Faculty of Health Sciences,
University of Copenhagen

Ph.D. thesis

Long-term prognostic factors after myocardial infarction: 17-year follow-up of the TRACE registry

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Department of Cardiology

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The Faculty of Health Science, Copenhagen University, Denmark has approved this PhD dissertation for public defense. The public lecture and defense will take place May 15th, 2012 at 14.00 in Hannover auditorium, the Panum Institute, Blegdamsvej 3, DK-2200 Copenhagen N, Denmark.

Preface

Despite several attempts, I had experienced little success with medical research and the publication of articles. Before starting a 1-year employment ("introduktionsstilling") at the department of Cardiology, Bispebjerg Hospital, I was advised to seek up Professor Christian Torp-Pedersen in order to pursue my interest in clinical research.

Christian was professor of cardiology at Bispebjerg Hospital and the leader of a research group with considerable success and interests in a wide spectrum of research areas, including epidemiology and clinical trials.

Although he did not know me, Christian gave me a warm welcome and outlined a project. As an introduction to a larger project, he suggested we started with a smaller "writing exercise" to evaluate my abilities and interest in the field of epidemiology.

As it turned out, this article took a long time to finish, which was not the plan at the beginning (as it seldom is). I had to learn Christian's method of working and the principles and methods of epidemiological research. I started to learn the use of SAS statistical software, which gives almost unlimited possibilities of analyzing data, but is difficult to employ, at least in the beginning. The greatest challenge, however, was the need to work on a project parallel with my clinical education, which did not leave much time for research. I soon realized that research is very different from clinical work.

At the conclusion of my employment at Bispebjerg Hospital, I was given a 5-year employment resulting in certification as a cardiologist ("hoveduddannelse"). The employment consisted of 2 years at the Department of Medicine, Glostrup Hospital and 3 years at the Department of Cardiology, Gentofte Hospital.

At Gentofte, I met Gunnar, who I also knew from Bispebjerg, where he was a very successful research fellow in Christian's group. Gunnar was finishing up his Ph.D. and, fortunately, needed the results of my first article as a reference. He helped me finish the manuscript, which was published in the European Journal of Heart Failure.

Christian then outlined the larger project: A long-term follow-up of prognostic factors in myocardial infarction patients with the use of the TRACE registry. I was very happy with the kind and skilful help Gunnar had given me, and luckily he accepted the role of academic advisor together with Christian and Lars, who had already led to my first real research success.

The course of my Ph.D. has been very positive and I would like to extend my gratitude to all my scientific advisors. As an inexperienced researcher, they have guided me through difficult epidemiological and statistical methods and my manuscripts have been repeatedly scrutinized in details until they were good enough to be submitted.

I was fortunate that Christian was able to guide me through the mysteries of SAS programming, and slowly I was able to work more independently.

I would like to thank Lars for always spotting out the weak points, for his excellent comments and academic insight.

Since the finishing of the first article, Gunnar has been closely involved in my project and has given me a lot of very usable criticism, always kind and constructive, and provided me with career guidance.

I would like to extend my thanks to Dr. Rikke Sørensen, M.D. for valuable help with SAS modelling and to all the institutions who have supported my research, including Gentofte Hospital, "Startpuljen", Snedkermester Sophus Jacobsen og hustru Astrid Jacobsens Fond and the Danish Heart Foundation. I would especially like to thank the Department of Cardiology, Gentofte Hospital for support and flexibility and for awarding me a 6-months half-time research employment, which helped bring the project a big step further.

I would like to extend my immense gratitude to cardiologist Frank Steensgaard-Hansen for many years of trying to pass on unrivalled skills in the field of echocardiography and for continuing support and guidance. Our professional corporation and the time we have spent together with our families is very deer to me. I am proud to call you my friend.

Finally, I want to thank Iben, my wife, for keeping up with me and given me the opportunity to work on my project. I want to thank her for always supporting me and driving me forward, when it was needed.

Unexpectedly, my father passed away January 8th, 2010. He would have loved to experience the finishing of my project and I feel sad that he is no longer here.

Thomas Kümler
September 2011

Table of Contents

List of Papers

This thesis was based on the following papers:

1.
Kumler T, Gislason GH, Kirk V, Bay M, Nielsen OW, Kober L, Torp-Pedersen C. Accuracy of a heart failure diagnosis in administrative registers. Eur J Heart Fail. 2008;10(7):658-660.

2.
Kumler T, Gislason GH, Kober L, Torp-Pedersen C. Persistence of the prognostic importance of left ventricular systolic function and heart failure after myocardial infarction: 17-year follow-up of the TRACE register. Eur J Heart Fail. 2010 Aug;12(8):805-11.

3.
Kumler T, Gislason GH, Kober L, Torp-Pedersen C. Diabetes is an independent predictor of survival 17 years after myocardial infarction: follow-up of the TRACE registry. Cardiovasc Diabetol. 2010 Jun 2;9:22.

4.
Kumler T, Gislason GH, Kober L, Gustafsson F, Schou M, Torp Pedersen C. Renal function at the time of a myocardial infarction maintains prognostic value for more than 10 years. BMC Cardiovascular Disorders. 2011, 11:37.

Summary

Long-term Prognostic Factors after Myocardial Infarction: 17-year follow-up of the TRACE Registry

Background and objectives

Cardiovascular diseases are the leading cause of morbidity and mortality in the industrialized world, with myocardial infarction (MI) and heart failure being among the most frequent conditions.

The randomised controlled trials of long-term medical therapy have evaluated treatments administered over a limited number of years, yet guidelines recommend treatment indefinitely.

Increasing prevalence of heart failure has been reported using administrative registers, which could be a result of changing recording habits. In addition the availability of administrative registers is increasing.

This thesis focused on analysis of the long-term persistence of prognostic factors after MI. The prognostic factors examined were left ventricular systolic function and heart failure, diabetes and renal function. Moreover, I analyzed the validity of a heart failure diagnosis in administrative registries to examine whether discharge coding of heart failure could be used for the study of the incidence and prevalence of heart failure.

Methods

For the study of the validity of a heart failure diagnosis, I used the Copenhagen Hospital Heart Failure Study (CHHF) registry. This trial included all consecutive patients above the age of 40 years admitted to one Copenhagen City hospital over a 12-month period. By comparing the diagnosis of heart failure made by the regular staff clinicians with the heart failure diagnosis according to the European Society of Cardiology criteria, I evaluated sensitivity, specificity, and predictive values.

I studied the long-term persistence of prognostic factors after MI using data from the The Trandolapril Cardiac Evaluation (TRACE) Registry, which consist of 6676 consecutive patients with MI. The study was conducted in 27 centres in Denmark from 1992 to 1994. Mortality was analysed with Kaplan-Meier survival curves and landmark analyses were used to illustrate the prognostic significance of risk factors in 2-year intervals. Relative risk estimates were derived from a Cox proportional-hazards regression model.

Results

A registered diagnosis of heart failure (n=126) carried a specificity of 99% and a sensitivity of 29% for all patients. The positive predictive value was 81% and the negative predictive value was 90%.

All the studied risk factors carried long-term prognostic significance. Left ventricular systolic function estimated as wall motion index (WMI) was a significant prognostic factor until 10 years of follow-up. The prognostic significance of HF persisted for 8 years.

Diabetes retained prognostic significance throughout the length of the follow-up period while renal function was a prognostic factor for 10-12 years depending on whether renal function was evaluated with se-creatinine or estimated GFR.

Conclusions

HF is severely underreported in the Danish National Hospital Register. Administrative registers can be used to identify large groups of patients with HF for epidemiological studies but is not suitable for use in studies of prevalence and incidence of HF in a population.

All the studied risk factors for all-cause mortality following MI showed long-term persistence. This underlines the importance of an evaluation of these risk factors in the risk stratification of patients with MI and indirectly supports the guideline recommended lifelong pharmacological therapy.

Dansk resumé

Langtids prognostiske faktorer efter myokardieinfarkt: 17-opfølgning af TRACE registret

Baggrund og formål

Kardiovaskulær sygdom er den hyppigste årsag til sygelighed og dødelighed i den industrialiserede verden. Myokardieinfarkt (MI) og hjertesvigt er blandt de hyppigste kardiovaskulære sygdomme.

Randomiserede kontrollerede kliniske undersøgelser af medicinsk behandling har fulgt patienterne et begrænset antal år men gældende retningslinjer anbefaler permanent medicinsk behandling.

Registerforskning har tydet på en øget prævalens af hjertesvigt, hvilket kunne skyldes en ændret indrapportering. Tilgængeligheden af administrative registre er stigende.

Denne afhandling analyserede langtids prognostiske faktorer efter MI i form af venstre ventrikel systolisk funktion, hjertesvigt, diabetes og nyrefunktion. Herudover analyseredes validiteten af hjertesvigtsdiagnosen i administrative registre for at fastlå om en udskrivningsdiagnose kunne anvendes til at vurdere incidensen og prævalensen af hjertesvigt.

Metode

I undersøgelsen af validiteten af hjertesvigtsdiagnosen anvendtes registret fra the Copenhagen Hospital Heart Failure Study (CHHF). Dette studie inkluderede konsekutivt alle patienter over 40 år, der blev indlagt på Amager Hospital over en 12 måneders periode. Ved at sammenligne udskrivningsdiagnosen indrapporteret af klinikerne med en diagnose baseret på de gældende kriterier fra European Society of Cardiology, beregnedes sensitivitet, specificitet, og prædiktive værdier.

Data fra The Trandolapril Cardiac Evaluation (TRACE) registret anvendtes til at undersøge den prognostiske værdi af kendte risikofaktorer efter MI med en lang opfølgningsperiode. TRACE registret består af 6676 konsekutive patienter med MI og blev gennemført på 27 kardiologiske afdelinger i Danmark fra 1992 til 1994. Mortaliteten analyseredes med Kaplan-Meier overlevelseskurver og landmark analyse blev brugt til at illustrere den prognostiske betydning af risikofaktorerne i 2-års intervaller. Relativ risiko blev estimeret v.h.a. cox-proportionalitetsmodeller.

Resultater

En diagnose af hjertesvigt indrapporteret til patientregistret (n=126) havde en specificitet på 99 % og en sensitivitet på 29 %. Den positive prædiktive værdi var 81 %, den negative prædiktive værdi var 90 %.

Alle de undersøgte risikofaktorer havde prognostisk effekt på lang sigt. Venstre ventrikels systoliske funktion funktion målt som wall motion indeks (WMI) var en signifkant prognostisk faktor i 10 år efter MI. Den prognostiske betydning af hjertesvigt persisterede i 8 år.

Diabetes havde prognostisk betydning gennem hele opfølgningsperioden mens nyrefunktion havde effekt i 10-12 år, afhængig af om nyrefunktionen evalueredes ved se-kreatinin eller beregnet GFR.

Konklusion

Hjertesvigt er massivt underrapporteret i det nationale patient register. Administrative registre kan bruges til identifikation af store grupper patienter med hjertesvigt til epidemiologiske studier, men kan ikke anvendes til at studere prævalens og incidens i en population.

Alle de undersøgte risikofaktorer for mortalitet efter MI viste prognostisk effekt på lang sigt. Dette understreger vigtigheden af at evaluere disse faktorer i risikostratificeringen af patienter med MI og støtter indirekte den permanente medicinske behandling, der anbefales i gældende retningslinjer.

Introduction

Cardiovascular diseases are the leading cause of morbidity and mortality in the industrialized world. In the year 2000, heart disease was the cause of almost 100000 hospitalizations in Denmark, which corresponds to approximately 9 % of all hospitalizations[1]. One of the most frequent, serious and feared cardiovascular conditions is myocardial infarction (MI). In 2003, 16300 hospitalizations with MI in 11000 patients were registered[2], corresponding to 320 MI hospitalizations per 100000 inhabitants in Denmark. The natural history of MI is difficult to characterize precisely because of the frequent occurrence of silent MI and the high frequency of death outside hospital, which still represents a major problem. Basic and clinical research has expanded our understanding of the patophysiology and nature of cardiovascular diseases. This has provided the framework for an improvement in treatment options leading to a better prognosis. Examples of treatment with proven benefit in MI patients these are aspirin[3, 4], beta-blockers[5-9]. statins[10, 11], fibrinolysis[12, 13] and coronary interventions[14]. As a result, there has been much improvement in the mortality of coronary heart disease[15].

Predictors of early mortality in MI patients are older age, higher Killip class, elevated heart rate, lower systolic blood pressure, anterior location of the infarct, previous infarction, height, time to treatment, diabetes, weight, and smoking status as identified in clinical trials and registries[16-18].

Among the most important risk factors for an adverse long-term outcome after MI are left ventricular systolic function and heart failure.

The prevalence of heart failure in the general population is 1-2%[19] as is the prevalence of asymptomatic left ventricular dysfunction, with coronary heart disease being the cause in 70% of the patients[20]. This means that at least 15 million people in the European Countries have HF, which is the cause of 5% of acute hospital admissions[21]. In some countries the age-adjusted mortality from HF is decreasing[22-25] but the prognosis associated with heart failure remains serious. Forty percent of patients admitted to hospital are dead within a year and 50 % of patients overall are dead at 4 years[26-29].

Left ventricular systolic dysfunction and heart failure following MI has proven prognostic value for up to 5 years[30-33]. The most recent European guidelines recommend evidence based treatment with ACE-inhibitors/angiotensin receptor blockers, β -blockers and in some cases aldosterone antagonists, cardiac resynchronisation therapy and implantable cardioverter defibrillator[34]. Recently, a large randomised controlled trial has indicated that treatment with a mineralocorticoid inhibitor (eplerenone) improves outcome in patients with systolic heart failure and mild symptoms[35], a treatment only previously recommended in the case of severe symptoms[36] or patients with systolic dysfunction after MI[37].

However, the randomised controlled trials of long-term medical therapy have evaluated treatments administered over a limited number of years, but guidelines recommend treatment indefinitely[38-40]. Further studies are unlikely to be performed, so a study of the time persistence of heart failure and left ventricular systolic function as prognostic factors would provide important information in the very-long term, possibly providing indirect evidence for continued treatment.

Increasing prevalence of heart failure has been reported[24, 28, 41, 42]. This is probably a result of a change in risk factors for heart failure, ageing of the population and increased survival of patients with ischemic heart disease. However, the changing prevalence could also be a result of changing recording habits. The present HF guidelines from the European Society of Cardiology state that substantial underreporting is suspected, but this is not documented. The availability of administrative registers is increasing. As a result, a study of the validity of a heart failure diagnosis in administrative registers are important to examine whether discharge coding of heart failure can be used for the study of incidence and prevalence of heart failure.

Heart failure is a common complication of diabetes, and diabetes is also a frequent and important risk factor in patients with ischemic heart disease. A high prevalence of diabetes and abnormal glucose tolerance has been shown in MI patients with no known diabetes[43], and abnormal glucose tolerance is almost twice as frequent in MI patients as hypertension and dyslipidemia[44]. Higher glucose levels on admission have been shown to be associated with a poorer outcome[45, 46]. Up to 20% of patients with MI have diabetes, a fraction which will probably increase in the years to come[47-49]. Patients with a need for glucose-lowering therapy have a risk of cardiovascular events equal to patients without diabetes with a previous MI[50]. Patients with diabetes and ST-elevation MI have twice the mortality when compared to patients without diabetes[51, 52]. Patients with diabetes should receive prophylactic treatment for cardiovascular disease, since treatment with statins, β-blockers and ACE-inhibitors are as effective and safe in patients with diabetes as in patients without diabetes[53-56]. As a result of underdiagnosis, many remain untreated, which is associated with poorer outcome[53, 57]. The long-term risk associated with diabetes have been described in three cohorts, with a follow-up time for 6, 8 and 10 years[58, 59]. However, there is a lack of information regarding the time dependent variation of the prognostic effect. As recent guidelines recommend that MI patients are screened for diabetes, with an oral glucose tolerance test when indicated, it is important to know that diabetes as a risk factor does not weaken over time, highlighting the importance of an aggressive diagnostic approach.

Chronic kidney disease is associated with an increased risk of recurrent hospitalization, subsequent CABG, and mortality independent of the risk associated with diabetes[60]. Declining renal function is associated with a rise in the prevalence of cardiovascular disease[61-64]. Cardiovascular outcomes have been examined in patients with end-stage renal disease[65-68]. For example, 2-year mortality rate among patients with ST-elevation myocardial infarction and creatinine clearance<30 mL/min is much higher than in patients without renal disease. This is probably explained by a higher proportion of cardiovascular risk factors in these patients, a less aggressive treatment strategy and a greater intolerance to the medical treatment. However, treatment recommendations do not

differ significantly between patients with and without renal failure. In patients with heart failure or asymptomatic left ventricular systolic dysfunction, impaired renal function is independently associated with higher risk for poor outcome[69,70]. However, existing data are limited by lack of data in MI patients with minor degrees of renal dysfunction, by short follow-up and by assessing renal function by creatinine measurement which is considered a suboptimal indicator of renal function. Moreover, no information on the influence of estimates of renal function on long-term prognosis after myocardial infarction is available.

Since long-term prognosis after myocardial infarction has generally improved over the last decades[71] it is of interest to study predictors of long-term prognosis.

In addition, the influence of new therapeutic options, such as large-scale reperfusion or device therapy, on the prognostic importance of known risk factors is unknown.

The importance of risk factors has only been proven for a limited period of time, before the introduction of new therapeutic options.

This thesis focused on analysis of the long-term persistence of prognostic factors after MI. The prognostic factors examined were left ventricular systolic function and heart failure, diabetes and renal function. Moreover, I analyzed the validity of a heart failure diagnosis in administrative registries to establish whether heart failure could be used as a valid endpoint in addition to all-cause mortality when using administrative registers.

Methods

To study the questions in this thesis, I chose an epidemiological approach using two different registers. This method is limited by its non-randomised nature and by the fact that we do not have information regarding the medical treatment of patients during the follow-up period. However, I have been able to study a large number of consecutive patients providing statistical power and making the results more representative of daily clinical practice. Moreover, our follow-up period is very long, which is a necessity in the study of temporal trends in the prognostic significance of risk factors following MI.

Analysis of registries does not include information regarding factors which could influence results, e.g. interaction with other medication and exacerbation of the disease.

Population

Paper I: I analysed patients from the Copenhagen Hospital Heart Failure Study (CHHF)[72]. This study aimed to include all consecutive patients above the age of 40 years admitted to one hospital (n=3644) over a 12 month period starting from April 1st 1998. Four hundred and thirty patients (12%) were excluded. The remaining 3214 patients (88%) gave written informed consent. Blood samples were available for 80 % of the study patients (N=2230). The study was conducted independently of the treatment of patients and clinicians were blinded to the data obtained in the study.

Patients were included consecutively from all departments in the hospital.

One of the study physicians (either Vibeke Kirk (V.K.) or Morten Bay (M.B.)) obtained a medical history and performed a clinical examination within 24 h of admission. The criteria for symptoms of heart failure were fatigue or shortness of breath at rest or during exercise. Clinical signs of heart failure were fluid accumulation or dyspnoea or need for diuretic therapy most likely explained by a cardiac condition. The other physician (V.K. or M.B.) then performed the echocardiographic evaluation. Both physicians were blinded to the results of the other's evaluation and the interobserver variation for echocardiographic evaluation of left ventricular ejection fraction was 4%. Abnormal NT-proBNP by ELISA-assay (Roche, Basal)[73] was defined as ≥100 pmol/l, corresponding to the optimal value of diagnosing LVEF<35% in a previous study using the same assay[74].

Papers II-IV: I analysed data from the The Trandolapril Cardiac Evaluation (TRACE) Registry[75, 76], which consist of 6676 consecutive myocardial infarction (MI) patients screened for entry in the TRACE study, a double-blind, randomized, parallel group, placebo-controlled study of trandolapril versus placebo in patients with left ventricular dysfunction after MI. The study was conducted in 27 centres in Denmark, and participating centres were required to screen consecutive patients admitted with MI 2-6 days after the infarction and provide data on each patient for the register. The diagnostic criteria of myocardial infarction were chest pain and/or electrocardiographic changes suggestive of ischemia or infarction, accompanied with elevated cardiac enzymes. Left ventricular systolic function was evaluated in a core lab as wall motion index using a 9-segment model and a reverse scoring system. Wall motion index multiplied by 30 approximates left ventricular ejection fraction. The technique has previously been described in detail and validated[77]. Of the screened patients, 1749 (26.2%) were randomised to trandolapril or placebo in the TRACE study. Patients with missing information or lost to follow-up (emigrating) were censored on the last day they were known to be alive.

Databases

The Danish National Patient Registry keeps records of all patients admitted to Danish hospitals since 1978. At discharge, one primary diagnosis and, if applicable, one or more secondary diagnosis are registered according to the International Classification of Diseases (ICD), until 1994 the 8th revision (ICD-8) and from 1994 the 10th revision (ICD-10).

All Danish citizens are given a unique and permanent person register number. The Central Population Registry contains information about vital status (dead or alive) and date of death. All deaths are registered within 2 weeks of occurrence and confirmed by a death certificate.

Outcomes

The following outcomes were used:

Paper I: A diagnosis of heart failure.
Registered heart failure (Reg-HF) corresponded to the primary or secondary diagnosis entered in the Danish National Patient Registry (ICD10, DI50.0–DI50.9) by the regular staff clinicians, who were blinded to the results obtained by the study staff. Following discharge, the study clinicians evaluated the patients together. Heart failure was defined as a patient with symptoms of heart failure and at least one echocardiographic abnormality. This definition is in accordance with the current ESC definition of heart failure[78].

Paper II-IV: All-cause mortality
Trends in mortality during the study period were provided by a computerized analysis from the Danish Central Personal Register by 16.06.2008.

Statistical Analysis

For descriptive statistics, the results were given as mean values with standard deviation or 95 % confidence intervals. P-values less than 0.05 were considered significant.

In paper I, discrete variables were analyzed by chi-square test and general linear models for continuous variables.

In article II-IV the base-line characteristics of the study population were compared with a t-test for continuous variables and a chi-square test for discrete variables. Mortality was analyzed with Kaplan-Meier curves. I used Landmark analyses to illustrate the prognostic significance of risk factors in 2-year intervals. Relative risk of death and the associated 95 percent confidence intervals were calculated as hazard ratios derived from a Cox proportional-

hazards regression model. We used stepwise models with increasing number of variables. The models fulfilled the Cox regression model assumptions (linearity of continuous variables, proportional hazards assumption and lack of interaction).

All statistical calculations were performed using the SAS statistical software package, SAS, version 9.1 (SAS Institute Inc., Cary, NC, USA).

Ethics

The Copenhagen Hospital Heart Failure Study (CHHF) was approved by the regional ethics committee of the city of Copenhagen. Participating patients provided informed consent.

The Trandolapril Cardiac Evaluation (TRACE) study including the register was approved by all regional ethical committees in Denmark and complies with the Declaration of Helsinki. The study was registered with the National Board of Health and the Danish Data Protection Agency. Participating patients provided informed consent.

Data from both studies were made available to us such that specific individuals could not be identified. No ethical approval is required for retrospective registry studies in Denmark.

Results – overview of papers

This section provides brief overview of the four papers enclosed in this thesis. The structure is the same for each paper; a short introduction describing the aim of each study, followed by methods and results sections and finally the main conclusion of the study. For further details, I refer to each of the four papers enclosed in the Appendix section of this thesis.

Paper I

Accuracy of a heart failure diagnosis in administrative registers

Introduction

The purpose of this study was to study the accuracy of a heart failure diagnosis reported to the Danish National Patient Registers during routine clinical work.

Material and methods

3644 consecutive patients admitted to all departments in one hospital (Amager) between April 1st 1998 and March 31st 1999. A study team evaluated each patient independently of routine care, performed an echocardiogram and evaluated whether clinical symptoms of heart failure were present.

Results

Patients with ESC-HF with or without Reg-HF were older (p<0.001), had a higher serum creatinine (p<0,001), lower left ventricular ejection fraction (p<0.001), higher NTproBNP (p≤0.001), and a greater proportion of cardiac abnormalities (p<0.001) compared to patients without ESC-HF. We found no significant difference with regard to haemoglobin level (p=NS), and systolic (p=NS) or diastolic blood pressures (p=NS).

Table 1: Characteristics of patients according to heart failure classification.

Explanatory variable	No heart failure		Heart failure according to ESC definition	
	No Reg-HF	Reg-HF	No Reg-HF	Reg-HF
	2742	30	303	126
Age, mean	69.7	79.5	76.8	78.0
Male sex	1894 (59.9 %)	22 (73.3 %)	165 (54.5 %)	54 (42.9 %)
LV diastolic diameter >56 mm	261 (11.3 %)	1 (4.6 %)	113 (39.9 %)	60 (51.3 %)
Posterior wall >11 mm	73 (3.4 %)	0 (0.0 %)	28 (10.7 %)	10 (9.5 %)
Mitral septal distance >7 mm	297 (14.5 %)	1 (5.6 %)	143 (61.1 %)	70 (69.3 %)
EF, mean	60.8	58.6	49.2	42.6
Sinus rhythm	2487 (91.8 %)	19 (67.9 %)	216 (71.3 %)	77 (61.6 %)
Valvular disease*	633 (24.6 %)	1 (4.2 %)	207 (69.9 %)	92 (76.0 %)
Raised NT-proBNP	880 (46.4 %)	16 (84.2 %)	186(84.6 %)	82 (94.3 %)
≥1 objective abnormality†	1009 (31.9 %)	1 (3.33 %)	303 (100 %)	126 (100 %)

ESC-HF refers to a diagnosis of heart failure by an independent screening of all admissions and with systematic registration of heart failure compatible with the European Society of Cardiology criteria.
Reg-HF refers to a diagnosis of heart failure reported to the National Hospital Register.
N specifies the number of patients
* Aortic or mitral valve disease on echocardiography
†Abnormality signs were: Ejection fraction<45 %, left ventricular diastolic diameter>56 mm, mitralseptal separation>7 mm, posterior wall thickness>11 mm or valvular disease.

A registered diagnosis of heart failure (n=126) carried a specificity of 99% and a sensitivity of 29% for all patients.

The sensitivity was a little higher in patients with low LVEF (39%). The positive predictive value was 81%, the negative predictive value 90%.

Conclusions

This study demonstrates that HF is severely underreported in the Danish National Hospital Register. The independent evaluation was able to confirm a diagnosis compatible with the ESC criteria in almost all of the reported cases. The sensitivity was a little higher in patients with low LVEF.

Table 2: 2 by 2 tables which demonstrate calculation of predictive values, sensitivity and specificity of a registered diagnosis of heart failure.

	No ESC-HF	ESC-HF	Total
No Reg-HF	2742	303	3045
Reg-HF	30	126	156
Total	2772	429	3201
Sensitivity=126/429=29 % Specificity=2742/2772=99% Positive predictive value=126/156=81 % Negative predictive value=2742/3045=90 %			

Paper II

Persistence of the prognostic importance of left ventricular systolic function and heart failure after myocardial infarction: 17-year follow-up of the TRACE register

Introduction

To systematically evaluate persistence of the prognostic importance of left ventricular systolic dysfunction and HF evaluated at the time of the index infarction.

Material and methods

6676 consecutive MI patients screened for entry in the Trandolapril Cardiac Evaluation (TRACE) study analysed by Kaplan-Meier survival analysis, landmark analysis and Cox proportional-hazard models.

Results

Baseline characteristics of the study population are listed in table 3, stratified according to gender. Women were older and had a higher frequency of hypertension, diabetes, previous stroke, heart failure and use of diuretic treatment. Women were less aggressively treated with thrombolytic therapy. Men had higher body mass index, creatinine and had a higher proportion of previous MI and current smokers. All the mentioned differences were statistically significant.

In unadjusted analysis lower WMI was consistently associated with higher mortality (figure 1). A corresponding analysis showed higher mortality in HF patients (figure 1).

To further clarify the continued importance of left ventricular function and HF we performed landmark analysis (figure 2) illustrating survival in classes of left ventricular function adjusted for age and sex and HF adjusted for age, gender and WMI, divided in time periods after the infarction. Landmark analysis showed a prognostic effect of WMI for 10 years and for HF for 8 years. After this period there was no or variable effect of the prognostic factors.

We constructed 4 Cox proportional-hazards models of total mortality with stepwise addition of variables (table 4). WMI was a significant prognostic factor until 10 years of follow-up with hazard ratio ranging between 0.74 (CI 0.71-0.78) and 0.90 (CI 0.82-0.98) associated with a 12% improvement in left ventricular ejection fraction (0,4 wall motion index units). The prognostic significance of HF persisted for 8 years with hazard ratio between 1.47 (CI 1.21-1.78) and 2.62 (95% CI 2.30-2.98) for the first 8 years.

Conclusions

WMI and HF are time-limited prognostic factors after MI conferring prognostic information for 10 and 8 years, respectively. Evaluation of these risk factors after MI are important to the risk stratification of patients.

Table 3: Baseline characteristics of the patient population

	Women (n=2172)	Men (n=4502)	P Value
Age, mean	71.3	65.4	<0.0001
BMI*, mean	24.9	26.1	<0.0001
Creatinine, mean, µmol/l	100	111	<0.0001
Hypertension, %	28.0	20.0	<0.0001
Diabetes %	13.7	9.4	<0.0001
Angina pectoris %	37.6	36.5	0.38
Previous MI, %	19.4	25.3	<0.0001
Heart failure, %	60.6	50.3	<0.0001
Current smoking, %	44.3	55.0	<0.0001
Thrombolysis, %	34.0	44.1	<0.0001
Previous stroke, %	9.41	7.58	0.0109
Diuretic treatment, %	52.1	41.1	<0.0001

P-values calculated with the use of chi2-test for discrete variables and t-test for continuous variables.
*BMI=Body Mass Index

Fig. 1: All cause mortality stratified by WMI class and HF

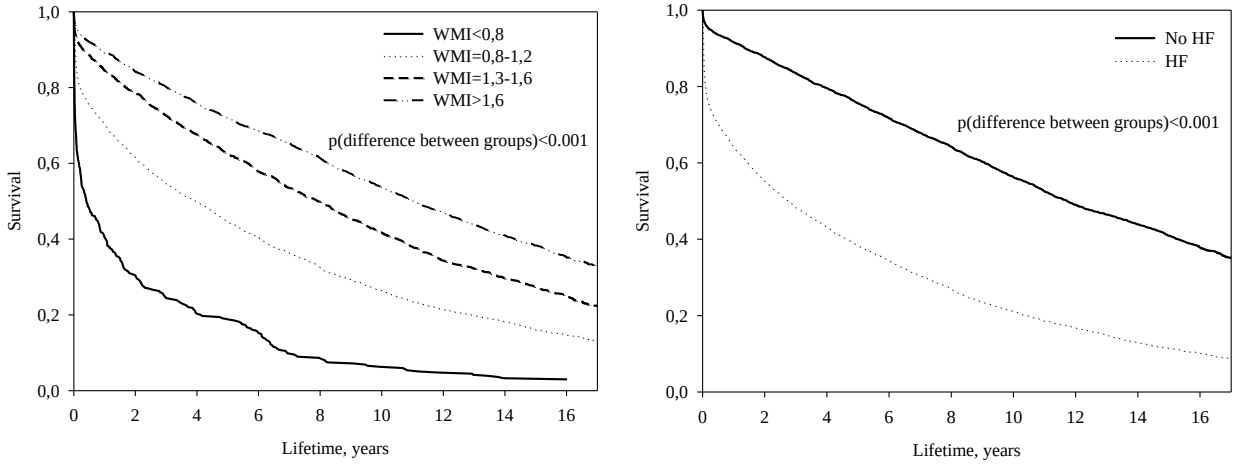


Fig. 2: Landmark analysis of the time dependent prognostic significance of WMI class adjusted for age and gender and HF class adjusted for age, gender and WMI.

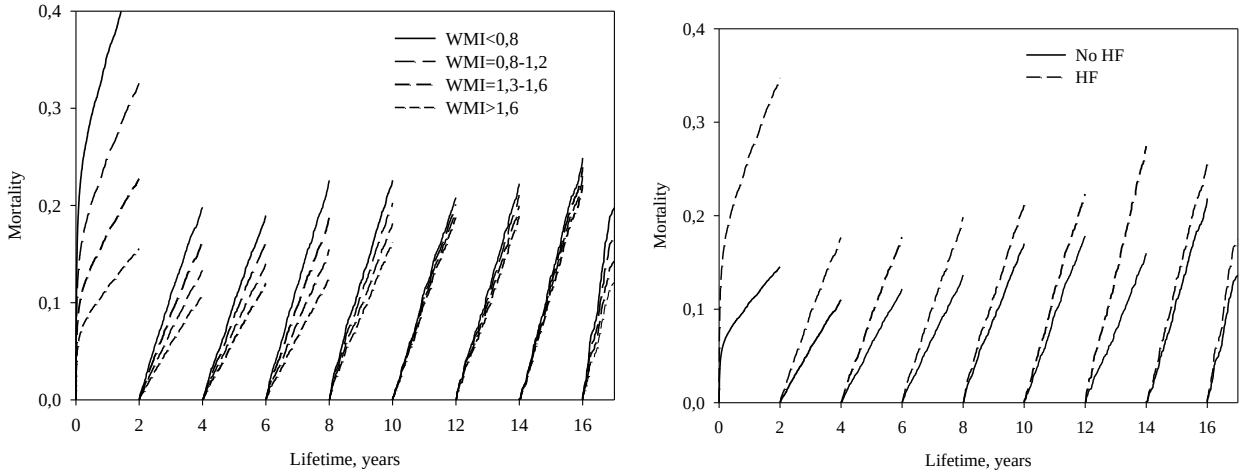


Table 4: Cox proportional hazards models of mortality as a function of time with stepwise addition of variables.

	0-2 years		2-4 years		4-6 years		6-8 years		8-10 years		10-12 years		12-14 years		14-16 years		16- years	
Variables	**RR**	**CI***	**RR**	**CI***	**RR**	**CI***	**RR**	**CI***	**RR**	**CI***	**RR**	**CI***	**RR**	**CI***	**RR**	**CI***	**RR**	**CI***
	Model 1																	
Male gender	1.015	0.924-1.114	1.327	1.125-1.566	1.003	0.839-1.200	1.219	1.005-1.479	1.174	0.958-1.438	1.582	1.248-2.000	1.028	0.801-1.318	1.031	0.794-1.337	1.052	0.710-1.559
Age**	1.860	1.774-1.949	2.023	1.877-2.199	1.895	1.741-2.080	2.080	1.895-2.303	2.080	1.877-2.303	2.119	1.895-2.389	2.119	1.860-2.411	1.967	1.708-2.261	2.100	1.692-2.617
	Model 2																	
Male gender	0.964	0.878-1.058	1.286	1.090-1.516	0.982	0.821-1.174	1.198	0.988-1.453	1.164	0.951-1.426	1.578	1.246-1.996	1.023	0.798-1.311	1.028	0.792-1.333	1.038	0.701-1.535
Age**	1.724	1.644-1.808	1.967	1.808-2.139	1.860	1.692-2.042	2.042	1.842-2.240	2.042	1.860-2.261	2.119	1.895-2.367	2.100	1.842-2.411	1.949	1.708-2.240	2.100	1.692-2.594
WMI***	0.652	0.629-0.676	0.806	1.061-1.079	0.844	0.784-0.908	0.808	0.748-0.872	0.886	0.814-0.964	0.962	0.874-1.059	0.939	0.845-1.044	0.956	0.855-1.070	0.823	0.698-0.972
	Model 3																	
Male gender	0.977	0.891-1.073	1.306	1.107-1.540	0.955	0.832-1.190	1.215	1.002-1.474	1.176	0.960-1.440	1.600	1.264-2.026	1.074	0.836-1.378	1.046	0.805-1.359	1.062	0.717-1.575
Age**	1.553	1.480-1.629	1.860	1.708-2.023	1.774	1.613-1.949	1.949	1.757-2.139	2.004	1.808-2.220	2.080	1.842-2.324	2.023	1.757-2.303	1.931	1.676-2.220	2.061	1.660-2.547
WMI***	0.696	0.670-0.723	0.840	0.785-0.898	0.873	0.809-0.942	0.834	0.771-0.902	0.905	0.830-0.986	0.980	0.888-1.081	0.982	0.881-1.095	0.971	0.866-1.089	0.842	0.710-0.997
HF	2.775	2.468-3.120	1.676	0.785-0.898	1.509	1.266-1.800	1.508	1.254-1.813	1.285	1.059-1.559	1.265	1.021-1.567	1.851	1.463-2.341	1.221	0.944-1.578	1.323	0.898-1.951
	Model 4 Other variables in the model were: Gender, age, WMI, HF, Body mass index, previous AMI, angina pectoris, creatinine, congestive heart failure, diabetes mellitus, wall motion index, systemic hypertension, thrombolytic therapy																	
Male Gender	0.986	0.887-1.096	1.289	1.079-1.541	1.026	0.848-1.242	1.310	1.065-1.610	1.077	0.868-1.335	1.638	1.265-2.117	1.047	0.799-1.371	1.105	0.821-1.487	0.987	0.635-1.534
Age**	1.452	1.370-1.538	1.708	1.553-1.877	1.692	1.524-1.860	1.877	1.692-2.100	1.895	1.692 2.100	1.986	1.741-2.240	1.967	1.708-2.282	1.895	1.644-2.199	2.139	1.676-2.714
WMI***	0.742	0.710-0.776	0.882	0.819-0.950	0.891	0.820-0.967	0.861	0.790-0.938	0.896	0.818-0.983	0.999	0.896-1.114	1.0008	0.898-1.131	0.978	0.867-1.105	0.846	0.707-1.012
HF	2.616	2.298-2.979	1.599	1.342-1.904	1.384	1.150-1.664	1.467	1.208-1.780	1.201	0.979-1.472	1.212	0.964-1.525	1.884	1.469-2.417	1.237	0.944-1.622	1.246	0.829-1.874

*95 % confidence interval

**Risk ratio associated with an increase in age of 10 years.

***Hazard ratio associated with a one group improvement in WMI.

Paper III

Persistence of the prognostic importance of left ventricular systolic function and heart failure after myocardial infarction: 17-year follow-up of the TRACE register

Introduction

The aim of this study was to systematically evaluate the development of diabetes as long-term prognostic factor after myocardial infarction (MI).

Material and methods

6668 consecutive MI patients screened for entry in the Trandolapril Cardiac Evaluation (TRACE) study analysed by Kaplan-Meier survival analysis, landmark analysis and Cox proportional-hazard models.

Results

Baseline characteristics of the 6668 patients showed that patients with diabetes were older, had more co-morbidity and risk factors, received more often diuretics but less often thrombolytic therapy, had poorer left ventricular function and were in higher New York Heart Association (NYHA) and Killip class (table 5). All the mentioned differences were statistically significant. As expected, patients with diabetes had a significantly higher mortality than patients without diabetes (figure 3, unadjusted analysis).

To clarify the importance of diabetes as a prognostic factor we performed landmark analysis illustrating survival in diabetics and non diabetics adjusted for age, sex and wall motion index in 2 year intervals after the infarction (figure 3). The Landmark analysis demonstrated that diabetes continued to have a significant prognostic effect throughout the duration of follow-up.

We constructed Cox proportional-hazards models of total mortality with stepwise addition of covariates. Overall, diabetes was a significant prognostic factor, hazard ratio 1.47 (CI 1.35-1.61) adjusted for all covariates. Greater significance of diabetes reflected in a higher hazard ratio was observed in the end of follow-up, however this did not reach statistical significance in the last period of follow-up, most likely as a result of lack of statistical power since only few patients with diabetes were still alive at this time. HR for diabetes varied between 1.19 (CI 1.04-1.37) and 2.13 (CI 1.33-3.42) in the fully adjusted models and reached significance in most of the 2-year intervals.

Conclusions

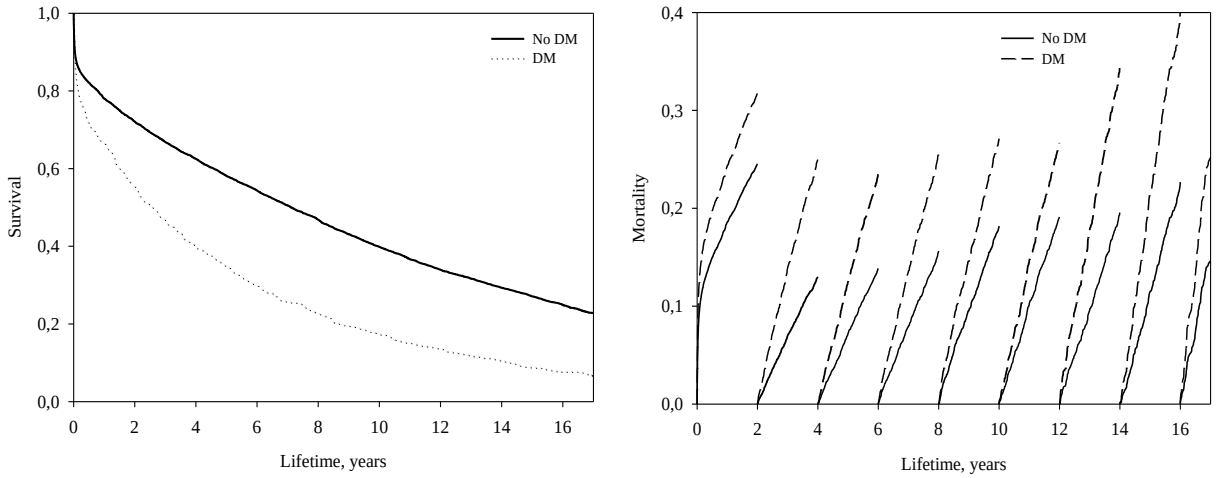
With a follow-up of 17 years, we found that diabetes continued to represent a strong independent prognostic factor for all-cause mortality. Our results expand on previous findings by documenting continued prognostic importance of diabetes with a follow-up period much longer than any other study of this subject.

Table 5: Patient characteristics according to diabetes classification.

	Diabetes (n=719)	No diabetes (n=5949)	P Value
Age	69.5	67.1	<0.0001
Gender, % **Women** **Men**	41.3 58.7	31.5 68.5	<0.0001
Body mass index	26.7	25.6	<0.0001
Creatinine (mean), µmol/l	117	107	<0.0001
Hypertension, %	36.3	21.0	<0.0001
Angina pectoris, %	48.1	35.5	<0.0001
Previous MI, %	32.3	22.3	<0.0001
Heart failure*, %	69.0	51.8	<0.0001
Current smoking, %	36.1	53.4	<0.0001
Thrombolysis, %	27.0	42.5	<0.0001
Previous stroke, %	13.2	7.6	<0.0001
Diuretic treatment, %	64.2	42.3	<0.0001
NYHA, % **Class I** **Class II** **Class III** **Class IV**	 47.0 34.8 6.9 9.0	 58.4 28.3 3.9 6.3	<0.0001
Killip, % **Class I** **Class II** **Class III** **Class IV**	 69.5 22.0 2.2 6.3	 79.9 14.2 2.11 3.8	<0.0001
Wall motion index, % **>1.6** **1.3-1.6** **0.8-1.2** **<0.8**	 21.1 20.9 40.1 8.2	 34.1 23.9 31.1 4.7	<0.0001

P-values calculated with the use of chi2-test for discrete variables and t-test for continuous variables.
*History of heart failure and in-hospital heart failure

Fig. 3: Unadjusted all-cause mortality stratified by diabetes and landmark analysis of the time dependent prognostic significance of diabetes adjusted for age and gender.



Paper IV

Persistence of the prognostic importance of left ventricular systolic function and heart failure after myocardial infarction: 17-year follow-up of the TRACE register

Introduction

The aim of this study was to systematically evaluate the importance of renal function as an independent prognostic factor evaluated at the time of the index infarction.

Material and methods

Follow-up of 6653 consecutive MI patients screened for entry in the Trandolapril Cardiac Evaluation (TRACE) study. Renal function was calculated as estimated GFR (eGFR) with the use of the four-component MDRD equation incorporating age, race, sex and serum creatinine level. The patients were analysed by Kaplan-Meier survival analysis, landmark analysis and Cox proportional hazard models and outcome measure was all-cause mortality.

Results

Baseline characteristics of the 6653 patients included in our study are presented in table 6. With declining renal function patients were older, had more co-morbidity, were less often treated with thrombolytic therapy but more often with diuretics, had worse left ventricular systolic function and were in a more severe clinical state evaluated by New York Heart Association (NYHA) and Killip class.

Renal function was inversely related to all-cause mortality (figure 4, unadjusted analysis). The mortality was 43.0% (eGFR group 1), 56.9% (eGFR group 2), 71.9% (eGFR group 3), 89.7% (eGFR group 4) at 10 years of follow-up and 57.7% (eGFR group 1), 71.3% (eGFR group 2), 83.6% (eGFR group 3), 95.4% (eGFR group 4) at 15 years of follow-up ($p<0.0001$ for difference between the 4 eGFR groups). To clarify the importance of renal function as prognostic factor we performed a Landmark analysis illustrating survival stratified by eGFR group and adjusted for age and sex in 2 year intervals after the infarction (figure 4).

We constructed 3 Cox proportional-hazards models of total mortality with a stepwise addition of covariates (table 7). When using eGFRgroup 1 (normal renal function) as reference in the model incorporating all covariates in the whole follow-up period, estimated GFR was a significant prognostic factor in eGFRgroups 3 (hazard ratio 1,19, CI 1,09-1,30) and 4 (hazard ratio 1,72, CI 1,56-1,91) but not in eGFRgroup 2 (hazard ratio 0,99, CI 0,91-1,07). Overall, there was a rise in hazard ratio with worsening renal function (figure 5).

Estimation of renal function has prognostic significance for up to 16 years following MI, even without adjustment for changing values of se-creatinine. Landmark analyses of 2-year periods shows that the statistic significance disappears after 12 years of follow-up, but hazard ratio is almost the same in the following years, so the lack of significance in this period is probably a result of lack of power. The hazard ratio is close to 1.00 only after 16 years of follow-up.

Conclusions

Renal function is a strong and independent long-term prognostic factor the first 10-12 years following a MI. Estimating GFR provides a more precise estimate of renal function than serum creatinine and carries stronger prognostic significance.

Table 6: Patient characteristics according to classification of renal function by eGFR.

	eGFR group 1 eGFR≥75.0 ml per minute per 1.73 m^2 (n=1772)	**eGFR group 2** 60.0≤eGFR≤74.9 ml per minute per 1.73 m^2 (n=2071)	**eGFR group 3** 45≤eGFR≤59.9 ml per minute per 1.73 m^2 (n=1726)	**eGFR group 4** eGFR<45 ml per minute per 1.73 m^2 (n=1107)	**P Value***
Age	59.7	66.6	71.1	75.0	<0.0001
Gender, %					
Women	16.9	28.4	42.5	49.9	<0.0001
Men	83.1	71.6	57.5	50.1	
Body mass index	25.8	25.9	25.6	25.2	<0.0001
Creatinine (mean), µmol/l	80.1	95.6	112.1	174.5	<0.0001
Hypertension, %	15.9	20.4	25.8	32.8	<0.0001
Diabetes, %	6.7	9.8	12.1	17.2	<0.0001
Angina pectoris, %	27.5	36.0	42.1	45.2	<0.0001
Previous MI, %	17.0	22.6	26.0	30.8	<0.0001
Heart failure, %	34.2	48.8	64.1	77.3	<0.0001
Smoking, %					
Previously	16.9	22.2	24.9	25.1	<0.0001
Currently	65.8	52.9	44.5	36.2	
Thrombolysis, %	49.7	45.3	37.4	23.7	<0.0001
Previous stroke, %	4.6	7.0	9.4	14.2	<0.0001
Diuretic treatment, %* **	25.2	40.2	53.7	70.0	<0.0001
Digoxin at discharge, %* **	7.2	13.9	21.0	31.3	<0.0001
ACE inhibitor at discharge, %* **	4.2	5.8	9.8	15.3	<0.0001
NYHA, %					
Class I	68.3	62.2	51.6	38.9	<0.0001
Class II	25.6	27.6	31.4	33.4	
Class III	2.2	3.8	5.4	6.6	
Class IV	2.6	4.3	7.8	15.5	
Killip, %**					
Class I	88.6	82.8	74.2	62.8	<0.0001
Class II	9.1	13.5	18.6	21.9	
Class III	0.5	1.3	2.6	5.4	
Class IV	1.9	2.3	4.7	9.9	
Wall motion index, %					
>1.6	42.5	33.4	28.9	21.8	<0.0001
1.3-1.6	24.7	24.5	22.4	21.8	
0.8-1.2	26.2	33.1	35.4	34.2	
<0.8	2.0	4.0	6.3	9.8	
Not classified	4.5	5.0	7.0	12.6	
Ventricular fibrillation.%**	5.4	6.5	9.3	8.0	<0.0001
Ventricular tachycardia, %**	12.2	12.8	13.1	12.6	0.8744
Atrial fibrillation, %**	12.3	18.2	25.6	32.4	<0.0001

*for difference between groups.

** Worst Killip class during index hospitalization

P-values calculated with the use of chi^2-test for discrete variables and t-test for continuous variables.

***At discharge.

****During hospital stay (day 5 to discharge)

Fig. 4. Unadjusted all-cause mortality stratified by eGFR group and landmark analysis of the time dependent prognostic significance of renal function adjusted for age and gender.

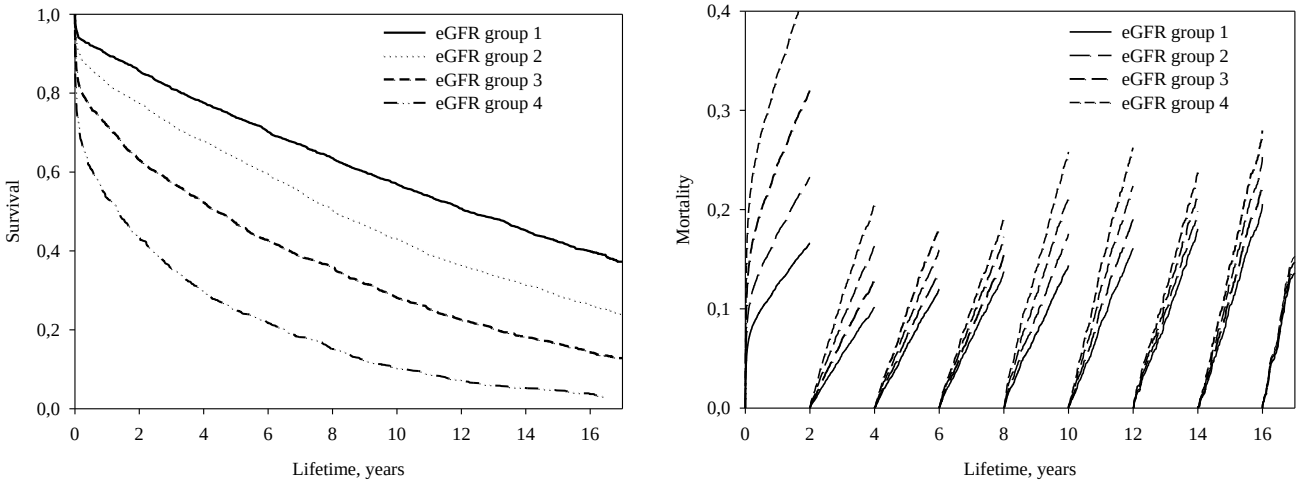


Figure 5. Relative risk as a function of follow-up time in Cox proportional-hazard model 2 (all covariates)-eGFRgroups 2-4 with eGFRgroup 1 as reference.

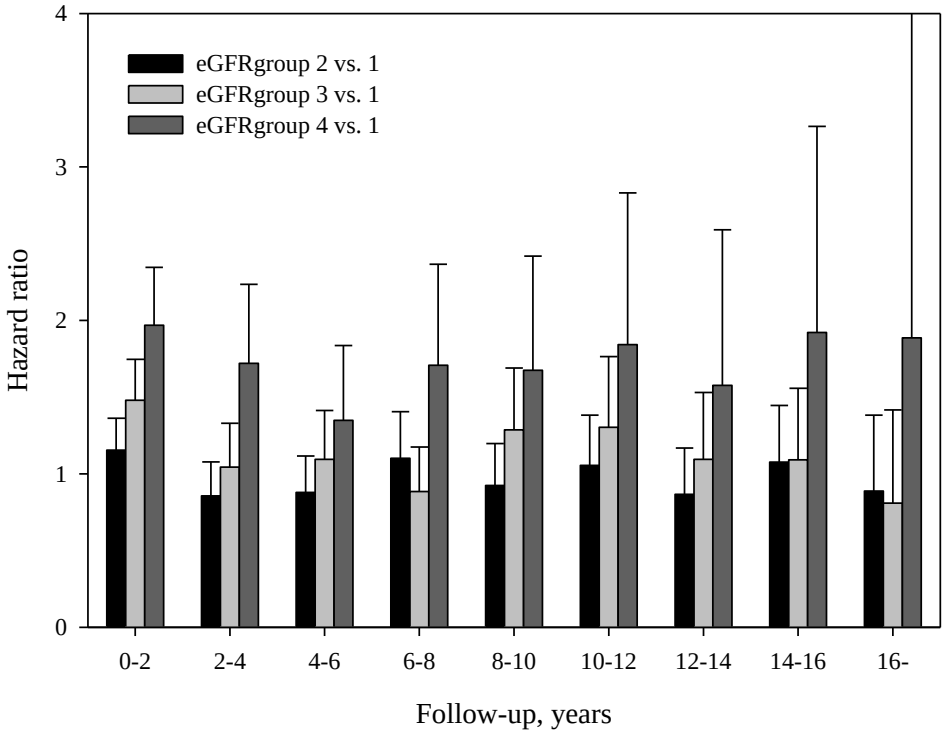


Table 7. Three proportional hazards models of mortality as a function of time with stepwise addition of variables

	0-2 years N=6676		2-4 years N=4702		4-6 years N=4022		6-8 years N=3474		8-10 years N=2978		10-12 years N=2526		12-14 years N=2152		14-16 years N=1854		16- years N=1576	
Variables	**RR**	**CI***	**RR**	**CI***	**RR**	**CI***	**RR**	**CI***	**RR**	**CI***	**RR**	**CI***	**RR**	**CI***	**RR**	**CI***	**RR**	**CI***
	Model 1																	
eGFRgroup**	1.77	1.69-1.85	1.57	1.46-1.70	1.45	1.33-1.58	1.43	1.30-1.56	1.53	1.39-1.68	1.42	1.27-1.58	1.40	1.24-1.58	1.36	1.20-1.55	1.28	1.04-1.57
Cregroup	2.09	1.96-2.23	1.95	1.71-2.22	1.89	1.61-2.21	1.58	1.30-1.91	1.68	1.36-2.06	1.51	1.17-1.95	1.55	1.14-2.10	0.91	0.63-1.33	1.57	0.93-2.63
	Model 2																	
Male gender	1.11	1.00-1.24	1.45	1.22-1.73	1.12	0.92-1.36	1.36	1.10-1.67	1.22	0.98-1.51	1.83	1.41-2.37	1.15	0.88-1.50	1.22	0.92-1.61	1.01	0.66-1.55
Age****	1.37	1.29-1.45	1.64	1.50-1.81	1.66	1.50-1.84	1.86	1.66-2.06	1.86	1.66-2.08	1.91	1.69-2.18	1.95	1.69-2.24	1.90	1.63-2.20	2.10	1.66-2.67
eGFRgroup**	1.27	1.20-1.34	1.21	1.11-1.32	1.12	1.01-1.23	1.10	0.99-1.22	1.20	1.07-1.34	1.19	1.05-1.35	1.11	0.96-1.29	1.13	0.97-1.31	1.01	0.79-1.29
Cregroup	1.34	1.24-1.46	1.30	1.12-1.51	1.47	1.24-1.74	1.10	0.90-1.36	1.30	1.05-1.63	1.25	0.96-1.62	1.28	0.93-1.76	0.76	0.52-1.11	1.35	0.79-2.32
eGFRgroup 2 vs. 1	1.15	0.98-1.36	0.86	0.68-1.08	0.88	0.69-1.12	1.10	0.86-1.41	0.92	0.71-1.20	1.06	0.81-1.38	0.87	0.64-1.17	1.08	0.80-1.45	0.89	0.57-1.38
eGFRgroup 3 vs. 1	1.48	1.26-1.75	1.04	0.82-1.33	1.10	0.85-1.41	0.89	0.67-1.18	1.29	0.98-1.69	1.30	0.96-1.76	1.10	0.78-1.53	1.09	0.76-1.56	0.81	0.46-1.42
eGFRgroup 4 vs. 1	1.97	1.65-2.35	1.72	1.32-2.24	1.35	0.99-1.84	1.71	1.23-2.37	1.68	1.16-2.42	1.84	1.20-2.83	1.58	0.96-2.59	1.92	1.13-3.26	1.89	0.78-4.55

In all models either cregroup or eGFR were included in the model.

*95 % confidence interval

**Hazard ratio associated with 1 eGFR group improvement

***Other covariates in model 2: Body mass index, previous AMI, angina pectoris, congestive heart failure, diabetes mellitus, wall motion index, systemic hypertension, thrombolytic therapy.

****Hazard ratio associated with an increase in age of 10 years.

Discussion

Main findings

The time variation of known risk factors following MI has been studied with a follow-up of 17 years. Moreover, we studied the validity of a heart failure diagnosis reported in administrative registers to establish whether heart failure could be used as an endpoint together with all-cause mortality. The 4 studies forming the basis for this thesis have the following main findings: 1) a diagnosis of heart failure reported in the Danish National Patient Register has a high specificity and a low sensitivity. The low sensitivity of the diagnosis precluded its use as an endpoint in the following papers. 2) when assessed during the index MI, left ventricular systolic function and heart failure carries prognostic significance for 10 years. 3) diabetes is an independent long-term prognostic factor after MI and continues to predict mortality for 17 years after MI. 4) one estimate of renal function is a strong and independent long-term prognostic factor the first 10-12 years following a MI.

Comparison with other studies

In the EuroHeart Failure survey, the sensitivity of a heart failure diagnosis was 71 % overall, but 53-59% in the northern European contries[79]. This is higher than the 29% sensitivity in our study, but is still low and thereby supports our conclusion that discharge coding diagnosis of heart failure cannot be used for studies of prevalence and incidence.

The validity of the discharge coding diagnosis of HF in administrative registries has been addressed in three recent studies, from Scotland, Canada and Sweden[80-82]. Lee et al found that the primary diagnosis of HF had a high positive predictive value[82]. In a study by Khand et al. the charts of 330 cases with heart failure or atrial fibrillation were identified, with 77% of ICD-10 discharge codes being correct. In addition, coding position (primary or secondary HF diagnosis) was not found to significantly influence accuracy of a code for HF. The diagnosis of HF was considerably underreported since only 66% of patients with probable or definite heart failure were identified by the discharge coding. The authors concluded that hospital discharge codes substantially underestimate hospital events related to heart failure in the UK[81]. Ingelsson et al found that 82% of patients with the discharge coding diagnosis of HF had definite HF.[80] The results of our study are supported by these studies, carried out in different countries. To our knowledge, our study is the first to systematically evaluate both sensitivity and specificity of a heart failure diagnosis.

Looking at the time variation of prognostic factors after MI, our results demonstrate that WMI is a powerful prognostic factor in MI patients, a finding that is in agreement with several other papers[83-85]. Incremental prognostic value of wall motion index was reported in MI patients who also had congestive heart failure compared to patients without congestive heart failure[86]. However, another study showed that a decrease in left ventricular ejection fraction of 0.1 was associated with a hazard ratio of 1.61 (95% CI 1.48-1.76) for MI patients without prior HF and a hazard ratio of 1.43 (1.38-1.48) for MI patients with prior HF[87]. The follow-up time was nine years. This difference could possibly be a result of analysis of two different databases with differences in the definition of heart failure.

In a publication from the VALIANT database, wall motion index has been shown to carry slightly more prognostic information in MI patients than LVEF measured by Simpsons biplane method, perhaps because of a higher sensitivity of regional assessment[88].

In concordance with our findings, diabetes has previously been described as a predictor for an adverse outcome following myocardial infarction[89]. It has been documented that patients with prediabetic conditions have an elevated risk of cardiovascular disease[90] and there may exist an association between blood glucose and cardiovascular risk even below a diabetic threshold[91]. Our long-term results are supported by a previous analysis from the TRACE registry suggesting that the magnitude of prognostic effect may increase with time[59].

A perception often encountered is that the glucose level as an expression of the glucometabolic state at the time of admission is inconsequential as it is only a sign of acute physiological stress. This might not be true, since it has been suggested that the glucometabolic state at admission carriers long-term prognostic information in patients with and without diabetes[92]. In addition, blood glucose concentration in MI patients at admission time are related to risk of death[93]. This close link between glucometabolic state in the acute phase and cardiovascular outcome could possibly be explained by a more extensive atherosclerosis in patients with diabetes or poorer glucometabolic state but studies have provided conflicting results[94, 95]. Another possibility could be that metabolic disturbance or stress provoked by MI could have a detrimental effect on the process of MI. This has been examined in randomized settings where intensive treatment with insulin to better glycemic status was compared with usual care. One smaller study showed no difference between intervention and control group[96]. Another study showed positive effects on long-term mortality but not short-term mortality in the intervention group[97]. Interestingly, a third study showed no benefit of intervention but confirmed that glucose level was a predictor of long-term mortality[98]. This is analogous with the results obtained in the study of long-term intensive glucose regulation. Here epidemiological studies have shown a clear association between haemoglobin A1C and the risk of cardiovascular events[99, 100]. Large studies have suggested a beneficial effect of intensive treatment on the risk of cardiovascular disease[101, 102]. However, recently three large randomised clinical studies failed to document an effect of intensive treatment[103-105].

With regard to renal function and cardiovascular risk, several studies have used serum creatinine instead of GFR to evaluate renal function[106-108]. The ideal approach to the evaluation of renal function is direct GFR measurement, which is often limited by practical considerations. The use of serum creatinine is limited because the association between serum creatinine and renal function is nonlinear since it varies with age, gender, ethnicity and lean body mass. The National Kidney Foundation uses GFR, not serum creatinine, to define chronic kidney disease[109].

Previous studies have documented adverse outcomes at 30 and 180 days in patients with reduced renal function of MI[63, 109-112]. The novelty of our results is the description of the prognostic effect of renal function in 2-year intervals with a very long follow-up period.

The relationship between renal function and cardiovascular outcomes has been examined in several large randomized controlled landmark studies: the Studies of Left Ventricular Dysfunction (SOLVD) trial, Trandolapril Cardiac Evaluation (TRACE) trial, Survival and Ventricular Enlargement (SAVE) trial and 2 analyses of the Valsartan in Acute Myocardial Infarction Trial (VALIANT) [64, 65, 113-115]. The SOLVD and SAVE studies and the analyses from VALIANT used the MDRD formula to estimate renal function. All studies found that reduced renal function was independently associated with an increased risk of death and cardiovascular outcomes. Our study also comprises a large cohort but with a broader spectrum of renal dysfunction, because all patients in the TRACE register was included irrespective of creatinine level [65, 113]. We included consecutive patients and our study had the longest follow-up time.

Several recent papers have examined the prognostic role of renal function in AMI patients. One study examined the prognostic significance of an acute worsening of renal function among patients hospitalized for MI surviving to hospital discharge. With a follow-up of at least 4 years, worsening renal function was independently associated with diabetes, left ventricular systolic dysfunction and a history of chronic kidney disease. After adjustment for factors associated with worsening renal function and long-term mortality, worsening renal function was independently associated with a higher risk of death[116]. In another study, the prognostic significance of chronic kidney disease and acute kidney injury on acute coronary syndrome was reviewed. This study stressed the importance of early measurement and monitoring of renal function, which is probably standard of care in most institutions[117]. The significance of creatinine clearance at the time of hospital admission as a predictor of in-hospital adverse events and mortality was examined using data from the global registry of acute coronary events (GRACE) comprising 11 774 patients hospitalized with ACS. The results showed that in comparison with patients with normal or minimally impaired renal function, patients with moderate renal dysfunction were twice as likely to die and those with severe renal dysfunction almost four times more likely to die after adjustment for other potentially confounding variables. The risk of major bleeding episodes increased as renal function worsened[118]. Data from GRACE also showed that initial serum creatinine concentration was among the nine factors that independently predicted death and the combined end point of death and myocardial infarction in the period from admission to six months after discharge[16]. An observational study of 57477 consecutive MI patients showed that declining GFR estimated by the MDRD formula was associated with an increased rate of complications and a higher rate of in-hospital mortality[119].

Many of the large landmark cardiovascular trials have excluded patients with renal function under a certain limit but patients with renal impairment can safely obtain the same benefits of cardiovascular medications and invasive procedures when appropriately monitored [120-125].

In our study, impaired renal function was associated with a higher frequency of hypertension, diabetes, angina pectoris and previous MI and it is likely that factors associated with renal decline partly explain the observed increase in risk of all-cause mortality with a decrease in eGFR [61, 62, 111, 126, 127]. We found that age was a significant risk factor for all-cause mortality throughout the length of follow-up and that with declining renal function, patients were older, more often women, and had a greater frequency of comorbidities. These findings are in accordance with previous studies[61, 118, 119, 126].

Regarding the association between diabetes and renal function, it has been documented that in patients with diabetes, the prevalence of renal dysfunction is higher, but the effect of renal function on cardiovascular risk is largely independent of diabetes status. Thus, a similar risk relation between renal function and CV risk exists in patients with and without DM [113].

Strengths and limitations

In paper I, we examined a large number of consecutive patients with a low dropout rate, consistent with daily clinical practice in a general city hospital.

In paper II-IV, we used The Danish National Patient Registry register for follow-up of patients screened for entry in the TRACE study. The strengths of this approach are the completeness of data and ability for comprehensive and long-term follow up. Moreover, our method has the strength of a large patient population and a very long period of follow-up, not often seen in published studies. The length of the follow-up makes it possible to study temporal trends in the significance of risk factors. Additionally, the population was recruited from 27 Danish hospitals with regional patient uptake, and must be concluded to be representative of a MI population admitted alive in a western industrialized country.

The papers that constitute this thesis have some limitations which need to be acknowledged.

Significant change in the treatment of MI patients has occurred since the screening of patients for entry in the TRACE study. Thrombolytic therapy previously was administered routinely to ST-elevation MI patients, while the present Danish and European guidelines recommend percutaneous coronary intervention in these patients[34, 128]. Almost all MI patients today receive clopidogrel[129], statins[10, 11, 130-135] and beta-blockers[6, 7, 9, 136-139]. Patients with left ventricular systolic dysfunction after MI as well as patients with chronic heart failure, depressed left ventricular systolic dysfunction and New York Heart Association class II-IV should receive spironolactone or eplerenone[35-37, 40, 140]. Patients with high risk of cardiovascular events should probably receive an ACE-inhibitor or angiotensin receptor blocker despite a normal left ventricular systolic function[141-144].

The changes in the management of patients with MI could significantly influence our results. However, a multivariable analysis from 1975 to the end of 2003 reveal only slight improvement in post discharge survival after MI[145], but this is probably explained by a lack of multivariate adjustment for MI complications, medical and interventional treatment, as the survivors had more aggressive treatment and fewer complications.

Regular clinical evaluation and measurement of WMI would have been interesting in order to establish whether the dismal prognosis is closely associated with changes in LV function or HF. Serial echocardiographic studies after MI have shown that LV dilatation is present 3 hours after onset of symptoms and that left ventricular volumes afterwards do not change until Day 6[146]. Repeated echocardiographic evaluation of WMI, 3 months, 6 months, and 1 year after MI, provides important prognostic information about worsening HF and death[147]. Wall motion index and HF assessed during the index hospitalization may not reflect long-term

LV function or the clinical situation. Left ventricular function may change following thrombolytic therapy, and HF may be transient.

Today, the echocardiographic approach would probably have included three-dimensional volumetric assessment as a golden standard for the diagnosis of left ventricular systolic function. The ability of tissue Doppler and speckle tracking echocardiography to show left ventricular systolic dysfunction not documented on two-dimensional echocardiography could have been studied. Today, a standard echocardiographic examination includes assessment of left ventricular diastolic function which has been demonstrated having independent prognostic value after MI in addition to left ventricular systolic function[148-150].

New pharmacological treatment combinations are available to patients with diabetes. The most recent guidelines state that patients with diabetes and albuminuria or hypertension should be treated with an ACE inhibitor or an angiotensin receptor blocker, even when the left ventricular systolic function is normal[151]. This was not the case at the start of the TRACE study, probably resulting in an under-treatment of patients with diabetes during the TRACE study period and the start of the follow-up.

We do not have information regarding the medical treatment of patients with and without diabetes during the follow-up period and thus cannot analyse potential differences. Since a number of patients without diabetes at the time of the infarction have developed diabetes later, the observed difference between patients with and without diabetes is smaller than the actual difference.

The data do not allow us to evaluate the effect of duration or changes in renal dysfunction. Contrast-medium-induced nephropathy related to coronary angiography cannot be evaluated. The MDRD equation used to evaluate renal function has limitations, because serum creatinine is influenced by non-renal factors. The baseline-estimated GFR can be affected by urinary excretion of protein, which we did not measure. Our study on the prognostic effect of renal function focuses solely on mortality, with no information on the effect of renal dysfunction on nonfatal outcomes. We do not have information regarding how many patients underwent coronary angiography or CABG during hospital stay or later. This treatment was not routine at the time of the trial (1992-1994). As a result, we cannot evaluate whether the frequency of invasive treatment differ in the eGFRgroups. It has previously been shown that early invasive therapy defined as revascularization within 14 days of admission was associated with greater 1-year survival in patients with non-ST-elevation myocardial infarction and mild-to-moderate renal insufficiency, but the benefit declined with lower renal function[152]. It might be argued that the long-term prognostic information is of lesser interest for renal function, which is frequently updated be creatinine measurement, than for other risk factors, for example systolic function by echocardiography, which is updated more rarely.

Novelty of the results

This thesis consists of 4 studies based on analysis of two different registries.

To our knowledge, paper I is the first study to evaluate both the sensitivity and specificity of a heart failure diagnosis in administrative registers in more than 3600 consecutive patients admitted to one hospital in the Copenhagen area.

Paper II-IV are characterised by a unique length of valid follow-up in a large patient population giving exceptional data on the temporal trends in prognostic factors after MI.

We are the first to evaluate the long-term prognostic effect of left ventricular systolic function and renal function following MI in consecutively admitted patients.

We believe that our documentation of the long-term prognostic significance of left ventricular function and heart failure provides indirect evidence in support of the current recommendations for long-term and probably indefinite medical therapy after MI.

Our results expands on previous findings by documenting that diabetes continues to constitute a prognostic factor for an adverse outcome with a follow-up time of 17 years, which is much longer than any other study of the subject.

By pinpointing diabetes as a continued negative prognostic risk factor our study underlines the necessity of an aggressive diagnostic approach towards the diagnosis and treatment of diabetes. The presence of diabetes aid in the risk stratification of MI patients, identifying patients who are candidates for continued aggressive medical therapy.

In the future, a greater prevalence of MI patients with renal dysfunction probably will be seen as a result of an ageing population with accumulation of risk factors, including hypertension and diabetes. Thus, the prognostic significance of renal function and diabetes will be increasingly important in the future.

Conclusions

The study of the validity of a heart failure diagnosis demonstrates that when using administrative registers, the sensitivity of a diagnosis is low, while the specificity is high. As a result, registers can be used to identify groups of patients with MI for epidemiological studies but not for the study of prevalence and incidence.

In examining the time variation of prognostic factors after MI, we show that three well known risk factors retain prognostic significance for many years after the index admission. This underlines the importance of an aggressive approach towards diagnosing these risk factors to identify patients at high risk. Moreover, the prevalence of risk factors will probably increase in the future as a result of an ageing population.

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Accuracy of a heart failure diagnosis in administrative registers

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Abstract

Background: The incidence of heart failure is frequently reported using hospital discharge diagnoses. The specificity of a diagnosis has been shown to be high but the sensitivity of a reported diagnosis is unknown.
Purpose: To study the accuracy of a heart failure diagnosis reported to the Danish National Patient Registers during routine clinical work.
Methods: The patient population consisted of 3644 consecutive patients admitted to all departments in one hospital. Diagnoses reported to the National Patient Register were recorded. A study team evaluated each patient independently of routine care, performed an echocardiogram and evaluated whether clinical symptoms of heart failure were present. Heart failure was defined in accordance with current ESC guidelines as symptoms of heart failure and evidence of cardiac dysfunction.
Results: A registered diagnosis of heart failure ($n=126$) carried a specificity of 99% and a sensitivity of 29% for all patients. The positive predictive value was 81%, the negative predictive value 90%.
Conclusion: The diagnosis of Heart Failure in the Danish National Registers is underreported, but very specific.

Keywords: Accuracy; Heart failure; Diagnosis

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Persistence of the prognostic importance of left ventricular systolic function and heart failure after myocardial infarction: 17-year follow-up of the TRACE register

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Aims Left ventricular systolic function and presence of heart failure (HF) are important prognostic factors and dictate future therapeutic strategies after myocardial infarction (MI). We evaluated persistence of the prognostic importance of left ventricular dysfunction and HF in consecutive MI patients screened for entry in the Trandolopril Cardiac Evaluation Registry (TRACE) study.

Methods and results The study population comprised 6676 MI patients screened for entry into the TRACE study, a double-blind, randomized, parallel group, placebo-controlled study of trandolapril vs. placebo in patients with left ventricular dysfunction after MI. In unadjusted analysis, patients with reduced left ventricular function and HF continued to show increased mortality. Landmark analysis and Cox proportional-hazards models showed that wall motion index (WMI) was a significant prognostic factor until 10 years of follow-up with hazard ratios ranging between 0.74 [confidence interval (CI) 0.71–0.78] and 0.90 (CI 0.82–0.98) associated with a 12% improvement in left ventricular ejection fraction (0.4 WMI units). The prognostic significance of HF persisted for 8 years with hazard ratios between 1.47 (CI 1.21–1.78) and 2.62 (95% CI 2.30–2.98) for the first 8 years.

Conclusion When assessed during the index MI, WMI and HF carry prognostic information for up to 10 years.

Keywords Myocardial infarction • Left ventricular systolic dysfunction • Heart failure • Prognosis

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CARDIO VASCULAR DIABETOLOGY

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Diabetes is an independent predictor of survival 17 years after myocardial infarction: follow-up of the TRACE registry

Thomas Kümler*[1], Gunnar H Gislason[2], Lars Køber[1] and Christian Torp-Pedersen[2]

Abstract

Background: In patients hospitalized for myocardial infarction, there are limited data examining the long-term prognostic effect of diabetes.

The aim of this study was to systematically evaluate the development of diabetes as an independent long-term prognostic factor after myocardial infarction.

Methods: Prospective follow-up of 6676 consecutive MI patients screened for entry in the Trandolapril Cardiac Evaluation (TRACE) study. The patients were analysed by Kaplan-Meier survival analysis, landmark analysis and Cox proportional hazard models and outcome measure was all-cause mortality.

Results: The mortality in patients with diabetes was 82,7% at 10 years of follow-up and 91,1% at 15 years of follow-up, while patients without diabetes had a mortality of 60,2% at 10 years of follow-up and 72,9% at 15 years of follow-up ($p < 0.0001$). Landmark analysis continued to show prognostic significance of diabetes throughout the duration of follow-up. Multivariable Cox proportional-hazards model showed that the hazard ratio for death in patients with diabetes overall was 1.47 (95% confidence intervals (CI) 1.35-1.61) and varied between 1.19 (CI 1.04-1.37) and 2.13 (CI 1.33-3.42) in the 2-year periods of follow-up.

Conclusions: Diabetes is an important independent long-term prognostic factor after MI and continues to predict mortality even 17 years after index MI.

This underscores the importance of aggressive diagnostic and therapeutic approach in diabetes patients with MI.

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RESEARCH ARTICLE Open Access

Renal function at the time of a myocardial infarction maintains prognostic value for more than 10 years

Thomas Kümler[1*], Gunnar H Gislason[2], Lars Kober[1], Finn Gustafsson[1], Morten Schou[3] and Christian Torp-Pedersen[2]

Abstract

Background: Renal function is an important predictor of mortality in patients with myocardial infarction (MI), but changes in the impact over time have not been well described.
We examined the importance of renal function by estimated GFR (eGFR) and se-creatinine as an independent long-term prognostic factor.

Methods: Prospective follow-up of 6653 consecutive MI patients screened for entry in the Trandolapril Cardiac Evaluation (TRACE) study. The patients were analysed by Kaplan-Meier survival analysis, landmark analysis and Cox proportional hazard models. Outcome measure was all-cause mortality.

Results: An eGFR below 60 ml per minute per 1.73 m^2, consistent with chronic renal disease, was present in 42% of the patients. We divided the patients into 4 groups according to eGFR. Overall, Cox proportional-hazards models showed that eGFR was a significant prognostic factor in the two groups with the lowest eGFR, hazard ratio 1,72 (confidence interval (CI) 1,56-1,91) in the group with the lowest eGFR. Using the eGFR group with normal renal function as reference, we observed an incremental rise in hazard ratio. We divided the follow-up period in 2-year intervals. Landmark analysis showed that eGFR at the time of screening continued to show prognostic effect until 16 years of follow-up. By multivariable Cox regression analysis, the prognostic effect of eGFR persisted for 12 years and of se-creatinine for 10 years. When comparing the lowest group of eGFR with the group with normal eGFR, prognostic significance was present in the entire period of follow-up with a hazard ratio between 1,97 (CI 1,65-2,35) and 1,35 (CI 0,99-1,84) in the 2-year periods.

Conclusions: One estimate of renal function is a strong and independent long-term prognostic factor for 10-12 years following a MI.

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