mm^2 to -0.05 mm^2, which is clearly larger than the 95%CI obtained with method 1, and close that the width obtained with method 3.

Table 1: Methods for estimating mean recoil in total population (n CSA=484, n patients=16)

Method	Clustering taken into account?	Statistical method	Level	Mean recoil (95% CI)
Use all CSAs as independent observations	No	Calculate mean+se/95% CI; Linear regression with one common intercept	CSA	-0.65 (-0.80 ; -0.49)
Use all CSAs as clustered observations	Yes	Multilevel linear regression	CSA	-0.66 (-1.27 ; -0.05)
Summarize CSAs per patients	Yes	Calculate mean+se/95% CI; Linear regression with one common intercept	Patient	-0.66 (-1.32;-0.01)

See appendix 2 for syntax for presented methods

When estimated with a naïve linear model, ignoring clustering, the mean recoil per plaque type was -0.75 mm^2 in fibro-cellular, -0.20 mm^2 in calcific, and -1.03 in fibro-necrotic plaques. The corresponding betas (95% confidence interval) were 0.54 mm^2 (0.19; 0.89) for fibro-cellular vs. calcific plaques and -0.29 mm^2 (-0.66; 0.09) for fibro-cellular vs. fibro-necrotic plaques (Table 2). When clustering was taken into account in the multilevel model, the differences were 0.60 mm^2 (0.21; 1.00) and -0.06 mm^2 (-0.38; 0.26), respectively. This difference could be explained by the fact that the multilevel model estimates conditional, or within patient differences. When all CSAs are considered independent, fibro-necrotic plaques have 0.29 mm^2 less recoil than fibro-cellular plaques. However, when we acknowledge that CSAs are clustered within patients, this difference almost disappeared (0.06 mm^2 less recoil). In this example the

29 mm^2 absolute recoil difference is contributed to a high or low recoil level in some patients, instead of to the plaque type itself. Within a patient, fibro-cellular plaques appear to give no more recoil than calcific plaques.

In this particular example the estimated mean recoil in the overall population was not largely affected by using a multilevel model, only the confidence interval increased. The estimated difference between plaque types was however affected. The difference between fibro-cellular and calcific plaques was only borderline significant in the multilevel model.

In general, the change in point estimates between naïve models and multilevel model will be influenced by the correlation within patients, and the difference in number of observations between patient. When both are small, point estimates are likely to be very similar between the methods. However, the standard error and confidence intervals will generally increase, and corresponding p values decrease when using a multilevel model. Ignoring clustering using naïve models will exaggerate statistical significance.

Table 2: Methods for difference in recoil between plaque types (n CSA=484, n patients=16)

Method	Clustering taken into account?	Statistical method	Level	Difference between plaque types (95% CI)
Use all CSAs as independent observations	No	Calculate mean+se/95% CI; Linear regression with one common intercept	CSA	-0.65 (-0.80 ; -0.49)
Use all CSAs as independent observations	No	Linear regression	CSA	0.54 (0.19 ; 0.89)* -0.29 (-0.66 ; 0.09)**
Use all CSAs as clustered observations	Yes	Multilevel linear regression	CSA	0.60 (0.21; 1.00)* -0.06 (-0.38; 0.26)**

* Difference between fibro-cellular (reference) and calcific plaques,

** Difference between fibro-cellular (reference) and fibro-necrotic plaques.

See appendix 2 for syntax for presented methods

Conclusion and recommendations

According to literature review, the current analytical approach to clustered data in the field of interventional cardiology, specifically OCT, is suboptimal. A large number of studies ignored the clustered nature of their data, or it was unclear which statistical methods were used. If we assume that observations within one patient are correlated, ignoring clustering may lead to wrong conclusions.

Our data example shows that indeed misleadingly small confidence intervals can be estimated with standard linear regression. The third method -summarizing CSAs per patient- is statistically correct when analyses on patient level are performed, but inefficient.

When observations within patients are not correlated, the clustering can theoretically be ignored. However, this is clinically unlikely. And, in the absence of correlation the results from standard and multilevel analysis will be the same. We therefore recommend to always use multilevel models when analyzing multiple observations per patient, to make correct statistical inferences and not inflate statistical power. These models are now widely available in statistical software, and syntax is provided in appendix 2.

References

1. Molenberghs G VG. Models for Discrete Longitudinal Data: Springer Berlin; 2005.

2. Austin PC, Tu JV, Alter DA. Comparing hierarchical modeling with traditional logistic regression analysis among patients hospitalized with acute myocardial infarction: should we be analyzing cardiovascular outcomes data differently? Am Heart J 2003;145(1):27-35.

3. Tanimoto S, Bruining N, van Domburg RT, Rotger D, Radeva P, Ligthart JM, Serruys PW. Late stent recoil of the bioabsorbable everolimus-eluting coronary stent and its relationship with plaque morphology. J Am Coll Cardiol 2008;52(20):1616-20.

Appendix 1

15 studies with inference based on clustered data; 5 clearly analyzed with taking structure into account

Author	Journal	Inferences made on clustered data?	Clustered data structure taken into account in analyses?
Fukunaga et al.	EI	Yes	Not clear
Wykrzkowska et al.	EI	No	n.a.
Alegría-Barrero et al.	EI	Yes	Not clear
Okamura et al.	EI	Yes	No
Sheehy et al.	EI	Yes	No
Brugaletta et al.	EI	Yes	No
Gomez-Lara et al.	EI	Yes	No
Belkacemi et al.	JACC	Yes	No
Van Geuns et al.	JACC CI	Yes	Yes
Kato et al.	JACC CI	No	n.a.
Räber et al.	JACC CI	Yes	Yes
Gutiérrez-Chico et al.	JACC CI	Yes	Yes
Guagliumi et al.	JACC CI	Yes	No
Ormiston et al.	Circulation CI	Yes	Not clear
Gutiérrez-Chico et al.	Circulation CI	Yes	Yes
Guagliumi et al.	Circulation CI	Yes	Yes
Tada et al.	Circulation CI	Yes	No

EI = EuroIntervention,

JACC = Journal of the American College of Cardiology

JACC CI = JACC cardiovascular interventions

Circulation CI = Circulation cardiovascular interventions

n.a.= not applicable

Fukunaga M, Fujii K, Nakata T, et al. Multiple complex coronary atherosclerosis in diabetic patients with acute myocardial infarction: a three-vessel optical coherence tomography study. EuroIntervention 2012; 8(8): 955-61.

Wykrzykowska JJ, Diletti R, Gutierrez-Chico JL, et al. Plaque sealing and passivation with a mechanical self-expanding low outward force nitinol vShield device for the treatment of IVUS and OCT-derived thin cap fibroatheromas (TCFAs) in native coronary arteries: report of the pilot study vShield Evaluated at Cardiac hospital in Rotterdam for Investigation and Treatment of TCFA (SECRITT). EuroIntervention 2012; 8(8): 945-54.

Alegria-Barrero E, Foin N, Chan PH, et al. Optical coherence tomography for guidance of distal cell recrossing in bifurcation stenting: choosing the right cell matters. EuroIntervention 2012; 8(2): 205-13.

Okamura T, Onuma Y, Garcia-Garcia HM, Bruining N, Serruys PW. High-speed intracoronary optical frequency domain imaging: implications for three-dimensional reconstruction and quantitative analysis. EuroIntervention 2012; 7(10): 1216-26.

Sheehy A, Gutierrez-Chico JL, Diletti R, et al. In vivo characterisation of bioresorbable vascular scaffold strut interfaces using optical coherence tomography with Gaussian line spread function analysis. EuroIntervention 2012; 7(10): 1227-35.

Brugaletta S, Gomez-Lara J, Bruining N, et al. Head to head comparison of optical coherence tomography, intravascular ultrasound echogenicity and virtual histology for the detection of changes in polymeric struts over time: insights from the ABSORB trial. EuroIntervention 2012; 8(3): 352-8.

Gomez-Lara J, Diletti R, Brugaletta S, et al. Angiographic maximal luminal diameter and appropriate deployment of the everolimus-eluting bioresorbable vascular scaffold as assessed by optical coherence tomography: an ABSORB cohort B trial sub-study. EuroIntervention 2012; 8(2): 214-24.

Belkacemi A, Agostoni P, Nathoe HM, et al. First results of the DEB-AMI (drug eluting balloon in acute ST-segment elevation myocardial infarction) trial: a multicenter randomized comparison of drug-eluting balloon plus bare-metal stent versus bare-metal stent versus drug-eluting stent in primary percutaneous coronary intervention with 6-month angiographic, intravascular, functional, and clinical outcomes. J Am Coll Cardiol 2012; 59(25): 2327-37.

van Geuns RJ, Tamburino C, Fajadet J, et al. Self-expanding versus balloon-expandable stents in acute myocardial infarction: results from the APPOSITION II study: self-expanding stents in ST-segment elevation myocardial infarction. JACC Cardiovasc Interv 2012; 5(12): 1209-19.

Kato K, Yonetsu T, Kim SJ, et al. Comparison of nonculprit coronary plaque characteristics between patients with and without diabetes: a 3-vessel optical coherence tomography study. JACC Cardiovasc Interv 2012; 5(11): 1150-8.

Raber L, Baumgartner S, Garcia-Garcia HM, et al. Long-term vascular healing in response to sirolimus- and paclitaxel-eluting stents: an optical coherence tomography study. JACC Cardiovasc Interv 2012; 5(9): 946-57.

Gutierrez-Chico JL, Gijsen F, Regar E, et al. Differences in neointimal thickness between the adluminal and the abluminal sides of malapposed and side-branch struts in a polylactide bioresorbable scaffold: evidence in vivo about the abluminal healing process. JACC Cardiovasc Interv 2012; 5(4): 428-35.

Guagliumi G, Sirbu V, Musumeci G, et al. Examination of the in vivo mechanisms of late drug-eluting stent thrombosis: findings from optical coherence tomography and intravascular ultrasound imaging. JACC Cardiovasc Interv 2012; 5(1): 12-20.

Ormiston JA, Serruys PW, Onuma Y, et al. First serial assessment at 6 months and 2 years of the second generation of absorb everolimus-eluting bioresorbable vascular scaffold: a multi-imaging modality study. Circ Cardiovasc Interv 2012; 5(5): 620-32.

Gutierrez-Chico JL, Wykrzykowska J, Nuesch E, et al. Vascular tissue reaction to acute malapposition in human coronary arteries: sequential assessment with optical coherence tomography. Circ Cardiovasc Interv 2012; 5(1): 20,9, S1-8.

Guagliumi G, Bezerra HG, Sirbu V, et al. Serial assessment of coronary artery response to paclitaxel-eluting stents using optical coherence tomography. Circ Cardiovasc Interv 2012; 5(1): 30-8.

Tada T, Kadota K, Hosogi S, et al. Optical coherence tomography findings in lesions after sirolimus-eluting stent implantation with peri-stent contrast staining. Circ Cardiovasc Interv 2012; 5(5): 649-56.

Appendix 2

Syntax code for the performed analyses in SPSS, SAS and R

SPSS

```
* Import data
GET DATA
 /TYPE=XLS
 /FILE='V:\UserData\MyPaper\data.xls'
 /SHEET=name 'recoil and plaque characteristi'
 /CELLRANGE=full
 /READNAMES=on
 /ASSUMEDSTRWIDTH=32767.
EXECUTE.
DATASET NAME DataSet1 WINDOW=FRONT.


* RQ 1, method 1
EXAMINE VARIABLES=Recoil
 /PLOT NONE
 /STATISTICS DESCRIPTIVES
 /CINTERVAL 95
 /MISSING LISTWISE
 /NOTOTAL.

COMPUTE constant = 1.
EXECUTE.

REGRESSION
 /MISSING LISTWISE
 /STATISTICS COEFF OUTS CI(95) R ANOVA
 /CRITERIA=PIN(.05) POUT(.10)
 /ORIGIN
 /DEPENDENT Recoil
 /METHOD=ENTER constant.
```

*** RQ 1, method 2**

```
MIXED Recoil WITH constant
  /CRITERIA=CIN(95) MXITER(100) MXSTEP(10) SCORING(1) SINGULAR(0.000000000001)
    HCONVERGE(0,
   ABSOLUTE) LCONVERGE(0, ABSOLUTE) PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=  constant | SSTYPE(3)
  /METHOD=ML
  /PRINT=SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(Patient) COVTYPE(VC).
```

*** RQ 1, method 3**

```
AGGREGATE
  /OUTFILE='V:\UserData\521825\Paper Eurointervention\aggr.sav'
  /BREAK=Patient
  /Recoil_mean=MEAN(Recoil).

GET
  FILE='V:\UserData\521825\Paper Eurointervention\aggr.sav'.
DATASET NAME DataSet2 WINDOW=FRONT.

EXAMINE VARIABLES=Recoil_mean
  /PLOT NONE
  /STATISTICS DESCRIPTIVES
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.
```

***RQ 2, method 1**

```
xGET DATA
 /TYPE=XLS
 /FILE='V:\UserData\521825\Paper Eurointervention\recoil and plaque characteristics data for Ron
   and Nico 08.04.22.xls'
 /SHEET=name 'recoil and plaque characteristi'
 /CELLRANGE=full
 /READNAMES=on
 /ASSUMEDSTRWIDTH=32767.
EXECUTE.
DATASET NAME DataSet1 WINDOW=FRONT.

COMPUTE x1=0 .
IF Plaque = 1 x1 = 1.
EXECUTE.

COMPUTE x2=0 .
IF Plaque = 2 x2 = 1.
EXECUTE.

REGRESSION
 /MISSING LISTWISE
 /STATISTICS COEFF OUTS CI(95) R ANOVA
 /CRITERIA=PIN(.05) POUT(.10)
 /NOORIGIN
 /DEPENDENT Recoil
 /METHOD=ENTER x1 x2.
```

*** RQ 2, method 2**

```
MIXED Recoil WITH x1 x2
 /CRITERIA=CIN(95) MXITER(100) MXSTEP(10) SCORING(1) SINGULAR(0.000000000001)
   HCONVERGE(0,
  ABSOLUTE) LCONVERGE(0, ABSOLUTE) PCONVERGE(0.000001, ABSOLUTE)
 /FIXED=  x1 x2 | SSTYPE(3)
 /METHOD=ML
 /PRINT=SOLUTION
 /RANDOM=INTERCEPT | SUBJECT(Patient) COVTYPE(VC).
```

SAS

```
proc import
  out=a
  datafile="V:\UserData\MyPaper\data.csv"
  dbms=csv
  replace;
  getnames=yes;
  datarow=2;
run;

title1 'Research Question 1';
title2 'Method 1';
title3 'First simply calculate overall mean and s.e.';
proc univariate data=a;
  var Recoil;
run;

title3 'Then calculate overall mean and s.e. using linear regression';
proc reg data=a;
  model Recoil = ;
run;


title2 'Method 2';
title3 'Calculate overall mean and s.e. using multilevel model';
proc mixed data=a;
  class Patient;
  model Recoil = / solution cl;
  random int / subject=Patient solution;
run;

title2 'Method 3';
title3 'First calculate means per patient';
proc means data=a;
  var Recoil;
  output out=b mean=PatAvg;
  by Patient;
run;
```

```
title3 'Then average the calculated means';
proc univariate data=b;
  var PatAvg;
run;

title1 'Research Question 2';
title2 'First a general linear model with Plaque as discrete predictor';
proc glm data=a;
  class Plaque Patient;
  model Recoil = Plaque / solution;
run;

title2 'Then a mixed model with Plaque as discrete predictor';
proc mixed data=a;
  class Plaque Patient;
  model Recoil = Plaque / solution cl;
  random int / subject=Patient solution;
run;
```

R

```
#load libraries
library(Hmisc)
library(rms)
library(foreign)
library(lme4)

#import data
data <- as.data.frame(read.table(file= 'V:\\UserData\\MyPaper\\data. csv',header=T,sep= ","))
names(data)
nrow(data)
attach(data)

#RQ 1, method 1a
mean1b <- mean(Recoil)
sd1b <- sd(Recoil)
n1b <- nrow(data)

se1b <- sd1b / sqrt(n1b)

cil1b <- mean1b - 1.96*se1b
ciu1b <- mean1b + 1.96*se1b
```

```
#RQ 1, method 1b
rq1mod1 <- lm(Recoil~1)
mean1a <-  coef(summary(rq1mod1))[1,1]
se1a <-  coef(summary(rq1mod1))[1,2]

cil1a <- mean1a - 1.96*se1a
ciu1a <- mean1a + 1.96*se1a

rq1method1a <- cbind('1a', round(mean1a,2), round(cil1a,2), round(ciu1a,2))

rq1method1b <- cbind('1b', round(mean1b,2), round(cil1b,2), round(ciu1b,2))

#RQ 1, method 2
rq1mod2 <- lmer (Recoil~1 + 1|Patient)
mean2 <- coef(summary(rq1mod2))[1,1]
se2 <-coef(summary(rq1mod2))[1,2]

cil2 <- mean2 - 1.96*se2
ciu2 <- mean2 + 1.96*se2

rq1method2 <- cbind('2', round(mean2,2), round(cil2,2), round(ciu2,2))

#RQ 1, method 3
meanRecoil <- tapply(Recoil, Patient, mean)
mean3 <- mean(meanRecoil)
sd3 <- sd(meanRecoil)
n3 <- length(meanRecoil)

se3 <- sd3 / sqrt(n3)

cil3 <- mean3 - 1.96*se3
ciu3 <- mean3 + 1.96*se3

rq1method3 <- cbind('3', round(mean3,2), round(cil3,2), round(ciu3,2))

summaryRQ1 <-rbind(rq1method1a, rq1method1b, rq1method2, rq1method3)
colnames(summaryRQ1) <- c('method','mean', 'lower 95% CI', 'upper 95% CI')
summaryRQ1
```

```
# RQ 2, method 1
rq2mod1 <- lm(Recoil~as.factor(Plaque))

beta1cat1 <- coef(summary(rq2mod1))[2,1]
beta1cat2 <- coef(summary(rq2mod1))[3,1]

se1cat1 <- coef(summary(rq2mod1))[2,2]
se1cat2 <- coef(summary(rq2mod1))[3,2]

cil1cat1 <- beta1cat1 - (1.96*se1cat1)
ciu1cat1 <- beta1cat1 + (1.96*se1cat1)

cil1cat2 <- beta1cat2 - (1.96*se1cat2)
ciu1cat2 <- beta1cat2 + (1.96*se1cat2)

rq2method1 <- cbind('1', round(beta1cat1,2), round(cil1cat1,2), round(ciu1cat1,2),round(beta1cat2,2),
   round(cil1cat2,2), round(ciu1cat2,2))

#RQ 2, method 2
rq2mod2 <- lmer (Recoil~ as.factor(Plaque) + (1|Patient))

beta2cat1 <- coef(summary(rq2mod2))[2,1]
beta2cat2 <- coef(summary(rq2mod2))[3,1]

se2cat1 <- coef(summary(rq2mod2))[2,2]
se2cat2 <- coef(summary(rq2mod2))[3,2]

cil2cat1 <- beta2cat1 - (1.96*se2cat1)
ciu2cat1 <- beta2cat1 + (1.96*se2cat1)

cil2cat2 <- beta2cat2 - (1.96*se2cat2)
ciu2cat2 <- beta2cat2 + (1.96*se2cat2)

rq2method2 <- cbind('2', round(beta2cat1,2), round(cil2cat1,2), round(ciu2cat1,2),round(beta2cat2,2),
   round(cil2cat2,2), round(ciu2cat2,2))

summaryRQ2 <-rbind(rq2method1, rq2method2)
colnames(summaryRQ2) <- c('method','beta1', 'lower 95% CI', 'upper 95% CI','beta2','lower 95% CI',
   'upper 95% CI')
summaryRQ2

#save data
save.image("V:\\UserData\\MyPaper\\Ranalysis.RData")
```

Part VII

Discussion

Chapter 20

Summary and discussion

In each year between 1900 and 2006 except for 1918, cardiovascular disease accounted for more deaths in the United States than any other major cause of death.[1] In the Netherlands, cardiovascular disease was the main cause of death until 2007: in 2007 mortality due to cardiovascular disease, and coronary artery disease in particular, had decreased considerably such that the total number of deaths due to cancer was higher (Statistics Netherlands, www.cbs.nl). This is the result of the combined effects of improvements in primary prevention, initial recognition of acute events, well organized care and effective treatment.

In the present thesis, we investigate relevant treatment evolutions in patients with heart disease, clinical outcomes of these patients, changes in outcome over time, and specific high risk groups that could benefit from tailored clinical care.

Changes in clinical profile, treatment, and mortality

The Thoraxcenter is one of the few centers worldwide that is able to compare clinical profile, treatment, and outcome of patients hospitalized for myocardial infarction over a calendar period of three decades. During this period, substantial improvements in acute and long term survival in these patients could be documented, most likely related to improved treatment (Chapter 3).

Cardiovascular disease is the single largest cause of death in patients with renal impairment, and these cardiovascular deaths often occur before end-stage renal failure has been reached.[2] We show that, during the past 25 years, there was a similar decline in mortality after myocardial infarction for all stages of kidney function, including stage 4-5 chronic kidney disease (CKD). Still, the prognosis remains poor for patients with stage 4-5 CKD: adjusted mortality was 8.6-fold higher at 30 days, compared with patients with normal renal function (Chapter 4).

Anemia usually develops during the course of chronic kidney disease and may be associated with adverse outcomes.[3] In acute coronary syndrome patients, little was known about the effect of anemia on outcome and about the interaction between anemia and renal impairment. We show that that the extent of anemia at hospital

admission for acute coronary syndrome is associated with increased both in-hospital and long-term mortality, and we discuss anemia as a potential treatment target in these patients (Chapter 5).

Ageing and glucose metabolisms: emerging risk factors

Approximately 80% of people who die of coronary artery disease are 65 years of age or older.[1] In chapter 6 we showed that, in absolute terms, older patients benefited most from the improved medical care for myocardial infarction during the past decades. Favorable changes with more frequent use of evidence-based medical care, also in the elderly, are documented in this chapter.

The western world has experienced substantial increases in the prevalence of diabetes mellitus over the past 20 years. In 2011 approximately 60 million adult Europeans were thought to have diabetes mellitus, half of them with a clinical diagnosis, the other half undetected. More than 50% of the mortality in people with diabetes mellitus is related to cardiovascular disease. Cardiovascular risk probably develops early, before onset of diabetes mellitus.[4]

Against this background we show that there is also an increasing prevalence of diabetes in patients with a myocardial infarction. In the most recent decade, diabetes was not associated with underuse of evidence-based therapies. The absolute long-term mortality rate remained about 1.5-fold higher in patients with diabetes compared with those without diabetes. Additionally, we show that admission glucose levels are strongly related with increased mortality (up to 20 years). Compared with diabetes, hyperglycemia is a better discriminator for short-term mortality. This is important because the prevalence of elevated admission glucose levels has also increased substantially over the last years. The association between hyperglycemia and short-term mortality was significantly stronger in the present decade when than in previous decades. Therefore, although we showed that mortality after acute myocardial infarction decreased from 1985 to 2008, the observed decrease was less pronounced in patients with hyperglycemia. Finally, we demonstrate that the association between admission glucose levels and short-term mortality was not dependent on diabetic

status; a high admission glucose level was a predictor of mortality in patients with diabetes and in those without previously diagnosed diabetes (Chapters 7, 8).

Gender differences

The total number of women who die of cardiovascular disease is higher than the number of men.[1] In Chapter 9 we demonstrate that women hospitalized for an acute myocardial infarction were more likely to present with a higher risk profile but were equally likely to receive pharmacological and invasive reperfusion therapy compared with men. The higher risk profile of women was mainly determined by an average age difference of 5 years between women and men. Women and men had the same adjusted mortality rates at 30 days, whereas during 20 years of follow-up, the mortality hazard was lower in women. Importantly, temporal improvements in 30-day mortality and long-term mortality hazard from 1985 to 2008 were substantial and at least as high in women as in men.

In Chapter 10 we provide an overview of long-term prognosis according to age and sex, based on contemporary mortality rates. Our results demonstrate that the overall median life-expectancy after myocardial infarction varies between 6 and more than 20 years, mainly depending on age at presentation. In this chapter, we compare survival in the general population with survival after myocardial infarction.

Traditional risk factors

Hypertension, dyslipidaemia, smoking and diabetes mellitus are traditional risk factors for the development of coronary heart disease in patients without established cardiovascular disease.[5, 6] Contrary to this, two recent studies of large populations of myocardial infarction patients admitted in the United States have shown the presence of these coronary heart disease risk factors to be associated with a significantly lower in-hospital mortality rate.[7, 8] We confirm this paradox: myocardial infarction patients with at least one compared with no modifiable coronary heart disease risk factor have a favorable unadjusted and adjusted short-term survival (Chapter 11). We are the first to show that with longer duration of follow-up this association was sustained for myocardial infarction patients admitted between 1990 and 2008 (Chapter 11). The interpretation of these findings is that the absence of coronary heart disease risk factors should not necessarily be viewed as a guarantee of favorable prognosis. It could

be that the management associated with the presence of coronary heart disease risk factors is causally related to better outcome.

Percutaneous coronary interventions

It has been estimated that percutaneous coronary interventions reduce mortality by more than 30% in patients who present with an acute myocardial infarction.[9, 10] In addition revascularization for acute coronary syndrome relieves symptoms and shortens hospital stay.[11] We assessed 7 year outcome after percutaneous coronary intervention in saphenous vein graft lesions, and compared the safety and efficacy of drug-eluting stents versus bare-metal stents. We show that the unrestricted use of drug-eluting stents in saphenous vein graphs remains safe and effective as compared to bare metal, as illustrated by similar mortality rates and clinically relevant lower rates of target vessel revascularization in patients treated with drug eluting stents (Chapter 12). There is no previous study with a comparable duration of follow-up. At last follow-up, nearly 50% of patients were dead, and almost 70% of deaths were due to cardiac causes.

We show that there was no difference in both short term (30-day) mortality and long term mortality up to 10 years among ST-segment elevation myocardial infarction (STEMI) patients who present during the weekend compared to weekdays in the three decades between 1985 and 2008 (Chapter13). This suggests that a system with immediate primary percutaneous coronary intervention for STEMI patients is as effective in weekend- compared to weekdays.

In two related studies we demonstrate that the syntax score, originally designed for quantifying stable coronary artery disease, can be usefully utilized in a STEMI population with disease in the native coronary arteries. We are the first to report the prognostic value of the syntax score in STEMI patients (Chapter 14). The syntax score, derived from angiography during primary percutaneous coronary intervention, predicts long-term mortality and major adverse cardiac event in patients with STEMI independently of the TIMI risk score (Chapter 14). In addition, the syntax score is an independent predictor of myocardial no-reflow in these patients. An syntax score of over 21 doubles the risk for developing no-reflow. Myocardial no-reflow carries a poor prognosis and an increased mortality rate (Chapter 15).

In a literature review on the benefits of PCI in patients with stable angina, we concluded that medical treatment should be the initial management of the patient with stable chest pain (Chapter 16). In addition, based on our literature search, percutaneous opening of a chronic total coronary occlusion is not recommended. We reviewed the most recent guidelines on myocardial revascularization.[12] Specifically, we recommend that the composition of such a guideline committee must be more representative of the medical profession at large (Chapter 16).

In another review article we argue that percutaneous coronary intervention seems the method of choice for single vessel disease, whereas bypass surgery (CABG) should be more suited for complex, multiple vessel or left main stem disease (Chapter 17). Also, we advocate the creation of a so-called 'Heart Team'. A Heart Team allows for a multidisciplinary decision-making process for a patient who qualifies for either one of these treatment options. In order of procedure effectiveness, myocardial revascularization is most effective in STEMI, non-STEMI, unstable angina, and (chronic) stable angina pectoris. In patients with mild-to-moderate angina, an initially cautious approach to coronary revascularization is reasonable: watchful waiting seems appropriate. In case percutaneous coronary intervention of coronary lesions of moderate severity is considered, a functional assessment of the stenosis, the determination of coronary flow reserve, is recommended (Chapter 17).

Methodology

The present thesis includes two methodological chapters. In chapter 18 we explain the need for an appropriate control group for an observational study design. In chapter 19 we reviewed the current analytical approach to clustered data in the field of OCT-imaging during percutaneous coronary intervention We conclude that these analyses are frequently performed suboptimal and this may lead to wrong inferences We recommend to always use multilevel models when analyzing multiple observations per patient.

References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation 2012;125(1):e2-e220.

2. Johnston N, Dargie H, Jardine A. Diagnosis and treatment of coronary artery disease in patients with chronic kidney disease: Ischaemic heart disease. Heart 2008;94(8):1080-8.

3. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 Suppl 1):S1-266.

4. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362(9):800-11.

5. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, De Backer G, Ebrahim S, Gjelsvik B, Herrmann-Lingen C, Hoes A, Humphries S, Knapton M, Perk J, Priori SG, Pyorala K, Reiner Z, Ruilope L, Sans-Menendez S, Op Reimer WS, Weissberg P, Wood D, Yarnell J, Zamorano JL, Walma E, Fitzgerald T, Cooney MT, Dudina A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Funck-Brentano C, Filippatos G, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Altiner A, Bonora E, Durrington PN, Fagard R, Giampaoli S, Hemingway H, Hakansson J, Kjeldsen SE, Larsen m L, Mancia G, Manolis AJ, Orth-Gomer K, Pedersen T, Rayner M, Ryden L, Sammut M, Schneiderman N, Stalenhoef AF, Tokgozoglu L, Wiklund O, Zampelas A. European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur J Cardiovasc Prev Rehabil 2007;14 Suppl 2:S1-113.

6. 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(18):1837-47.

7. Canto JG, Kiefe CI, Rogers WJ, Peterson ED, Frederick PD, French WJ, Gibson CM, Pollack CV, Jr., Ornato JP, Zalenski RJ, Penney J, Tiefenbrunn AJ, Greenland P. Number of coronary heart disease risk factors and mortality in patients with first myocardial infarction. JAMA 2011;306(19):2120-7.

8. Roe MT, Halabi AR, Mehta RH, Chen AY, Newby LK, Harrington RA, Smith SC, Jr., Ohman EM, Gibler WB, Peterson ED. Documented traditional cardiovascular risk factors and mortality in non-ST-segment elevation myocardial infarction. Am Heart J 2007;153(4):507-14.

9. Cucherat M, Bonnefoy E, Tremeau G. Primary angioplasty versus intravenous thrombolysis for acute myocardial infarction. Cochrane Database Syst Rev 2000(2):CD001560.

10. Fox KA, Poole-Wilson P, Clayton TC, Henderson RA, Shaw TR, Wheatley DJ, Knight R, Pocock SJ. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. Lancet 2005;366(9489):914-20.

11. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011;32(23):2999-3054.

12. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. Eur Heart J 2010;31(20):2501-55.

Chapter 21

Conclusion

In this thesis we aimed to expand the knowledge on treatment, risk factors and outcome in patients with coronary artery disease. Specifically, we documented changes over the past decades: the temporal trends shown in this thesis, covering 24 years of observation, are unique.

The main conclusions of this thesis are as follows:

In patients hospitalized for myocardial infarction acute (30 day) mortality has decreased over the past decades, and the decrease in short-term mortality is sustained during long-term follow-up. These improvements in outcome relate to improved acute- as well as long-term treatment.

Renal impairment, anemia and older age are important predictors of mortality after myocardial infarction. We demonstrate a substantial mortality decrease over the past decades in older patients and those with renal impairment; this mortality decrease is comparable with the decrease in younger patients and those with normal renal function, respectively.

Diabetes and hyperglycemia are emerging risk factors. Optimal medical care for these patients and awareness of their high-risk profile remains warranted.

Women were equally likely to receive pharmacological and invasive reperfusion therapy compared with men. Women and men had the same adjusted mortality rates at 30 days, whereas during 20 years of follow-up, the mortality hazard was lower in women.

Relative survival, which is the survival among patients divided by the expected survival of a the general population, may well be an appropriate and useful measure for assessment of survival after myocardial infarction.

Chapter 22

About the author

Sjoerd Toussaint Nauta was born on the 25th of November 1986, in Wageningen, the Netherlands. He graduated from secondary school in 2005 (Marnix College Ede). In 2006 he started Medicine at the Erasmus Medical Center, Rotterdam. He graduated cum laude as Master of Science in Clinical Research in 2011 and as Medical Doctor in 2012. While studying he was involved in a number of research projects at the department of Cardiology and the related Clinical Epidemiology unit of the Erasmus University Medical Center. The present thesis is the result of the research projects performed between 2008 and 2012.

Chapter 23

PHD portfolio

	Year	ECTS
Acedemic education		
Medicine, Erasmus University, Rotterdam	2012	N.A.
Master of Science in Clinical Research, NIHES, Rotterdam	2011	N.A.
Summer session in public health (post-graduate courses), Harvard University, Boston	2010	N.A.
In-depth courses (46,2)		
Working with SPSS for Windows	2010	0,3
Scientific Writing in Eng. for Publ.	2010	2,0
Principles of Research in Med. and Epid.	2008	0,7
Introduction to Data-analysis	2009	1,0
Regression Analysis	2009	1,9
Methods of Clinical Research	2008	0,7
Clinical Trials	2008	0,7
Topics in Meta-analysis	2009	0,7
Pharmaco-epidemiology	2008	0,7
Health Economics	2010	0,7
Survival Analysis	2009	1,9
Case-control Studies	2008	0,7
Causal Inference	2010	0,7
Introduct.to Decision-making in Medicine	2008	0,7
Study Design	2008	8,5
Bayesian Statistics	2010	1,1
Missing Values in Clinical Research	2010	0,7
Courses for the Quantitative Researcher	2009	1,4
Introduction to Clinical Research	2009	0,9
Adv.Topics in Decision-making in Med.	2009	1,9
Pharmaco-epidemiology and Drug Safety	2011	1,9
Intervention Res.and Clinical Trials	2009	0,9
Diagnostic Research	2009	0,9
Advanced Topics in Clinical Trials	2011	1,9
Advanced Analysis of Prognosis Studies	2011	0,9
Prognosis Research	2009	0,9
Princ.of Epidemiologic Data-analysis	2011	0,9
Management of Health Care Organizations	2010	2,0
Society and Heatlh	2010	2,0
Seminars and lectures	2011	6

	Year	ECTS
Presentations at conferences (4,2)		
American Heart Association scientific sessions (Chicago)	2010	0,7
European Society of Cardiology congress (Paris)	2011	0,7
European Society of Cardiology congress (Munich, 3x)	2012	2,1
Acute Cardiac Care congress (Istanbul)	2012	0,7
Netherlands Society of Cardiology congress (Noordwijkerhout, 2x)	2011	1,4
International congresses, attended (8,4)		
American Heart Association scientific sessions (Chigaco)	2010	1,4
European Society of Cardiology congress (Paris)	2011	1,4
European Society of Cardiology congress (Munich)	2012	1,4
Cardiology and Vascular Medicine congress (Rotterdam)	2010	1,4
Cardiology and Vascular Medicine congress (Rotterdam)	2011	1,4
Acute Cardiac Care congress (Istanbul)	2012	1,4
Lecturing (13,4)		
Lecturer for second year students (topic: acute coronary syndrome)	2012	1,4
Supervising Master's theses (4x)	2012	12,0

Chapter 24

List of publications

Medical Journals

1. **Nauta ST**, Deckers JW, Akkerhuis KM, van Domburg RT. Short- and long-term mortality after myocardial infarction in patients with and without diabetes: changes from 1985 to 2008. Diabetes Care. 2012 Oct;35(10):2043-7.

2. **Nauta ST**, Deckers JW, Akkerhuis KM, van Domburg RT. Age-dependent care and long-term (20 year) mortality of 14,434 myocardial infarction patients: changes from 1985 to 2008. Int J Cardiol. 2013 Aug 10;167(3):693-7.

3. **Nauta ST**, Deckers JW, Akkerhuis M, Lenzen M, Simoons ML, van Domburg RT. Changes in clinical profile, treatment, and mortality in patients hospitalised for acute myocardial infarction between 1985 and 2008. PLoS One. 2011;6(11):e26917.

4. **Nauta ST**, Deckers JW, van der Boon RM, Akkerhuis KM, van Domburg RT. Risk factors for coronary heart disease and survival after myocardial infarction. Eur J Prev Cardiol. 2012 Sep 13.

5. **Nauta ST**, Deckers JW, van Domburg RT, Akkerhuis KM. Sex-related trends in mortality in hospitalized men and women after myocardial infarction between 1985 and 2008: equal benefit for women and men. Circulation. 2012 Oct 30;126(18):2184-9.

6. **Nauta ST**, Gaspersz M, Deckers JW. The new European Society of Cardiology guidelines on myocardial revascularisation: an appraisal. Heart. 2012 Jan;98(1):11-4.

7. **Nauta ST**, Van Domburg R. Choosing an appropriate control group for an observational study design. Pharmacoepidemiol Drug Saf. 2012 Mar;21(3):341.

8. **Nauta ST**, van Domburg RT, Nuis RJ, Akkerhuis M, Deckers JW. Decline in 20-year mortality after myocardial infarction in patients with chronic kidney disease: evolution from the prethrombolysis to the percutaneous coronary intervention era. Kidney Int. 2013 Aug;84(2):353-8.

9. **Nauta ST**, Van Mieghem NM, Magro M, Deckers JW, Simsek C, Van Geuns RJ, Van Der Giessen WJ, De Jaegere P, Regar E, Van Domburg RT, Serruys PW. Seven-year safety and efficacy of the unrestricted use of drug-eluting stents in saphenous vein bypass grafts. Catheter Cardiovasc Interv. 2012 May 1;79(6):912-8.

10. **Nauta ST**, Dickman PW, Van Domburg RT, Van Steenbergen LN, Jansen-Heijnen M, Deckers JW, Kardys, I. Long-term (20-year) survival rates of myocardial infarction patients achieved in the early 21st century: a period analysis including relative and conditional survival. Submitted for Publication. 2012.

11. **Nauta ST**, van Domburg RT, Akkerhuis M, Deckers JW. Observations in Rotterdam during a quarter of a century: major improvements in survival after myocardial infarction.[Dutch]. Cordiaal. 2012;(5):148-151.

12. Deckers JW, Khatibi S, Feng Y, **Nauta ST**. ESC-EACTS guidelines: myocardial revascularisation. Hosp Cardiol Eur 2012;1:9-11.

13. Deckers JW, van Domburg RT, Akkerhuis M, **Nauta ST**. Relation of admission glucose levels, short- and long-term (20-year) mortality after acute myocardial infarction. Am J Cardiol. 2013 Nov 1;112(9):1306-10.

14. Magro M, **Nauta S**, Simsek C, Onuma Y, Garg S, van der Heide E, van der Giessen WJ, Boersma E, van Domburg RT, van Geuns RJ, Serruys PW. Value of the SYNTAX score in patients treated by primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: The MI SYNTAXscore study. Am Heart J. 2011 Apr;161(4):771-81.

15. Magro M, **Nauta ST**, Simsek C, Boersma E, van der Heide E, Regar E, van Domburg RT, Zijlstra F, Serruys PW, van Geuns RJ. Usefulness of the SYNTAX score to predict "no reflow" in patients treated with primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Am J Cardiol. 2012 Mar 1;109(5):601-6.

16. Lingsma H, **Nauta S**, van Leeuwen N, Borsboom G, Bruining N, Steyerberg E. Tools & Techniques: Analysis of clustered data in interventional cardiology: current practice and methodological advice. EuroIntervention. 2013 May 20;9(1):162-4.

17. Snelder SM, **Nauta ST**, Akkerhuis KM, Deckers JW, van Domburg RT. Weekend versus weekday mortality in ST-segment elevation acute myocardial infarction patients between 1985 and 2008. Int J Cardiol. 2013 Sep 30;168(2):1576-7.

18. Younge JO, **Nauta ST**, Akkerhuis KM, Deckers JW, van Domburg RT. Effect of anemia on short- and long-term outcome in patients hospitalized for acute coronary syndromes. Am J Cardiol. 2012 Feb 15;109(4):506-10.

19. Simsek C, Magro M, Boersma E, Onuma Y, **Nauta S**, Daemen J, Gaspersz M, van Geuns RJ, van der Giessen W, van Domburg R, Serruys P. Comparison of six-year clinical outcome of sirolimus- and paclitaxel-eluting stents to bare-metal stents in patients with ST-segment elevation myocardial infarction: an analysis of the RESEARCH (rapamycin-eluting stent evaluated at Rotterdam cardiology hospital) and T-SEARCH (taxus stent evaluated at Rotterdam cardiology hospital) registries. J Invasive Cardiol. 2011 Aug;23(8):336-41.

20. Simsek C, Magro M, Boersma E, Onuma Y, **Nauta S**, Valstar G, van Geuns RJ, van der Giessen W, van Domburg R, Serruys P. Impact of renal insufficiency on safety and efficacy of drug-eluting stents compared to bare-metal stents at 6 years. Catheter Cardiovasc Interv. 2012 Jul 1;80(1):18-26.

21. Simsek C, Magro M, Boersma E, Onuma Y, **Nauta ST**, Gaspersz MP, van der Giessen WJ, van Domburg RT, Serruys PW. The unrestricted use of sirolimus- and paclitaxel-eluting stents results in better clinical outcomes during 6-year follow-up than bare-metal stents: an analysis of the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated At Rotterdam Cardiology Hospital) registries. JACC Cardiovasc Interv. 2010 Oct;3(10):1051-8.

22. Magro M, Wykrzykowska J, Serruys PW, Simsek C, **Nauta S**, Lesiak M, Stanislawska K, Onuma Y, Regar E, van Domburg RT, Grajek S, Geuns RJ. Six-month clinical follow-up of the Tryton side branch stent for the treatment of bifurcation lesions: a two center registry analysis. Catheter Cardiovasc Interv. 2011 May 1;77(6):798-806.

23. van der Boon RM, Van Mieghem NM, Theuns DA, Nuis RJ, **Nauta ST**, Serruys PW, Jordaens L, van Domburg RT, de Jaegere PP. Pacemaker dependency after transcatheter aortic valve implantation with the self-expanding Medtronic CoreValve System. Int J Cardiol. 2013 Sep 30;168(2):1269-73.

Book chapters / printed matter

1. **Nauta ST**, van Domburg RT, Deckers JW. Clinical presentation, treatment en 30-day mortality after admission for myocardial infarction: observations in Rotterdam from 1985 to 2009.[Dutch] Chapter 3 in: Koopman C, van Dis I, Visseren FLJ, Vaartjes I, Bots ML. Hart- en vaatziekten in Nederland 2012, cijfers over risicofactoren, ziekte en sterfte. Den Haag: Hartstichting, 2012.

2. Henny W, De Lijster L, Schalken M, van de Velde K, **Nauta S** 2009. First aid Syllabus year 1. Manatory study material for medical students.

3. Henny W, De Lijster L, Schalken M, van de Velde K, **Nauta S** 2010. First aid Syllabus year 1 to 3. Manatory study material for medical students.

isbn 9789462286054