HEART FAILURE OUTCOMES

Jan C. van den Berge

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Colofon

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Heart Failure Outcomes

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CHAPTER 1

General introduction and outline of thesis

1

Heart failure (HF) is "a clinical syndrome characterized by typical symptoms that may be accompanied by signs caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress"[1]. HF can be caused by myocardial abnormalities or other causes including valve dysfunction, arrhythmias and pericarditis.[1] Numerous risk factors for the development of HF have been established.[2] Ischemic heart disease is the most common myocardial abnormality causing HF.[2] Toxin-mediated cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy, inflammatory cardiomyopathy and peripartum cardiomyopathy are frequent non-ischemic origins of systolic and/or diastolic myocardial dysfunction.[1]

Classification of HF cannot only be made based on the etiology but also in relation to the time course: acute versus chronic HF. Acute HF, in turn, is either new-onset HF or worsening of signs and symptoms of pre-existent, chronic HF. Acute HF mostly occurs after a cardiac (e.g. myocardial infarction, arrhythmia, acute valve insufficiency) or non-cardiac (e.g. hypertension, drug/diet non-adherence, pulmonary embolism or infection) trigger.[1] Once patients have had an episode of HF they will be considered chronic HF patients.

Furthermore, left ventricular function in terms of ejection fraction is a common measure to classify HF. Traditionally, the parameter divided HF into two categories: HF with reduced ejection fraction en HF with preserved ejection fraction. Since 2016, the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology has added a third category, namely HF with mid-range ejection fraction.[3]
It has been observed that a significant number of patients with HF with reduced ejection fraction may develop an improvement in their left ventricular ejection fraction (LVEF).[4, 5] Several factors were found to be associated with LVEF improvement,[6-9] such as female sex. The comorbidities hypertension and diabetes have also been correlated with LVEF improvement, especially upon treatment of the underlying condition. Furthermore, it has been observed that LVEF improvement was more common in patients with HF of non-ischaemic cause than in those with ischaemic HF. Also, HF medication was found to improve the LVEF.[4]

Since left ventricular remodeling and LVEEF improvement have been described, a new discussion on implantable cardioverter defibrillator (ICD) implantation for primary prevention in HF patients with poor left ventricular function is justified, especially since the relevant studies included patients about 20 years ago.[10-12] In that period, only few pharmacological treatment options were available. Nowadays, medical therapy has been improved and, as a result, the risk of ventricular tachycardia and fibrillation has decreased. Therefore, it is currently less cost-effective to implant an ICD for primary prevention than a few decades ago. The recommended cut-off value for preventive ICD implantation is currently still an LVEF <35%.[3] However, this might be criticized because the majority of the included patient in the so-called landmark trials had an LVEF <30% and were thus included in an era with less optimal pharmacological HF medication as

compared to the treatment patients receive nowadays.[10-12] The appropriateness of ICD implantation in patient with an LVEF between 30 and 35% may thus be questioned.

Epidemiology

Worldwide, HF is a major public health issue with a prevalence of 1 to 14% depending on definition and population characteristics.[2, 13] As a result of improved treatment of other cardiovascular diseases (especially ischemic heart disease and acute coronary syndrome), and giving an aging population and increasing prevalence of diabetes, obesity and atrial fibrillation, HF prevalence is expected to increase further in the next decades.[2, 14]

In the United States and Europe, HF is a leading cause of hospitalisation. HF-rehospitalization rates up to 27% within 30 days after initial hospitalization are not uncommon.[2] Since HF-rehospitalizations were found to be associated with increased mortality,[15, 16] such events are not innocent and negligible facts. Therefore, limiting the HF-rehospitalization rate should be a therapeutic goal. The 30-day mortality in patients with acute HF was found to be in the broad range of 4 and 30%.[17] Studies investigating long term mortality have reported 1-year mortality rates of 20-30%[18-21] and 5-year mortality rates of 45-75%[2, 22]. Indeed, HF patients have a poor prognosis. The prognosis of HF is at least as poor as that of several common cancers,[23, 24] a fact few people are aware of.
In addition to HF-rehospitalization,[15, 16] numerous other risk factors for mortality have been identified.[1, 25, 26] The demographic variables older age and male sex have been found to be associated with a worse prognosis. The presence of cardiovascular (including atrial fibrillation, peripheral artery disease and previous stroke) and non-cardiovascular (including diabetes, anemia, chronic obstructive pulmonary disease and depression) comorbidities are also associated with an impaired prognosis. Furthermore, patients with non-ischemic HF have a better prognosis than those with ischemic HF. Importantly, improvement in left ventricular function is also associated with improvement in prognosis.[25, 26] Several risk scores have been made in order to predict the prognosis of individual HF patients. However, these models were found to be only moderately useful in clinical practice.[25, 26]

During the last decades, HF treatment has seen major improvements. Other than diuretics and lifestyle interventions, no other HF treatment was available before the 1980s. Since that time, angiotensin converting enzyme inhibitors and beta-blockers have been introduced in the 1980s and 1990s. Later, mineralocorticoid receptor antagonists were added to the therapeutic options. More recently, ivabradine and angiotensin receptor neprilysin inhibitor have been shown to be effective as HF treatment. In addition to new medical therapeutic options, new devices have been developed and introduced. Not only ICDs and cardiac resynchronization therapy became available for HF treatment but also left ventricular assist devices are gaining ground in HF therapy.[27, 28]

This improvement in HF therapy has resulted in improved prognosis during the last decades.[22, 29, 30] However, above mentioned therapeutics were predominantly therapies

for chronic HF and have benefitted patients with chronic conditions. In contrast, hardly any therapeutic development for acute HF treatment has become available. Indeed, although much research has been invested in this topic, significant results have not been obtained.[31]

In addition to improvement in HF prognosis, optimal medical treatment also induces left ventricular remodeling.[4] This reverse remodeling was mainly found in patients with non-ischemic etiology of HF. Several other factors were also found to be associated with left ventricular remodeling like age, gender, diabetes and hypertension.[32]

Patient-reported outcomes

Traditionally, prognosis has been used as the main outcome measure in clinical HF trials. However, the use of patient-reported outcome has been advocated[33, 34] and is increasingly becoming a more important study endpoint, in addition to mortality and HF rehospitalization. 'Patient-reported outcomes' is a comprehensive term including a great variety of outcomes reported by patients themselves. For example health-related quality of life (HRQoL), symptom occurrence, symptom burden and physical limitation are relevant in this perpective.[33] Especially for HF patients with preserved LVEF, patient-reported outcome is an important parameter because there is limited prognostic benefit from current pharmacological treatment in this predominantly older population.[35] Since the majority of HF patients prefer quality of life above longevity per se,[36, 37] patient-reported outcomes are also important from a clinical perspective.

In addition to a poor prognosis, HF patients were also found to have an impaired HRQoL.[38] This HRQoL was not only worse than that of the general population but also worse than in patients with other chronic conditions.[39, 40] Factors influencing HRQoL become more and more clear and important. Age, sex, clinical status, presence of (non-) cardiac comorbidities but also socioeconomic status and symptom occurrence and symptom burden are determinants of HRQoL.[41-43] Overall, patient-reported outcomes are increasingly relevant topics in HF research but many questions remain.

Aims and outline of this thesis

This thesis has several aims: First, to study the impact of improved HF therapy on prognosis over time. In addition to short- and long-term mortality, also other end-points have been included. Furthermore, we investigated determinants of patient reported outcomes like HRQoL and symptom status. Lastly, we studied prediction models and associations in heart failure patients at a population level.

In the first part of this thesis, trends in mortality of patients admitted with acute HF are described. To this end, we used a prospective database of patients admitted to the (Intensive) Coronary Care Unit of the Erasmus Medical Center in the period of 1985 until 2008. The trends in mortality were also studied in several subgroups defined by

sex, diabetes mellitus status and presence or absence of kidney disease or anemia. Furthermore, the use of conditional survival versus the 'conventional' survival time is described in detail. We also studied reverse remodeling in patients with non-ischemic and ischemic HF based on data of a retrospective study among patients admitted with de novo HF. Lastly, this part includes a review in which the current selection criteria for ICDs in patient with HF are questioned.

The second part of this thesis is on patient reported outcomes. We studied whether there were differences in HRQoL between HF patients with and without the comorbidities chronic obstructive pulmonary disease, cerebrovascular accident, diabetes mellitus and chronic kidney disease. Second, we investigated the differences in symptom occurrence and symptom burden in HF patients with and without depression using data from the TRIUMPH study, a prospective, multicenter study enrolling acute HF patients.[44]

The last part of this thesis includes investigations based on data of the Rotterdam Study.[45] Therefore, this section is not based on data of patients, but of a selection of population based data. This allowed us to perform an analysis on prediction of HF events. To this end, we compared the relatively simple ACC/AHA risk score[46] with the more complex Health ABC model[47] and ARIC model[48]. Furthermore, we studied difference in risk factors for longitudinal changes in left ventricular diastolic function between men and women.

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PART I

Impact of improved heart failure therapy on left ventricular remodeling and prognosis

CHAPTER 2

Temporal trends in long-term mortality of patients with acute heart failure: Data from 1985-2008.

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Abstract

Background – Heart failure (HF) has a poor prognosis. Patients with acute heart failure in particular have a high risk of dying. However, there is a lack of data regarding their long-term mortality and changes there-in with time. The aim of our study was to describe trends in short- and long-term mortality of patients hospitalized with acute HF in the period from 1985 through 2008. In addition, we determined the prognostic worth of the aetiology of HF.

Methods and results – We included a consecutive series of 1810 patients with acute HF in this prospective registry in the period of 1985 through 2008. The cumulative one-year mortality rate of the patients was 35%. The short-term prognosis remained unchanged over the decades. However, the cumulative mortality rate ten years after admission was lowest in the last decade (73% in 2000-2008 vs. 78% in 1985-1999, p=0.001). After multivariable adjustment, the ten-year mortality rate was lower in the last decade as compared to the first decade (hazard ratio (HR) 0.83; 95% confidence interval (CI) 0.71-0.96). Ischemic cardiomyopathy was associated with a higher mortality (HR 1.32; 95% CI 1.12-1.54) when compared to other causes of HF.

Conclusions – Patients admitted with acute HF were found to have both high short-term and long-term mortality. Long-term prognostic improvement in the last decade was observed among patients with a reduced ejection fraction. While patients with HF due to valvular heart disease had the best prognosis, an ischemic aetiology of HF was associated with the worst outcome.

Introduction

Worldwide, heart failure (HF) is a major public health issue. Its prevalence is 2%, but since HF increases with age, the prevalence is much higher in the elderly.[1, 2] There are many different causes for HF,[3] but ischemic heart disease is the most common aetiology of HF.[1] Other frequent aetiologies include HF secondary to uncontrolled hypertension as well as to valvular heart disease.[4] The cause of HF is related to prognosis.[5]

Since the 2000s, several registries have investigated the short-term outcome in this population. In-hospital mortality rates range from 4% to 30%,[4] whereas one-year mortality rates are reported to be as high as 20% to 30%.[6-10] One study has even reported a one-year mortality rate of almost 50% in patients with acute HF admitted to the intensive care or cardiac care unit.[11] With respect to longer-term outcome, prognosis is even worse, and five-year mortality figures in the order of 45-75% have been published.[1, 12]

In the last decades, several advances in the treatment of HF have taken place. Amongst others, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and mineralocorticoid receptor antagonists (MRAs) have been introduced in clinical practice. [13-21] Furthermore, the increasing use of implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy in the last decades may also have contributed also to a better prognosis.[22-26] Nevertheless, despite these improvements in the management and treatment of HF, the condition is and remains one with high mortality. [1, 2, 27] Importantly, there is no data regarding the trends in ten-year mortality in patients hospitalized with acute HF. Therefore, the aim of our study was to describe the trends in short- and long-term mortality of patients hospitalized with acute HF in the period from 1985 through 2008. In addition, we determined the impact of the aetiology of HF on long-term mortality.

Methods

Inclusion

This prospective registry included all consecutive patients from 18 years and older admitted with acute HF to the Intensive Coronary Care Unit (ICCU) of the Erasmus Medical Centre. The inclusion period started on 1st January 1985 and ended on 31st December 2008. The Erasmus Medical Centre is a tertiary referral centre in the South-West of The Netherlands and the only referral centre for advanced HF with need for mechanical circulatory support or heart transplantation for almost half of The Netherlands. Following their initial hospitalization and treatment at our centre, most patients are subsequently transferred to a referring hospital after stabilization.

Patients were included when a diagnosis of acute HF or cardiogenic shock was made by the physician at admission. Both patients with a rapid, new onset of HF symptoms or

patients with worsening of symptoms of chronic HF were included. Patients admitted for acute HF caused by an acute coronary syndrome without evidence of sustained systolic or diastolic dysfunction were excluded. If patients were admitted for acute HF more than once during the study period, only the first admission was included.

Ethics statement

This was a prospective cohort registry. During the enrolment of the patients, approval from the local research ethics committee to conduct this study was not required. The study was conducted according to the Helsinki Declaration.[28]

Baseline variables

The baseline variables were extracted from the patient records or discharge letters. Only the variables until discharge from the ICCU were available as most patients are routinely transferred to a referring non-tertiary hospital after stabilization. The demographic variables age and gender were collected. The following clinical variables were also collected: prior myocardial infarction, coronary revascularization (coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)), cardiac surgery other than CABG, heart transplantation or waiting for heart transplantation, rhythm or conduction disturbance, previous HF, hypertension and diabetes), aetiology of the HF, Body Mass Index (BMI), left ventricular ejection fraction (LVEF) and heart rate at moment of admission. Furthermore, the treatment at the ICCU was registered.

Diabetes mellitus was considered to be present when patients received antidiabetic therapy. The LVEF was classified into the following qualitative categories: good, moderate and poor. If quantitative outcome for the LVEF was used, we applied the following cut-offs: ≥45%, 30-44% and <30% for good, moderate and poor LVEF, respectively. The aetiology of HF was categorized into four groups: ischemic cardiomyopathy, non-ischemic cardiomyopathy, cardiac dysfunction due to valvular heart disease, and other/unknown aetiology. The non-ischemic cardiomyopathy group included patients with hypertensive cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy, immune-mediated cardiomyopathy, toxic cardiomyopathy, endocrine/nutritional cardiomyopathy, and peripartum cardiomyopathy.

End-point

The primary study endpoint was of all-cause mortality at one and ten years. Heart transplantation and implantation of a left ventricular assist device (LVAD) should be considered as equivalent to death.

Survival status was obtained from the Municipal Civil Registries in January 2016. The survival status was available for 98% of all included patients.

Statistical analysis

The population was divided into the following time periods: 1985-1989, 1990-1999 and 2000-2008. Categorized variables are presented as frequencies and percentages. Continuous variables are presented as mean values and standard deviation. The categorized variables were compared with the χ^2 test or the Fisher-Freeman-Halton exact test. The continuous variables were compared by using one-way ANOVA.

Data for LVEF was not complete in 28% of the patients: 51% missing in the 1980s, 23% in the 1990s and 18% in the 2000s. Therefore, multiple imputation was applied using baseline characteristics as predictors. Pooled means were given for LVEF.

Cumulative mortality curves are presented by the Kaplan-Meier method. For comparing the mortality curves, the log-rank test was used. As a secondary analysis, landmark analyses were performed for the 30-day survivors. The Cox proportional hazard model was used for comparing ten-year mortality rates, adjusted for period of admission, age, gender, history of HF, prior rhythm- or conduction disorder, diabetes in history, aetiology of HF and LVEF.

All tests were two-tailed and p-values <0.05 were considered statistically significant. Results of the Cox proportional hazard model were reported in hazard ratios (HRs) with their corresponding 95% confidence interval (95% CI). All data were analysed using SPSS software (SPSS 21.0, IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

In total, 1810 patients were included, all hospitalized for acute HF in the period between 1985 and 2008. Over these periods, their baseline characteristics slightly changed (Table 1). Over time, the mean age remained stable although the percentage of patients older than 75 years increased. In addition, the proportion of male patients decreased, although male sex still represented the majority in each decade. Also, with time, patients less often had a history of prior myocardial infarction. Still, they were more likely to have undergone coronary revascularization, and to have rhythm- or conduction disorders, hypertension and diabetes mellitus. The aetiology of HF changed over time: the number of patients with ischemic cardiomyopathy decreased, while the number of patients with a non-ischemic cardiomyopathy increased. Valvular heart disease became a less common cause of HF. The distribution of LVEF did not change over time.

Table 1. Baseline characteristics

	1985-1989	1990-1999	2000-2008	p-value
No. of patients	389	842	579	
Baseline				
Age (mean, y)	62±13	64±15	64±15	0.24
Age categories				0.008
18-54 years	100 (26%)	209 (25%)	142 (25%)	
55-64 years	102 (26%)	170 (20%)	127 (22%)	
65-74 years	129 (33%)	258 (31%)	171 (30%)	
75 years and older	58 (15%)	205 (24%)	139 (24%)	
Male	273 (70%)	510 (61%)	370 (64%)	0.005
BMI	24±5.2	25±4.4	26±5.4	0.01
Medical history				
Myocardial infarction	185 (48%)	332 (39%)	197 (34%)	<0.001
Coronary revascularization*	78 (20%)	150 (18%)	162 (28%)	<0.001
Heart surgery (not CAGB)	52 (13%)	103 (12%)	82 (14%)	0.56
Heart transplantation	1 (0.3%)	5 (0.6%)	3 (0.5%)	0.83
Waiting for heart transplantation	9 (2%)	14 (2%)	12 (2%)	0.68
Heart failure	188 (48%)	403 (48%)	297 (51%)	0.42
Rhythm- or conduction disorder	90 (23%)	183 (22%)	173 (30%)	0.001
Hypertension	91 (23%)	275 (33%)	224 (39%)	<0.001
Diabetes	56 (14%)	174 (21%)	154 (27%)	<0.001
Heart failure				
Aetiology of heart failure				0.02
Ischemic cardiomyopathy	171 (44%)	332 (39%)	237 (41%)	
Non-ischemic cardiomyopathy	61 (16%)	198 (24%)	143 (25%)	
Valvular heart disease	91 (23%)	178 (21%)	101 (17%)	
Other/unknown	66 (17%)	134 (16%)	98 (17%)	
Atrial fibrillation at admission	79 (20%)	181 (22%)	131 (23%)	0.69
Left ventricular ejection fraction				NS
Good	112 (29%)	255 (30%)	159 (27%)	
Moderate	83 (21%)	208 (25%)	139 (24%)	
Poor	195 (50%)	379 (45%)	281 (49%)	

The median length of stay at the ICCU was 2 days (interquartile range: 1 to 4 days) and did not differ between the three decades (p=0.28). The heart rate at admission was 106±26 beats per minute and was similar in all periods (p=0.68). Therapy during ICCU hospitalization changed over time (Table 2). For instance, more patients received mechanical ventilation in the most recent decade. In the period 1990-1999, inotropic drugs and nitrates were more often prescribed than in the other decades, while the use of mechanical circulatory support increased. The use of beta-blockers and ACE-inhibitors or angiotensin receptor blockers (ARBs) increased over time, while therapy with digitalis decreased.

Table 2. Therapy during ICCU hospitalization

	1985-1989	1990-1999	2000-2008	p-value
Intubation	29 (8%)	104 (12%)	114 (20%)	<0.001
Resuscitation	18 (5%)	36 (4%)	18 (3%)	0.41
Mechanical circulatory support*	12 (3%)	56 (7%)	37 (6%)	0.04
Inotropics	103 (27%)	306 (36%)	170 (29%)	0.001
Beta-blocker	17 (4%)	94 (11%)	195 (34%)	<0.001
Antiarrhythmics	58 (15%)	128 (15%)	131 (23%)	<0.001
Calcium antagonist	76 (20%)	128 (15%)	57 (10%)	<0.001
Digitalis	213 (55%)	383 (46%)	146 (25%)	<0.001
ACE-inhibitor or ARB	136 (35%)	456 (54%)	377 (65%)	<0.001
Diuretics	361 (93%)	746 (89%)	527 (91%)	0.05
Nitrates	87 (22%)	375 (45%)	183 (32%)	<0.001
Nitroprusside	71 (18%)	81 (10%)	9 (2%)	<0.001
Antiplatelet agents	27 (7%)	176 (21%)	266 (46%)	<0.001
Oral anticoagulant	227 (58%)	469 (56%)	206 (36%)	<0.001

Mortality over time

During the whole follow-up time, 1555 (86%) patients reached the primary endpoint: 1474 (81%) patients died, 77 (4%) patients underwent heart transplantation and 4 (0.2%) LVAD implantation. The cumulative mortality rate at one and ten years was 35% and 76%, respectively. The ten-year cumulative mortality curve of the three periods is depicted in *Figure 1*. Early mortality rates at 30 days and 1 year after admission were similar in all decades. In contrast, the cumulative mortality rate ten years after admission was lowest in the last decade (73% in 2000-2008 vs. 78% in the combined period 1985-1999, p=0.001). After multivariable adjustment, ten-year mortality was significantly lower in the last decade as compared to the first decade (adjusted HR 0.83; 95% CI 0.71-0.96). No difference in the mortality was found between the first and the second decade (adjusted HR 1.00; 95% CI 0.87-1.15). (Table 3)

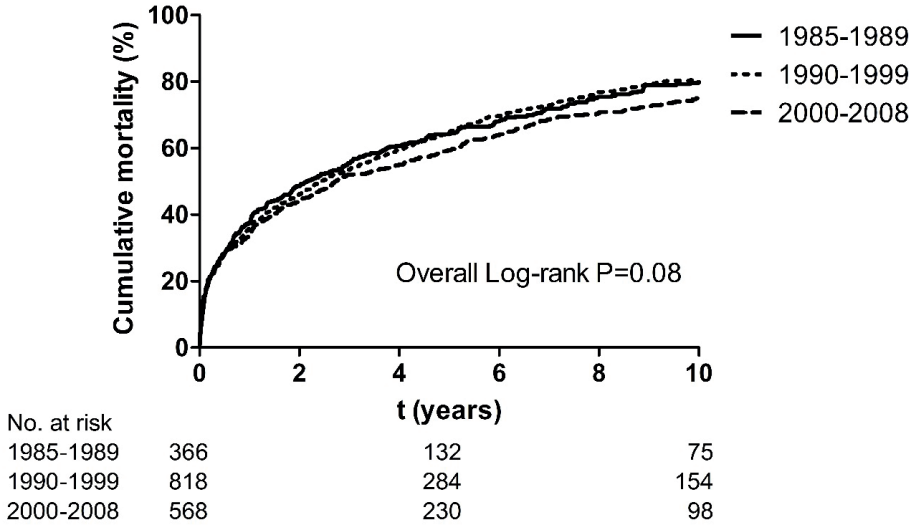


Figure 1. Kaplan-Meier curve total population

Table 3. Univariable and multivariable adjusted associating factors for primary outcome at 10-year follow-up

	Univariable	Multivariable
Admission period		
1985-1990	Reference	Reference
1990-2000	1.02 (0.89-1.16)	1.02 (0.88-1.17)
2000-2008	0.89 (0.76-1.03)	0.83 (0.71-0.97)
Age	1.016 (1.012-1.020)	-
Age categorical		
18-54 years	Reference	Reference
55-64 years	1.25 (1.07-1.48)	1.24 (1.05-1.46)
65-74 years	1.38 (1.19-1.61)	1.37 (1.17-1.60)
75 years and older	1.81 (1.54-2.12)	2.00 (1.69-2.36)
Male gender	1.26 (1.13-1.41)	1.23 (1.10-1.38)
Medical history		
Myocardial infarction	1.35 (1.21-1.50)	-
Coronary revascularisation*	1.05 (0.92-1.19)	-
Heart surgery (not CAGB)	0.90 (0.77-1.06)	-
Heart transplantation	4.48 (2.32-8.65)	-
Waiting for heart transplantation	2.50 (1.75-3.56)	-
Heart failure	1.71 (1.54-1.90)	1.66 (1.48-1.86)
Rhythm- or conduction disorder	1.24 (1.10-1.40)	1.05 (0.92-1.19)
Hypertension	0.98 (0.88-1.10)	-

	Univariable	Multivariable
Diabetes	1.20 (1.06-1.36)	1.16 (1.02-1.32)
Aetiology of heart failure		
Ischemic cardiomyopathy	Reference	Reference
Non-ischemic cardiomyopathy	0.80 (0.69-0.92)	0.98 (0.85-1.14)
Valvular heart disease	0.65 (0.56-0.75)	0.81 (0.69-0.95)
Other/unknown	0.86 (0.74-0.996)	1.02 (0.87-1.19)
Atrial fibrillation at admission	1.00 (0.88-1.13)	-
Left ventricular ejection fraction		
Good	Reference	Reference
Moderate	1.06 (0.89-1.28)	0.99 (0.80-1.22)
Poor	1.55 (1.33-1.81)	1.39 (1.16-1.66)

Results given in hazard ratio with corresponding 95% confidence interval. Dark cells indicate significant results
CABG, coronary artery bypass graft; *Percutaneous coronary intervention and/or CABG

When the analysis was restricted to the 30-day survivors, more pronounced differences in long-term mortality between the last decade and the other two decades became apparent (Figure 2). The cumulative mortality after ten years was lower in the period 2000-2008 than in the period 1985-1999 (69% vs. 77%, p=0.004). After adjustment for baseline characteristics, the adjusted ten-year mortality rate was also significantly lower in the last decade than in the first decade (adjusted HR 0.72; 95% CI 0.61-0.87) in the 30-day survivors.

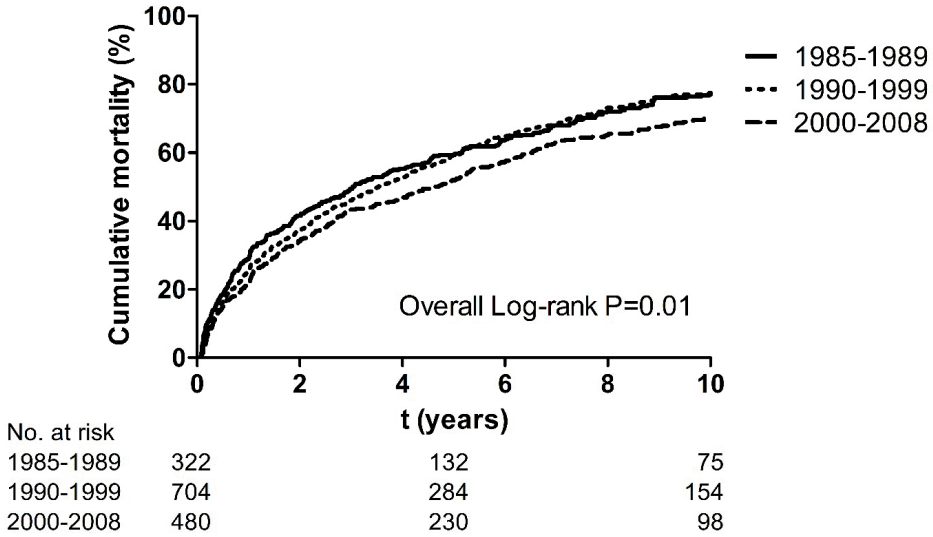
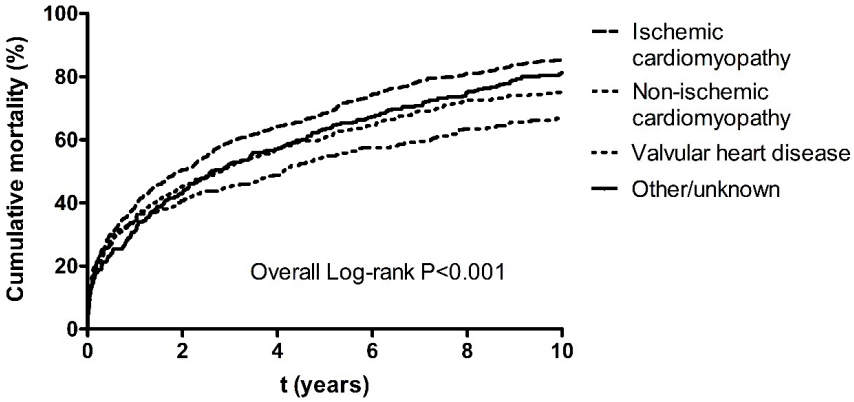


Figure 2. Kaplan-Meier curve 30-day survivors

Furthermore, we analysed the mortality over time among patients with preserved LVEF (LVEF≥45%) and those with a reduced LVEF (LVEF<45%). The ten-year mortality of the patients with a preserved LVEF was not different in the last decade as compared to the first decade (adjusted HR 0.95; 95% CI 0.70-1.29). However, the ten-year prognosis of the patients with a reduced LVEF improved in the last decade (adjusted HR 0.81; 95% CI 0.68-0.95).

Aetiology and mortality

The survival curves of all patients according to the four groups categorized on the basis of the aetiology of HF are shown in *Figure 3*. Patients with an ischemic cause of HF were found to have the worst prognosis. Patients with a non-ischemic cardiomyopathy and with HF due to valvular heart disease had the lowest mortality rates.



No. at risk			
Ischemic cardiomyopathy	712	225	96
Non-ischemic cardiomyopathy	389	152	77
Valvular heart disease	360	162	109
Other/unknown	291	108	46

Figure 3. Kaplan-Meier curve split up in etiology

After univariable adjustment, ischemic cardiomyopathy was found to have the worst prognosis, compared to all other aetiologies. After multivariable adjustment, ischemic cardiomyopathy was associated with a higher mortality (adjusted HR 1.32; 95% CI 1.12-1.54) only when compared to HF due to valvular heart disease (Table 3).

Other clinical parameters independently associated with a poor outcome in multivariable analysis were advanced age (per one year increase HR 1.018; 95% CI 1.014-1.023), male sex (HR 1.23; 95% CI 1.10-1.38), previous heart failure (HR 1.66; 95% CI 1.48-1.86), diabetes (HR 1.16; 95% CI 1.02-1.32) and poor LVEF (HR 1.39; 95% CI 1.16-1.66).

Discussion

In this study of patients hospitalized with acute HF, we found high mortality rates, both for the short-term and the long-term. Within a period of ten years after their initial hospitalization, approximately three-quarter of the patients had died. Although the long-term prognosis of the studied patients was poor in all three decades, an improvement in outcome was observed in the most recent decade. Compared to those hospitalized in the 1980s and 1990s, patients admitted in the last decade had a significantly lower ten-year mortality. Importantly, the improved prognosis was found in the patients with a reduced LVEF and not in those with a preserved LVEF. No difference in long-term mortality was found between the first two decades. When we analysed the prognosis of the 30-day survivors, a more pronounced ten-year mortality benefit of the patients admitted in the last decade could be established. Importantly, no change was observed in short-term mortality between the last three decades, with identical one-year mortality rates in the order of 35%.

An additional aim of this study was to determine the influence of the aetiology of HF on long-term mortality. The conclusion from our data is that, relative to other causes of HF, acute HF based on ischemic heart disease carried the worst prognosis, both with respect to the short and the long term. This remained significant after multivariable adjustment and, compared to valvular heart disease, the presence of ischemic cardiomyopathy remained associated with the highest mortality.

Importantly, the characteristics of the patients changed during the course of our study. The number of patients of 75 years and older increased, although the mean age did not change. Moreover, the percentage of women increased, and fewer patients experienced a previous myocardial infarction. Nevertheless, the number of patients who had previously undergone coronary revascularization increased. There was some decrease in the number of patients with HF based on ischemic heart disease. These findings are consistent with a lower incidence of myocardial infarction and a more contemporary management of coronary artery disease in the last study period. The number of patients with valvular heart disease decreased over time, while non-ischemic cardiomyopathy as an aetiology of acute HF was found to have increased in the last decades.

Since short-term mortality rates were identical, the observed mortality benefit in the last decade was most likely due to therapeutic improvements initiated after hospital discharge. Treatment with beta-blockers as well as ACE inhibitors has been shown to reduce mortality in patients with HF.[13-20] In accordance with the implementation and subsequent application of these new drugs in clinical practice, treatment with both drugs in our study increased over time. Although we were unable to establish which medication our patients were using following their hospitalization, we found increased use of ACE-inhibitors and beta-blockers already during the course of their hospitalization. It is reasonable to assume that such treatment was continued in patients on these drugs or was initiated in those not already taking these drugs. Since it takes time to titrate patients to the optimal dose of ACE-inhibitors and beta-blockers[29], the optimal treatment period would most likely have been reached during the course of follow-up.

Furthermore, ICDs have been found to induce a survival benefit when using for primary or secondary prevention in patients with HF.[22, 23] Since the new therapeutic options have shown their efficacy in HF with a reduced LVEF, the decline in mortality rate in the last decade among patients with a reduced LVEF corresponds well with the development of these new treatment modalities. Therefore, the lower long-term mortality that we observed in patients hospitalized in the last decade most likely was not related to an improved treatment in the acute phase, but rather a combination of better medical and device treatment in the follow-up period after hospital discharge.

Our study is the first to report ten-year mortality rates of patients hospitalized with acute HF. The longest follow-up time reported in the literature is only five years.[8, 12, 30, 31] Our results extend various previous findings. The finding that patients with HF based on ischemic heart disease have the worst outcome is in agreement with results from other studies. [5, 12, 32] The one-year mortality rate of about 35% in our study is relatively high compared to other publications that reported one-year mortality rates between 20% and 30%.[6-10] The fact that the current analysis was done in a tertiary referral ICCU population is a plausible explanation. Selection bias might have occurred due to admission of a more selected population of patients with severe and advanced acute HF. However, our one-year mortality rate was lower than reported in another study performed at an ICCU in France.[11] The high mortality rate in that study was most likely related to the high number of patients with cardiogenic shock. In addition, compared to our study, more respiratory support and positive inotropic drugs were used. We observed no clear temporal trend in improved outcome at one, three or five years of follow-up like other studies.[12, 30-34] This was also true when we limited the analysis to the 30-day survivors as suggested by others.[12, 31-33] The improvement in mortality rate that we observed was not as pronounced as in other studies.[12, 30-33] This might be due to the character of our patients and centre: a tertiary referral hospital as ours is most likely to recruit the most critical ill patients. The fact that our study population comprised patients who were much younger, who had less diabetes and hypertension and who were more men than in other studies,[4, 8, 12, 30-33] supports the specific nature of our study participants. In line with this, our patients were more often treated with inotropics, mechanical circulatory support and mechanical ventilation.[4, 8] The fact that our patients were relatively young, and had less co-morbidity tan the elderly patients with HF, strengthens the finding that acute HF on its own carries such a poor prognosis.

The finding that the prognosis improved among the patients with a reduced LVEF (and not among those with a preserved LVEF) is consistent with findings from Cole et al.[34]

While this study had unique strengths, some limitations deserve to be mentioned. We registered all-cause mortality, heart transplantation and LVAD implantation during follow-up, and other outcome measures or interventions were not collected. In addition, we were unable to consider the therapeutic regimen following the discharge of our patients from the ICCU. However, given the nature of our observational study, these parameters might be of little additive value.

In conclusion, patients admitted with acute HF were found to have both high short-term and long-term mortality. A temporal trend in improvement of one-year mortality could not be established. However, an improvement in long-term prognosis was observed with significant lower ten-year mortality rates in the last decade. This prognostic improvement was only found in patients with a reduced LVEF and not in those with a preserved LVEF. While patients with HF due to valvular heart disease had the best prognosis, an ischemic aetiology of HF was associated with the worst prognosis. Our findings thus underscore the very poor long-term prognosis of patients with acute HF who require admission to an ICCU, and underscore the need for measures to prevent acute HF to develop, as well as to improve treatment of patients admitted with acute HF, especially for those with preserved LVEF.

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CHAPTER 3

Trends in long-term mortality in women compared to men with acute heart failure between 1985 and 2008

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Submitted

Abstract

Background: There are limited and inconsistent data regarding sex-related long-term mortality in patients with acute heart failure.

Objectives: To determine the sex-related short- and long-term prognosis in relation to etiology and left ventricular ejection fraction, and further, to investigate whether the temporal trends in prognosis over time were comparable in men and women.

Methods: This prospective registry includes all patients admitted with acute heart failure in the period of 1985 through 2008.

Results: We included 1810 patients (36% women). Women had lower event rates than men at both one- (30% vs. 38%) and ten-year follow-up (72% vs. 79%). The prognostic advantage in women was found in both ischemic and non-ischemic HF. The long-term mortality among patients with preserved left ventricular ejection fraction was identical in both sexes (HR 0.95; 95% CI 0.77-1.18), while the event rate was lower in women among those with a reduced left ventricular ejection fraction (HR 0.75; 95% CI 0.65-0.87). The prognostic improvement in the last decade was in the same order of magnitude in men (HR 0.85; 95% CI 0.74-0.98) and women (HR 0.87; 95% CI 0.71-1.06).

Conclusions: Women admitted with acute heart failure had better short- and long-term prognosis. Although the prognosis of acute heart failure was poor, an improvement in long-term prognosis was found that was identical in women and men. This suggests that both sexes had a comparable survival benefit from the new developed therapies, however there is still need for new therapeutic options in both men and women with acute heart failure.

Introduction

Heart failure (HF) is a clinical syndrome with a high incidence and prevalence and an increasing burden to the health-care system.(1) Both men and women are almost equally affected. However, the sex-related distribution of HF patients is age dependent: while men are more often affected with HF until the age of 80 years, octogenarian patients with HF are more likely to be females.(2)

It has been reported that male and female patients with HF have different clinical characteristics. Female HF patients are generally older, have more comorbidities like hypertension and diabetes, and more often have HF with preserved left ventricular ejection fraction (LVEF). In contrast, male patients with HF more often have a history of ischemic heart disease with a reduced LVEF.(3) Accordingly, the etiology of HF is not identical among men and women. While ischemic heart disease is the most common cause of HF in male patients, valvular heart disease and hypertension are the more common etiologies in female patients with HF.(3, 4)

Although the sex-related mortality has received considerable attention in *chronic* HF, the sex issue in *acute* HF remains controversial. Most studies have consistently reported comparable in-hospital mortality rates in men and women,(5-8) but the sex-specific longer-term outcome is still a matter of debate. Some studies reported equal long-term mortality rates between men and women with acute HF,(5, 9, 10) but others found that male sex was associated with an adverse long-term outcome.(11, 12) Furthermore, it has been suggested that both the short- and the long-term prognosis of acute HF have improved over the last decades both for men and women,(13-16) but with a lower magnitude of survival benefit over time in female patients in Swedish and Australian cohorts.(13, 16)

Given the limited and inconsistent data regarding sex-related long-term outcome in patients with acute HF, we undertook the current study with the following aims: to determine the sex-related short-term and long-term prognosis in relation to the etiology of HF and the left ventricular function, and further, to investigate whether the temporal trends in prognosis over the last few decades are comparable in men and women.

Methods

Patients

The study design and population has been described previously.(17) In brief, between January 1985 and December 2008, all consecutive patients aged 18 years and older admitted with acute HF at the (Intensive) Coronary Care Unit ([I]CCU) of the Erasmus Medical Centre were included in this prospective registry. Patients admitted at the (I) CCU comprised both patients who were admitted at our Intensive Care Unit and those admitted at our Coronary Care Unit. Our hospital is a tertiary referral center. As a

consequence, most patients were transferred to a referring hospital within a few days after their initial treatment.

Patients were included when the diagnosis at admission was acute HF. Acute HF was defined as new onset of HF symptoms or worsening of the symptoms of chronic HF. In patients who were admitted more than once during the inclusion period, only the first admission was used for the analysis.

This was a prospective cohort registry. During the enrolment of the patients, approval from the local research ethics committee to conduct this study was not required. The study was conducted according to the Declaration of Helsinki.(18)

Data collection

The demographic and clinical variables were collected from discharge letters and patient records. For most of the patients, only the variables until discharge from the (I)CCU were available. The clinical variables included medical history, Body Mass Index, heart rate at admission, LVEF, etiology of HF and therapy at the (I)CCU.

Diabetes mellitus was considered to be present when patients received antidiabetic therapy. The LVEF was classified into the following qualitative categories: good, moderate and poor. If quantitative outcome for the LVEF was used, the following cut-offs were applied: ≥45%, 30-44% and <30% for good, moderate and poor LVEF, respectively. A preserved ejection fraction was defined as good LVEF (≥45%), a reduced ejection fraction as a moderate (30-44%) or poor (<30%) LVEF. The etiology of HF was categorized into two groups: HF based on ischemic heart disease and HF with a non-ischemic origin.

Endpoint

The main outcome measure comprised the composite endpoint of all-cause mortality, heart transplantation and implantation of a left ventricular assist device at one and ten years.

The survival status was acquired in January 2016 by use of the Municipal Civil Registries and was available for 98% of the patients.

Statistical analysis

The included patients were divided into three categories: 1985-1989, 1990-1999 and 2000-2008. Continuous variables were presented as mean with standard deviation. They were compared by using Student's t-test or ANOVA. Categorized variables were given in frequencies and percentages. The χ^2 test was used for comparing categorized variables. Data for LVEF and etiology was not complete in 28% and 12% of the patients, respectively. Therefore, multiple imputation was applied using baseline characteristics as predictors. Pooled means were given for LVEF and etiology.

Cumulative event rate was estimated according to the Kaplan-Meier method. The overall log-rank test was used for comparing the survival curves. Cox proportional hazard models were used for estimating the association between sex and prognosis at one- and ten-year follow-up. In multivariable analyses was adjusted for the baseline variables that were significant predictors of outcome in univariable analyses including age, admission period, etiology of HF, LVEF, as well as a history of HF, myocardial infarction, heart surgery (not coronary artery bypass graft), rhythm- or conduction disorders, diabetes and hypertension. All variables were categorical except for age, which was analyzed as a continuous variable.

All tests were two-tailed and p-values <0.05 were considered statistically significant. Results of the Cox proportional hazard model were reported in hazard ratios (HRs) with their corresponding 95% confidence interval (95% CI). All data were analyzed using SPSS software (SPSS 21.0, IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

In total, we included 1810 patients with acute HF, of whom 657 (36%) were women and 1153 (64%) men. The baseline characteristics of men and women differed considerably (Table 1). Women were older and had a different medical history than men. Men more frequently had an ischemic origin of HF while women mostly suffered from a non-ischemic cause of HF. While men were more likely to have a poor LVEF, women more often had preserved LVEF. These sex-specific differences in baseline characteristics were present in all three decades.

Table 1. Baseline characteristics by sex

	Women	**Men**	**p-value**
No. of patients	657	1153	
Baseline			
Age (mean, y)	65 ± 15	62 ± 14	<0.001
BMI	26 ± 6	24 ± 4	<0.001
Admission period			0.01
1985-1989	116 (18%)	273 (24%)	
1990-1999	332 (51%)	510 (44%)	
2000-2008	209 (32%)	370 (32%)	
Medical history			
Myocardial infarction	192 (29%)	522 (45%)	<0.001
Coronary revascularization*	104 (16%)	286 (25%)	<0.001

	Women	Men	p-value
Heart surgery (not CABG)	102 (16%)	135 (12%)	0.02
Heart transplantation	3 (0.5%)	6 (0.5%)	1.00
Waiting for heart transplantation	4 (0.6%)	31 (3%)	0.001
Heart failure	283 (43%)	605 (53%)	<0.001
Rhythm- or conduction disorder	146 (22%)	299 (26%)	0.08
Diabetes	161 (25%)	223 (19%)	0.01
Hypertension	261 (40%)	329 (29%)	<0.001
Heart failure			
Etiology of heart failure			<0.001
Ischemic origin	233 (35%)	583 (51%)	
Non-ischemic origin	424 (65%)	570 (49%)	
Atrial fibrillation at admission	154 (23%)	237 (21%)	0.15
Left ventricular ejection fraction			<0.001
Good	268 (41%)	283 (25%)	
Moderate	177 (27%)	264 (23%)	
Poor	212 (32%)	606 (53%)	
Therapy during (I)CCU hospitalization			
Intubation	73 (11%)	174 (15%)	0.02
Resuscitation	25 (4%)	47 (4%)	0.78
Mechanical circulatory support†	21 (3%)	84 (7%)	<0.001
Inotropics	175 (27%)	404 (35%)	<0.001
Beta-blocker	126 (19%)	180 (16%)	0.05
Antiarrhythmics	84 (13%)	233 (20%)	<0.001
Calcium antagonist	100 (15%)	161 (14%)	0.46
Digitalis	256 (39%)	486 (42%)	0.19
ACE-inhibitor or ARB	346 (53%)	623 (54%)	0.57
Diuretics	600 (91%)	1034 (90%)	0.26
Nitrates	249 (38%)	396 (34%)	0.13
Nitroprusside	65 (10%)	96 (8%)	0.26
Antiplatelet agents	174 (27%)	295 (26%)	0.68
Oral anticoagulant	318 (48%)	584 (51%)	0.36

ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blocker; BMI, Body Mass Index; CABG, coronary artery bypass graft; (I)CCU, (intensive) cardiac care unit; *Percutaneous coronary intervention and/or CABG †Intra-aortic balloon pump and/or left ventricular assist device and/or extracorporeal membrane oxygenation

Over time, we observed a trend towards a higher prevalence of hypertension and diabetes in women. In both men and women, the distribution of etiology and LVEF was almost stable over time (Supplemental Table 1).

Regarding therapy during admission at the (I)CCU, men more often received mechanical ventilation, mechanical circulatory support and inotropic drug therapy than women (Table 1). There was no difference between men and women with regard to the prescription of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers. Over time, comparable trends in therapy were observed in men and women (Supplemental Table 2).

Sex-specific outcome

During a follow-up period up to 30 years, a total of 551 (84%) women and 1004 (87%) men reached the composite end-point of all-cause mortality, heart transplantation and implantation of a left ventricular assist device. Women had a significantly lower cumulative event rate, both at short- and at long-term (Figure 1). The one-year event rate in women was lower than in men (30% versus 38%; unadjusted HR 0.74; 95% CI 0.63-0.88; p=0.001) and this difference persisted after multivariable adjustment (adjusted HR 0.85; 95% CI 0.71-1.01; p=0.07).

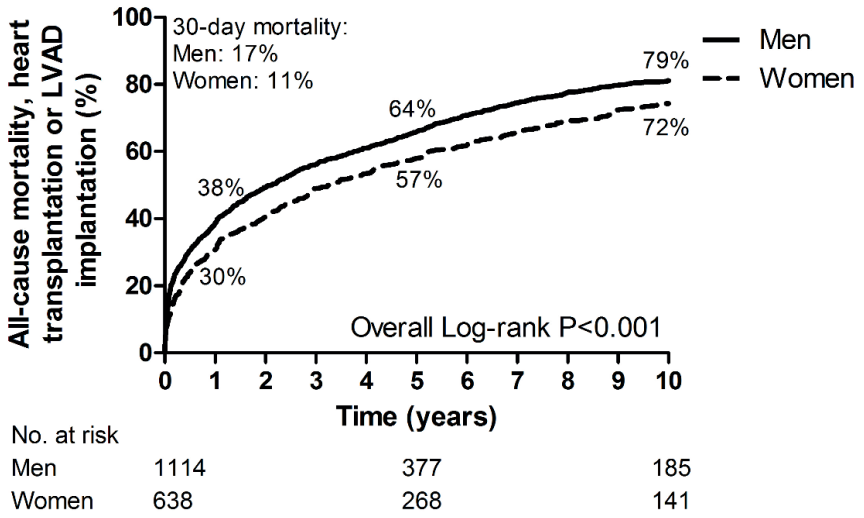

Figure 1. Kaplan-Meier curve of cumulative mortality: women vs. men

Similarly, at ten-year follow-up, women remained at lower risk for reaching the composite end-point than men (72% versus 79%; unadjusted HR 0.79; 95% CI 0.71-0.89; p<0.001). After multivariable adjustment, the association between female sex and better outcome at ten years remained statistically significant (adjusted HR 0.75; 95% CI 0.65-0.85;

p<0.001). The decreased event rate in women was independent of the etiology of HF (i.e. ischemic versus non-ischemic origin, Figure 2). Regarding the left ventricular function, no statistically significant difference in prognosis was found between men and women with HF with preserved ejection fraction (HR 0.95; 95% CI 0.77-1.18; p=0.65). Contrary, the long-term prognosis among patients with a reduced LVEF was significantly lower in women than in men (HR 0.75; 95% CI 0.65-0.87; p<0.001; Figure 2).

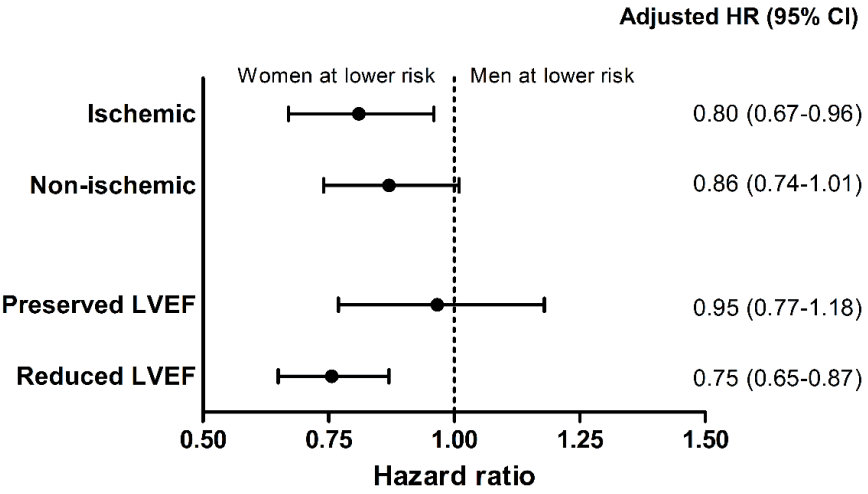

Figure 2. Multivariable adjusted mortality risk at ten years of women vs. men with acute heart failure (HF) by etiology and left ventricular ejection fraction.
CI, confidence interval; HR, Hazard ratio; LVEF, left ventricular ejection fraction

Trends in prognosis

There was no significant difference in short- and long-term prognosis between patients admitted in the 1990s as compared to those admitted in the 1980s, both among men and women (adjusted HR 1.05 [95% CI 0.89-1.25] and adjusted HR 1.06 [95% CI 0.83-1.37], respectively). Therefore, for the purpose of comparison to the outcome of patients admitted in the third decade, patients admitted in the first and second decade were pooled into one group, also reflecting the introduction of novel HF treatment as standard care in the period 2000-2008. With respect to short-term follow-up (i.e. one year), no temporal trend in prognosis was present in both men and women over the three decades.

Compared to the first two decades, men admitted in the last period had a lower event rate at ten-year follow-up (adjusted HR 0.85; 95% CI 0.74-0.98; p=0.03 Figure 3). This difference was more pronounced when only the 30-day survivors were included in the analysis (adjusted HR 0.79; 95% CI 0.68-0.93; p=0.01). The same temporal trend was found in women, both in the total population (adjusted HR 0.87; 95% CI 0.71-1.06; p=0.18) as well as in the 30-day survivors (adjusted HR 0.83 95% CI 0.67-1.04; p=0.11).The temporal trend in prognosis was comparable between men and women (p for interaction = 0.77).

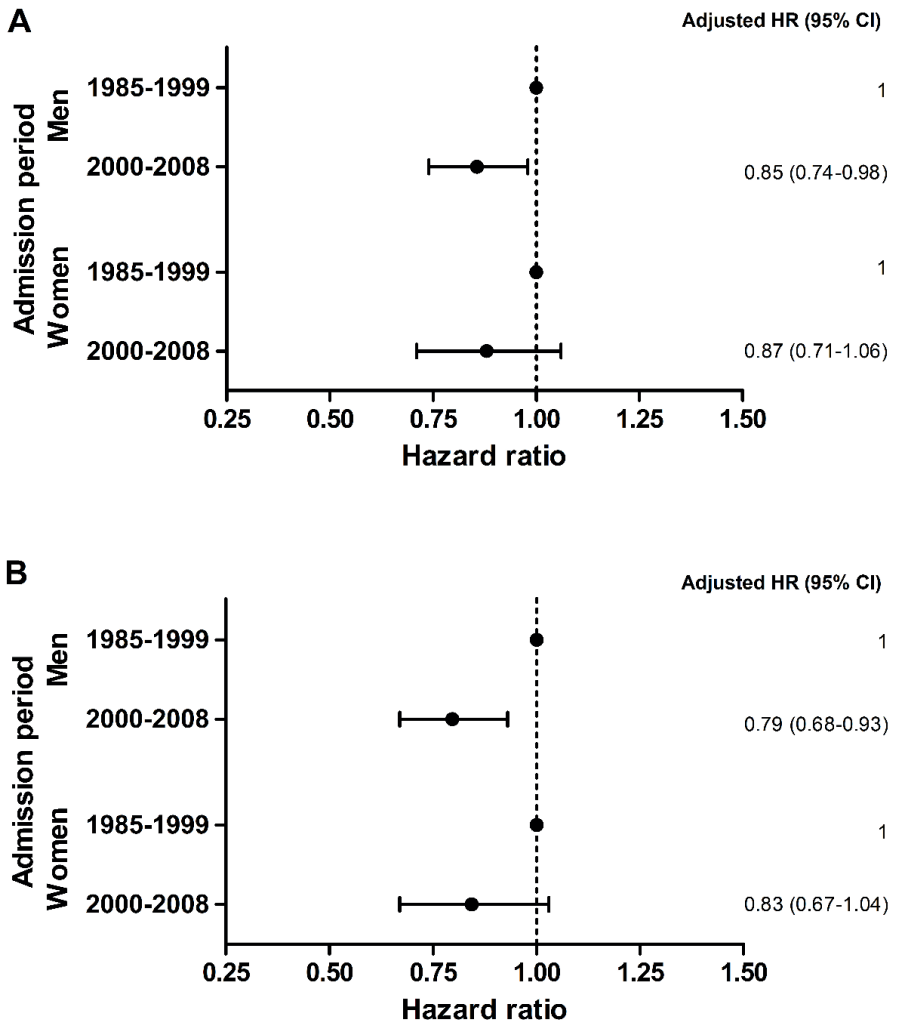

Figure 3. Temporal trends in multivariable adjusted, ten-year mortality of acute heart failure (HF) by sex in (**A**) the total population and (**B**) the 30-day survivors.
CI, confidence interval; HR, Hazard ratio

Discussion

In this study of patients admitted with acute HF during a period of 24 years, we found that women, as compared to men, had the best prognosis in the short-term as well as in the long-term. The better prognosis of women was most pronounced in the patients with a reduced LVEF. Importantly, this study is the first to show that the improvement in long-term prognosis improved equally in both men and women.

Findings of our study confirmed that, compared to men, women were on average older, were less likely to have a history of myocardial infarction or coronary revascularization, and had more diabetes and hypertension. In addition, women less commonly had an ischemic origin of HF and they had less HF with a reduced LVEF. These sex differences correspond with results previously presented in the literature.(3, 11, 12, 19)

Sex-related outcome ten years after acute HF

Our study is the first to report trends in sex-specific prognosis for a period of ten years after initial hospitalization for acute HF. Compared to previous findings, the lower long-term event rate that we reported among women corresponds with other studies.(11, 12) However, whereas others reported a comparable prognosis of men and women during the first years of follow-up,(5, 9, 10) we found better prognosis both at one year as well as during the whole ten-year follow-up period in women. One explanation for these conflicting results may be the different characteristics of the study populations. Our population was up to ten years younger, had less often diabetes and had less frequently an ischemic origin of their HF than described in other publications.(5, 9, 10)

We thus showed better long-term prognosis in women with acute HF, irrespective of etiology of their HF. Two other studies determined trends in mortality with separate analyses for sex and etiology, but did not investigate whether there is an association between sex-specific outcome and etiology.(13, 14) In chronic HF, the association between sex-specific mortality and HF etiology has been studied previously. Some studies suggested equal survival probability of men and women with ischemic HF, although women had lower mortality rates in patients with non-ischemic HF.(20-22) Two studies reported a prognostic advantage in women irrespective of etiology.(3, 23) Of note, the prognostic advantage of women with chronic HF was more pronounced in patients with non-ischemic HF as suggested by Martínez-Sellés et al.(3) Since we observed lower event rates in women, irrespective of ischemic or non-ischemic etiology, the etiology of HF could not explain the difference in prognosis between men and women. One potential explanation for the different prognosis between men and women in our study is the lower event rate in the acute phase (<30 days) among women. However, when we excluded the patients who died within the first 30 days after admission, women were still found to have a lower event rate. Therefore, the better prognosis of women in the acute phase does not fully explain the sex-specific difference in outcome.

It is well known that a reduced LVEF is associated with an impaired prognosis.(24, 25) Since women less commonly had a reduced LVEF, this may well be an explanation for their lower long-term event rate. Moreover, in patients with a reduced LVEF (the group with the poorest prognosis), women were found to have a prognostic advantage compared to men. This suggests that a reduced LVEF has less prognostic value in women than in men. This is in accordance with other findings showing the negative prognostic impact of a reduced LVEF in men, and not in women.(26) Although we found an association between low LVEF and a worse outcome, the prognostic difference between men and women

may also be influenced by other factors that we did not measure. Genetic, cellular and molecular responses are reported to be different in men and women(27, 28) and could provide an alternative potential explanation for the better prognosis of women. However, more research is required to confirm this hypothesis.

Sex-related prognosis over time

Prior studies, with a maximum follow-up of five years, reported an improved survival in both men and women in the last decades,(13-16) with possibly less prognostic improvement in women.(13, 16) We found a temporal trend towards an improved ten-year survival rate in both men and women admitted with acute HF in the last decade as compared to those admitted in the first two decades. The improvement was in the same order of magnitude in both sexes.

In the 2000s, new treatment options for HF such as ACE-inhibitors, beta-blockers, mineralocorticoid receptor antagonists, implantable cardioverter defibrillators and cardiac resynchronization therapy were introduced.(29-34) The survival benefit among men and women as we presented is most likely caused by the combined therapeutic improvements. Since men and women had a comparable improvement in outcome, we can conclude that men and women equally benefited from the new therapeutic regimens.

It has been suggested that women, compared to men, have a lower prescription rate of some medication, for instance ACE-inhibitors and beta-blockers.(19, 35, 36) However, we found an equal use of drug therapy (in particular ACE-inhibitors and beta-blockers) in both sexes during admission. Since we did not have information about the therapy after discharge, we cannot exclude the possibility that the inequality in prescription of medication in our population may have developed post-discharge during the long-term follow-up.

Strengths and limitations

The unique strength of our study is that we investigated sex-specific prognosis and temporal trends in prognosis among men and women ten years after their initial hospitalization. The maximum follow-up described in the literature in this type of patients is five years.

Since this registry was performed in a tertiary referral hospital, our patient population could be somewhat different relative to the general population of patients with acute HF and this could affect the external validity of the results. On the other hand, the relatively young age of our patients should be considered to present a strength of this paper. The young age of our patients implicates that they were less likely to have other diseases (like cancer) that could affect their prognosis. This most likely increases the specificity of the present findings. Although this study was done in a tertiary referral hospital, this does not imply we did not include 'secondary' or even 'primary' referrals. On the contrary, a substantial part of the patients in our hospital fell in both categories. As a result, our study population consisted of patients with the whole spectrum of HF and with different grades

of severity of the disease. Moreover, patients included in this registry were admitted to the (I)CCU. As a consequence, our patients were more likely to have more severe HF than patients admitted to a regular Cardiology Ward. Therefore, it may not be appropriate to extrapolate our results directly to non-critical care patients with acute HF.

Conclusion

In conclusion, in this study of patients with acute HF, women were found to have a better prognosis in both the short- and the long-term than men. Although the prognosis of men and women with acute HF was poor, we could establish an improvement in long-term prognosis that was in the same order of magnitude in both sexes. This suggests that both men and women had a comparable survival benefit from new therapeutic modalities that have become available in the most recent study period. This temporal trend is encouraging but, since acute HF continues to have a poor prognosis, there is need for the development of new therapeutic options in both men and women with these conditions.

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Supplemental material

Supplemental Table 1. Baseline characteristics over time in women and men

	Women				Men			
	1985-1989	1990-1999	2000-2008	p-value	1985-1989	1990-1999	2000-2008	p-value
No. of patients	116	332	209		273	510	370	
Baseline								
Age (mean, y)	65 ± 13	66 ± 15	64 ± 17	0.32	62 ± 13	63 ± 15	63 ± 15	0.43
BMI	27 ± 8	26 ± 6	27 ± 6	0.43	23 ± 3	24 ± 4	25 ± 5	0.004
Medical history								
Myocardial infarction	36 (31%)	104 (31%)	52 (25%)	0.25	149 (55%)	228 (45%)	145 (39%)	0.001
Coronary revascularization*	17 (15%)	43 (13%)	44 (21%)	0.04	61 (22%)	107 (21%)	118 (32%)	0.001
Heart surgery (not CABG)	25 (22%)	52 (16%)	25 (12%)	0.07	27 (10%)	51 (10%)	57 (15%)	0.03
Heart transplantation	0 (0%)	2 (0.6%)	1 (0.5%)	1.00	1 (0.4%)	3 (0.6%)	2 (0.5%)	1.00
Waiting for heart transplantation	1 (0.9%)	1 (0.3%)	2 (1%)	0.51	8 (3%)	13 (3%)	10 (3%)	0.97
Heart failure	55 (47%)	139 (42%)	89 (43%)	0.57	133 (49%)	264 (52%)	208 (56%)	0.16
Rhythm- or conduction disorder	31 (27%)	69 (21%)	46 (22%)	0.41	61 (22%)	113 (22%)	127 (34%)	<0.001
Diabetes	23 (20%)	79 (24%)	59 (28%)	0.22	33 (12%)	95 (19%)	95 (26%)	<0.001
Hypertension	30 (26%)	137 (41%)	94 (45%)	0.002	61 (22%)	138 (27%)	130 (35%)	0.001
Heart failure								
Etiology of heart failure				>0.05				>0.05
Ischemic origin	38 (33%)	122 (37%)	73 (35%)		151 (55%)	247 (48%)	186 (50%)	
Non-ischemic origin	78 (67%)	210 (63%)	136 (65%)		122 (45%)	263 (52%)	184 (50%)	
Atrial fibrillation at admission	26 (22%)	88 (27%)	40 (19%)	0.14	53 (19%)	93 (18%)	91 (25%)	0.06
Left ventricular ejection fraction				<0.05				>0.05
Good	53 (46%)	144 (43%)	71 (34%)		69 (25%)	122 (24%)	92 (25%)	
Moderate	19 (17%)	91 (27%)	67 (32%)		64 (23%)	120 (24%)	80 (22%)	
Poor	44 (38%)	98 (29%)	70 (34%)		140 (51%)	268 (53%)	197 (53%)	

BMI, Body Mass Index; CABG, coronary artery bypass graft; *Percutaneous coronary intervention and/or CABG

Supplemental Table 2. Therapy over time during ICCU hospitalization in women and men

	Women				Men			
	1985-1989	1990-1999	2000-2008	p-value	1985-1989	1990-1999	2000-2008	p-value
Intubation	8 (7%)	31 (9%)	34 (16%)	0.01	21 (8%)	73 (14%)	80 (22%)	<0.001
Resuscitation	8 (7%)	13 (4%)	4 (2%)	0.08	10 (4%)	23 (5%)	14 (4%)	0.80
Mechanical circulatory support*	1 (0.9%)	11 (3%)	9 (4%)	0.19	11 (4%)	45 (9%)	28 (8%)	0.047
Inotropics	27 (23%)	96 (29%)	52 (25%)	0.39	76 (28%)	210 (41%)	118 (32%)	<0.001
Beta-blocker	7 (6%)	49 (15%)	70 (34%)	<0.001	10 (4%)	45 (9%)	125 (34%)	<0.001
Antiarrhythmics	9 (8%)	44 (13%)	31 (15%)	0.18	49 (18%)	84 (17%)	100 (27%)	<0.001
Calcium antagonist	19 (16%)	60 (18%)	21 (10%)	0.04	57 (21%)	68 (13%)	36 (10%)	<0.001
Digitalis	70 (60%)	145 (44%)	41 (20%)	<0.001	143 (52%)	238 (47%)	105 (28%)	<0.001
ACE-inhibitor or ARB	37 (32%)	179 (54%)	130 (62%)	<0.001	99 (36%)	277 (54%)	247 (67%)	<0.001
Diuretics	112 (97%)	295 (89%)	193 (92%)	0.03	249 (91%)	451 (88%)	334 (90%)	0.43
Nitrates	26 (22%)	147 (44%)	76 (36%)	<0.001	61 (22%)	228 (45%)	107 (29%)	<0.001
Nitroprusside	26 (22%)	36 (11%)	3 (1%)	<0.001	45 (17%)	45 (9%)	6 (2%)	<0.001
Antiplatelet agents	11 (10%)	72 (22%)	91 (44%)	<0.001	16 (6%)	104 (20%)	175 (47%)	<0.001
Oral anticoagulant	70 (60%)	185 (56%)	63 (30%)	<0.001	157 (58%)	284 (56%)	143 (39%)	<0.001

ICCU, intensive cardiac care unit; ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blocker; *Intra-aortic balloon pump and/or left ventricular assist device and/or extracorporeal membrane oxygenation

CHAPTER 4

Short- and long-term prognosis of patients with acute heart failure with and without diabetes: Changes over the last three decades

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Abstract

Objective: We studied differences in long-term (i.e. 10 year) prognosis among patients with acute heart failure (HF) with and without diabetes over the last three decades. In addition, we investigated whether the degree of prognostic improvement in that period was comparable between patients with and without diabetes.

Research Design and Methods: This prospective registry included all consecutive patients aged 18 years and older admitted to de (Intensive) Coronary Care Unit with acute HF in the period of 1985-2008. A total of 1810 patients were included, 384 patients (21%) had diabetes. The outcome measure was the composite of all-cause mortality, heart transplantation and left ventricular assist device implantation after 10 year follow-up.

Results: The 10-year outcome in patients with diabetes was significantly worse than in those without diabetes (87% vs. 76%; adjusted hazard ratio [HR] 1.17; 95% confidence interval [CI] 1.02-1.33). Patients admitted in the last decade had a significantly lower 10-year event rate than patients admitted in the first two decades, both among patients without diabetes (adjusted HR 0.86; 95% CI 0.75-0.99) and patients with diabetes (adjusted HR 0.80; 95% CI 0.63-1.00).

Conclusions: The long-term outcome of patients with diabetes is worse than that of patients without diabetes. However, the long-term prognosis improved over time in both groups. Importantly, this improvement in long-term prognosis was comparable in patients with and without diabetes. Despite these promising results, more awareness for diabetes in patients with acute HF is necessary and there is still need for optimal treatment of diabetes in acute HF.

Introduction

The prevalence of both heart failure (HF) and diabetes has increased over the last decades and is expected to do so in the upcoming decades.(1; 2) Therefore, the presence of diabetes in patients with HF is also likely to increase and this is anticipated to become a major health concern. The actual prevalence of diabetes in patients with acute HF in different registries has varied, but may be as high as 45%.(3) Because the structure and function of the heart is directly influenced by the presence of diabetes, diabetes is to be considered to represent more than just a comorbid condition in HF.(4)

Diabetes has shown to be an independent risk factor for the development of HF.(5; 6) Moreover, this risk has been shown to be age- and sex-dependent. Compared to patients without diabetes, the presence of diabetes doubles the risk of HF in men, while the risk of developing HF in women may be as much as four times higher.(5) These associations may even be stronger in younger patients.(5) Furthermore, the presence of diabetes has been associated with longer duration of hospitalization and higher rates of rehospitalization among patients with acute HF.(7; 8) Importantly, in patients with HF, it has been established that the presence of diabetes is not only associated with an increased cardiovascular morbidity, but also with an increased mortality.(9-13) However, the prognostic value of diabetes on in-hospital and long-term mortality among patients with acute HF is still controversial.(7; 14-19)

Since the 2000s, several new treatment modalities have been added to the therapeutic regime of chronic HF, resulting in an improved prognosis of these patients.(20-23) However, it has not been established whether the improvement of prognosis in patients with acute HF patients was influenced by the presence of diabetes. For these reasons, we studied differences in long-term prognosis among patients with acute HF with and without diabetes over the last three decades. In addition, we investigated whether the degree of prognostic improvement in that period was comparable between patients with and without diabetes.

Research Design and Methods

Inclusion

The study population and the design of the study have been described previously.(23) Briefly, all patients aged 18 years and older admitted at the Intensive Coronary Care Unit (ICCU) with acute HF were included in this prospective registry. The inclusion period was from 1985 until 2008. All patients were recruited from the Erasmus Medical Center.

Patients were included when the admitting physician established a diagnosis of acute HF or cardiogenic shock. We included patients with acute, new onset HF as well as patients with decompensated chronic HF. Patients admitted for acute HF caused by an acute coronary syndrome without evidence of sustained systolic or diastolic dysfunction were excluded. If a patient was admitted more than once with acute HF, only the first admission was taken into account.

Ethics statement

This was a prospective cohort registry. During the enrolment of the patients, approval from the local research ethics committee to conduct this study was not required. The study was conducted according to the Declaration of Helsinki.(24)

Baseline variables

Patient records and discharge letters were used for the collection of the baseline variables. Age and gender were collected as demographic variables. The following clinical variables were collected: previous medical history, etiology of HF, left ventricular ejection fraction (LVEF) and BMI. Also, the type of treatment at the ICCU was registered.

Diabetes mellitus was considered to be present when patients received oral antidiabetic therapy and/or subcutaneous insulin prior to admission. The LVEF was classified into the following qualitative categories: good, moderate and poor. Quantitative measures for LVEF were categorized as follows: >45%, 30-44% and <30% for preserved, moderately depressed and severely depressed LVEF, respectively. The etiology of HF was categorized into ischemic HF and non-ischemic HF.

Endpoint

The outcome measure of this study was the composite of all-cause mortality, heart transplantation and implantation of a left ventricular assist device (LVAD) 10 years after the initial hospitalization.

Survival status was assessed by using the Municipal Civil Registries in January 2017 and was available for 98% of the included patients.

Statistical analysis

The study population was categorized into three groups: patients admitted in 1985-1989, 1990-1999 and 2000-2008. We chose these time frames according to the development of heart failure therapy (in particular angiotensin converting enzyme [ACE] inhibitors and beta-blockers). In the 1980s, there was no evidence-based therapy for heart failure. New drug therapy like ACE-inhibitors and beta-blockers were developed and subsequently implemented in daily practice in the 1990s and it had become common practice to prescribe them in the 2000s. Therefore, we hypothesized that the prognosis of patients admitted in the first decade was worse and that the prognosis would improve in the second decade and continued to improve in the last decade. Moreover, we have also performed additional statistical analyses with the study population divided into three equal groups of periods of eight years (1985-1992, 1993-2000, 2001-2008) in order to make sure the results were not depending on the chosen time period.

Data was summarized as mean with standard deviation for continuous variables and as frequencies with percentage for categorized variables. The Student's t-test or ANOVA was used for comparing continuous variables and the χ^2 test for comparing categorized variables.

Since the LVEF was not reported in 28% of the patients and the etiology was not reported in 12% of the patients, we applied multiple imputation. Baseline characteristics were used as predictors. Pooled means were given for LVEF and etiology.

The Kaplan-Meier method was used to present the cumulative event curves. The log-rank test was applied for comparing the Kaplan-Meier curves. Landmark analyses for the 30-day event-free survivors (defined as patients who did not reach the composite endpoint) were done as secondary analyses. We used logistic regression for 30-day outcome and the Cox proportional hazard model for 1- and 10-year outcome in order to evaluate the independent association between diabetes and the composite endpoint of all-cause mortality, heart transplantation and LVAD implantation. In multivariable analysis for 30-day and 1-year outcome, adjustments were made for age, gender, BMI, atrial fibrillation at admission, etiology of HF, LVEF and a history of HF, rhythm- or conduction disorder and hypertension. In the analysis of the 10-year outcome , corrections were made for age, gender, BMI, etiology of HF, LVEF, period of admission and a history of myocardial infarction, HF and rhythm- or conduction disorder. All variables were categorical, except for age which was retained as a continuous variable. Results of logistic regression and the Cox proportional hazard model were reported as odds ratios (ORs) and hazard ratios (HRs), respectively, with their corresponding 95% confidence interval (95% CI).

All tests were two-tailed and p-values <0.05 were considered statistically significant. All data were analyzed using SPSS software (SPSS 21.0, IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

We identified 1810 patients admitted with acute HF to our ICCU in the period of 1985 until 2008. Of these, 384 patients (21%) had diabetes. The prevalence of diabetes increased: in the 1980s, 14% of the patients had diabetes, compared to 21% in the 1990s and 27% in the most recent study period (p for trend <0.001). Baseline characteristics of patients with and without diabetes were different (Table 1). On average, patients with diabetes were 5 years older, were more often female and had a higher BMI as compared to patients without diabetes. Furthermore, patients with diabetes more frequently had history of hypertension, myocardial infarction and coronary revascularization. Presence of diabetes was more commonly associated with ischemic HF, while patients without diabetes more often sustained HF of a non-ischemic origin. The distribution of the left ventricular function was not influenced by the presence of diabetes.

Table 1. Baseline characteristics of patients with and without diabetes

	Total population	Patients with diabetes	Patients without diabetes	p-value*
No. of patients	1810	384	1426	
Age (mean, y)	63.5 ± 14.8	67.1 ± 11.1	62.3 ± 15.5	<0.001
Male	1153 (64%)	223 (58%)	930 (65%)	0.01
Body Mass Index	25.1 ± 4.9	27.1 ± 6.3	24.6 ± 4.5	<0.001
Medical history				
Myocardial infarction	714 (39%)	188 (49%)	526 (37%)	<0.001
Coronary revascularization†	390 (22%)	108 (28%)	282 (20%)	<0.001
Heart surgery (not CABG)	237 (13%)	38 (10%)	199 (14%)	0.04
Heart transplantation	9 (0.5%)	1 (0.3%)	8 (0.6%)	0.69
Waiting for heart transplantation	35 (2%)	4 (1%)	31 (2%)	0.15
Heart failure	888 (49%)	184 (48%)	704 (49%)	0.61
Rhythm- or conduction disorder	445 (25%)	83 (22%)	362 (25%)	0.13
Hypertension	590 (33%)	184 (48%)	406 (29%)	<0.001
Heart failure				
Etiology of heart failure				<0.001
Ischemic origin	845 (47%)	239 (62%)	606 (42%)	
Non-ischemic origin	965 (53%)	145 (38%)	820 (58%)	
Atrial fibrillation at admission	391 (22%)	75 (20%)	316 (22%)	0.27
Left ventricular ejection fraction				>0.05
Preserved	522 (29%)	122 (32%)	400 (28%)	
Moderately depressed	427 (24%)	91 (24%)	336 (24%)	
Severely depressed	861 (48%)	171 (44%)	690 (48%)	

CABG, coronary artery bypass graft; *Comparison between patients with and without diabetes †Percutaneous coronary intervention and/or CABG

Diabetes and mortality

Compared to patients without diabetes, patients with diabetes less frequently reached the composite endpoint of all-cause mortality, heart transplantation and LVAD implantation at 30 days (9% vs 16%; unadjusted OR 0.51; 95% CI 0.35-0.75; Figure 1). After multivariable adjustment, the difference in the 30-day event rate was somewhat attenuated but remained lower in patients with diabetes (adjusted OR 0.61; 95% CI 0.41-0.92). The cumulative 1-year event rate was comparable between patients with and

without diabetes (p=0.13; Figure 1A). When the analysis was restricted to the 30-day event-free survivors only, the number of patients who reached the composite endpoint was almost identical in patients with diabetes and in those without diabetes (26% and 25%, respectively; p=0.63; Figure 1B).

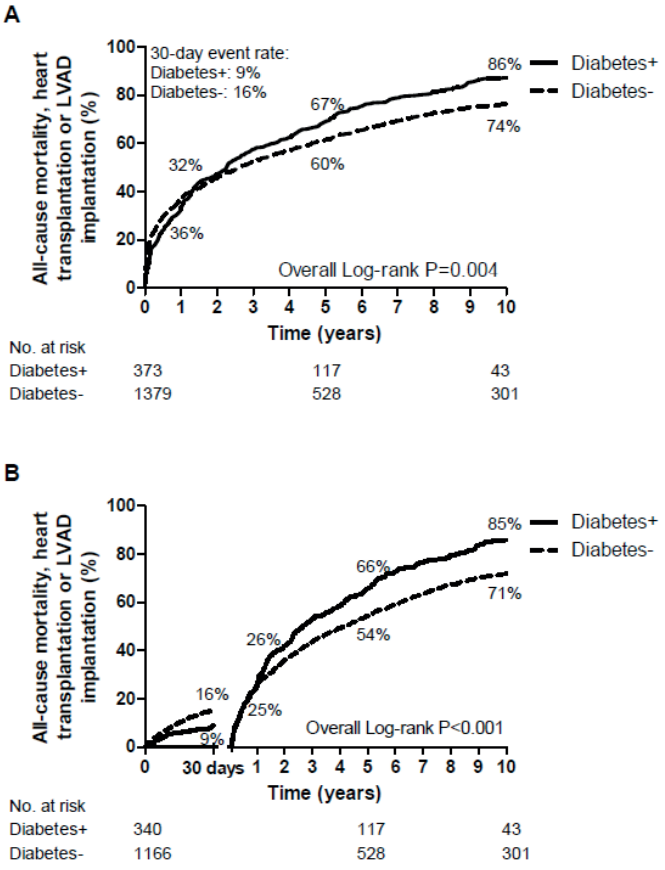

Figure 1. Kaplan-Meier curve of the cumulative incidence of reaching the composite endpoint of all-cause mortality, heart transplantation and left ventricular assist device (LVAD) implantation in (**A**) the total population and a landmark analysis in (**B**) the 30-day event-free survivors: patients with diabetes vs. those without diabetes

The number of patients who reached the composite endpoint of all-cause mortality, heart transplantation and LVAD implantation after 10 years of follow-up was higher in patients with diabetes than in those without diabetes (87% vs. 76%; unadjusted HR 1.19 [95% CI 1.06-1.36]; Figure 1A) and this remained the case after multivariable adjustment (adjusted HR 1.17 [95% CI 1.02-1.33]). A more pronounced difference in the 10-year event rate between patients with and without diabetes became apparent when the analysis was restricted to the 30-day event-free survivors (adjusted HR 1.33 [95% CI 1.15-1.53]; Figure 1B).

Patients with diabetes more frequently had prior myocardial infarction and an ischemic cause of HF was more common among these patients. However, since we did not find a significant interaction in the multivariable Cox proportional hazard model neither between diabetes and previous myocardial infarction (p=0.95) nor between diabetes and etiology of HF (p=0.95), there was no difference in impact on long-term outcome of these factors between patients with and without diabetes.

Long-term prognosis over time

The baseline characteristics of patients with and without diabetes changed during the three decades of observation (Supplemental Table 1). With time, the presence of coronary revascularization, rhythm- or conduction disorder and hypertension became more frequent among both subgroups. In addition, the patients without diabetes more commonly were women and had less prior myocardial infarction over time. The distribution of etiology of HF and LVEF remained stable over time in both patients with and without diabetes.

The short- and long-term event rate of patients admitted in the second decade was comparable with the outcome in the first decade, independent of the presence of diabetes whether or not. For the purpose of comparison with the outcome of patients studied in the most recent time period, patients admitted from 1985 until 1999 were pooled into one group. This comparison demonstrated that the 1-year outcome did not significantly improve over time, neither in patients with diabetes nor in those without diabetes (adjusted HR 0.93 [95% CI 0.64-1.36] and adjusted HR 0.92 [95% CI 0.76-1.12], respectively). In contrast, the long-term event rate showed improvement, both in acute HF patients with and in those without diabetes (Figure 2). Patients without diabetes admitted in the last decade less frequently reached the composite endpoint 10 years after initial hospitalization than patients admitted in the first two decades (adjusted HR 0.86; 95% CI 0.75-0.99). A similar improvement in long-term outcome was found among the patients with diabetes (adjusted HR 0.80; 95% CI 0.63-1.00). This improvement in long-term outcome over time was more pronounced in both patients without and those with diabetes when the analysis was restricted to the 30-day event-free survivors (adjusted HR 0.81 [95% CI 0.69-0.95] and adjusted HR 0.74 [95% CI 0.58-0.95], respectively).

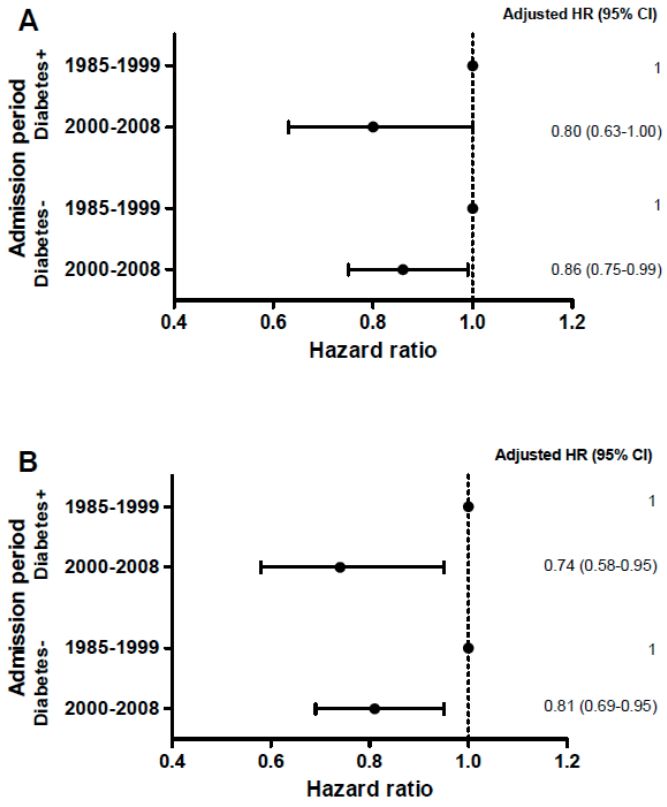

Figure 2. Multivariable adjusted trends in 10-year prognosis among patients with acute heart failure: patients with diabetes vs. those without diabetes. Analyses were separately done in (**A**) the total population and in (**B**) the 30-day event-free survivors. The dataset was divided according to the three decades.
CI, confidence interval; HR, hazard ratio.

When we analyzed the temporal trend in the long-term prognosis of the patients divided into three equal groups of periods of eight years, we found that the prognosis of patients admitted in the first period (1985-1992) was comparable with the outcome in the patients admitted in the period of 1993 until 2000. Therefore, we pooled these patients into one group and compared their long-term outcome with the outcome in patients admitted in the period 2001-2008 (Figure 3). The outcome of these analyses was comparable to the results of the analyses in patients divided according to the decades. Hence, we can conclude that the results were not dependent on the division of the dataset in the chosen time periods.

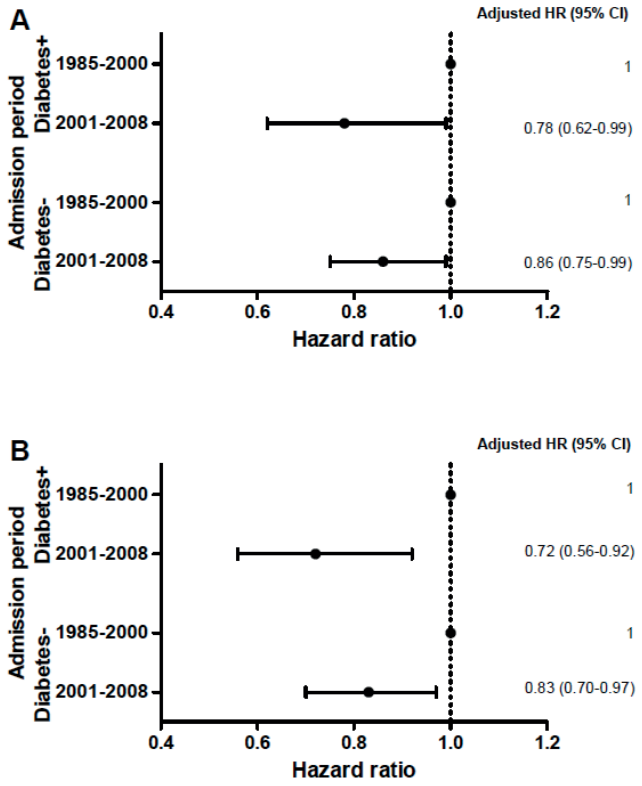

Figure 3. Multivariable adjusted trends in 10-year prognosis among patients with acute heart failure: patients with diabetes vs. those without diabetes. Analyses were separately done in (**A**) the total population and in (**B**) the 30-day event-free survivors. The dataset was divided according to the three groups of equal length in years.
CI, confidence interval; HR, hazard ratio.

Discussion

In this cohort study of patients with acute HF, studied over a period of 24 years, the prevalence of diabetes increased over time, with almost 30% of the patients found to have diabetes in the last decade. This study shows that among patients with acute HF, the presence of diabetes is associated with a clear prognostic disadvantage at long-term (i.e. 10 years) when compared to those without diabetes. More important, we clearly demonstrated that the temporal reduction in long-term outcome (i.e. the composite of all-cause mortality, heart transplantation and LVAD implantation) in patients admitted with acute HF, achieved in the last decade, was at least as high in patients with diabetes and in those without diabetes.

Short- and long-term outcome in patients with and without diabetes

This study added results to the controversial evidence available in literature about prognostic impact of diabetes on the 1-year prognosis among patients admitted with acute HF. We found that patients with and without diabetes equally reached the composite endpoint of all-cause mortality, heart transplantation and LVAD implantation after 1 year follow-up. This endorsed the findings by others who reported a comparable prognosis in patients with and without diabetes.(19) However, our findings were also in contrast with previous studies. DIAMOND-CHF was a large, Danish trial with more than 5000 patients reporting higher 1-year mortality rates among patients with diabetes.(14) Two other European registries also found a prognostic disadvantage of diabetes on the 1-year prognosis.(15; 18) Last, a large retrospective, Scottish population study found also a prognostic disadvantage after 1 year follow-up of patients with diabetes.(16) A potential reason for these discrepancies is the difference in study population. Generally, patients in our study were younger, more commonly had a myocardial infarction or HF in history and were found to have less frequently a history of hypertension.

Importantly, after a longer follow-up duration, acute HF patients with diabetes had a prognostic disadvantage compared to those without diabetes. This resulted in a higher 10-year event rates among patients with diabetes. These results confirmed the results reported by others.(14; 25; 26)

The poorer long-term prognosis in patients with diabetes is an important finding and has implications for the future. Since the incidence of diabetes in HF patients is likely to further increase in the future, this will become a major healthcare problem with high morbidity and mortality, as well as high costs for society.(27) Therefore, it is important to recognize diabetes in patients with HF and to start an adequate therapy for the diabetes. However, there is little evidence for the best therapy of glycemic control in HF patients in practice.(28) For that reason, more future clinical research is required for the medical treatment of diabetes in patients with HF. We believe that better glycemic control in that specific subset of patients may contribute to a further improvement in prognosis.

Temporal trends in long-term prognosis

Several previous studies have reported trends in long-term outcome,(20-23) but temporal trends among acute HF patients stratified by the presence of diabetes have not been described previously, neither short-term trends nor long-term trends. Novel treatment modalities for HF, like ACE-inhibitors, beta-blockers, mineralocorticoid receptor antagonists, implantable cardioverter defibrillators and cardiac resynchronization therapy have all been implemented in clinical practice in the last decades. This change in the therapeutic regimen was associated with a lower long-term mortality in the total population with acute HF,(20-23) and it caused the improved long-term prognosis of the patients without diabetes.

However, our study cannot definitely elucidate the mechanisms that resulted in the improved long-term prognosis among the diabetes subgroup. Since the novel treatment modalities have been found to have comparable mortality benefit in both in patients with and without diabetes,(27) it is possible that this is the (only) reason for the improved long-term prognosis among the acute HF patients with diabetes. On the other hand, previous studies among patients with diabetes (not in an acute HF population) showed an improved survival over the last decades,(29; 30) which attributed to a growing awareness of diabetes, more focus on cardiovascular prevention by treating comorbidities and an improvement in the treatment of acute myocardial infarction.(29-31) We hypothesized that the improved prognosis among acute HF patients with diabetes may a result from the combination of both above-mentioned potential mechanisms. Therefore, despite the impaired prognosis associated with diabetes in acute HF, both patients admitted with acute HF with diabetes and those without diabetes showed a comparable improvement over time in long-term prognosis.

Thirty-day outcome of patients with and without diabetes

Contrary to expectations, we found that patients with acute HF with diabetes less frequently reached the composite endpoint at 30 days than those without diabetes. This is not a unique finding, but data on this topic vary. Some studies reported comparable in-hospital mortality in patients with and without diabetes,(7) but other analyses described worse in-hospital outcome in patients with diabetes.(17; 18) A large Scottish database reported that diabetes was associated with lower 30-day mortality.(16) The hypothesis put forward by these investigators was that patients with diabetes would most likely have a better ejection fraction than subjects without diabetes. Since the authors were unable to adjust for LVEF, they could not establish this hypothesis. When we adjusted for LVEF in our analyses, we found that – despite this – patients with diabetes continued to have better 30-day outcome.

We think there might be two potential reasons for this prognostic disadvantage of the patients without diabetes in our study. First, the patients without diabetes who reached the composite endpoint within 30 days were most likely predominantly patients with end-stage HF or, given the fact that patients without diabetes more often were treated with mechanical circulatory support, patients with cardiogenic shock. It is well known that cardiogenic shock is associated with elevated in-hospital mortality.(32; 33) The second reason why patients without diabetes were found to have poorer 30-day prognosis may be due to the fact that the patients in our survey were admitted at an intensive care unit. A lower in-hospital mortality among patients with diabetes admitted at a general intensive care unit has also been described by Graham et al. and Martin et al.(34; 35) These two studies constitute the largest reports that investigated in the in-hospital prognosis among patients with diabetes admitted at the general intensive care unit. However, the mechanism of the lower in-hospital mortality among these patients with diabetes admitted at an intensive care unit was not stipulated.

Strengths and limitations

This study has several strengths. First, we studied long-term outcome (i.e. 10 years) in a large population of patients with acute HF over a study period of 24 years. Furthermore, this is the first study reporting temporal trends in prognosis among acute HF patients with diabetes and those without diabetes.

Despite these unique strengths, some limitations should be acknowledged. First, this study was performed in a single center. Therefore, this could result in a lower external validity. Furthermore, no distinction was made between type 1 and type 2 diabetes. Also, any information regarding the development of diabetes during follow-up among the patients without diabetes at baseline was not available. Development of diabetes during follow-up may also have influenced the prognosis. Finally, information about drug therapy of diabetes was not reported in our database. This may be of added value because the type of diabetes treatment could influence HF symptoms, hospitalization and mortality.(36-38)

Conclusion

In conclusion, we showed that patients admitted with acute HF had a poor prognosis. Moreover, the long-term outcome (i.e. the composite of all-cause mortality, heart transplantation and LVAD implantation) of patient with diabetes is worse as compared to those without diabetes. However, the long-term mortality prognosis improved over time as a result of an improved treatment of HF. Importantly, this improvement in long-term prognosis was at least as high in patients without diabetes as in those with diabetes. This study does not only emphasize the need to improve the treatment of HF, but this also emphasizes the need for optimal treatment of diabetes in acute HF as well as to create more awareness for diabetes in patients with acute HF.

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Supplemental Table 1. Baseline characteristics over time from patients with and without diabetes

	Patients with diabetes				Patients without diabetes			
	1985-1989	1990-1999	2000-2008	p-value	1985-1989	1990-1999	2000-2008	p-value
No. of patients	56	174	154		333	668	425	
Baseline								
Age (mean, y)	65.7 ± 11.0	67.5 ± 10.9	67.2 ± 11.4	0.57	61.9 ± 13.4	63.1 ± 15.8	62.2 ± 16.5	0.44
Age categories				0.23				0.01
18-54 years	7 (13%)	27 (16%)	15 (10%)		93 (28%)	182 (27%)	127 (30%)	
55-64 years	14 (25%)	35 (20%)	45 (29%)		88 (26%)	135 (20%)	82 (19%)	
65-74 years	26 (46%)	65 (37%)	59 (38%)		103 (31%)	193 (29%)	112 (26%)	
75 years and older	9 (16%)	47 (27%)	35 (23%)		49 (15%)	158 (24%)	104 (25%)	
Male	33 (59%)	95 (55%)	95 (62%)	0.43	240 (72%)	415 (62%)	275 (65%)	0.01
BMI	23.9 ± 6.6	27.0 ± 6.1	28.2 ± 6.2	0.11	24.2 ± 5.0	24.5 ± 4.0	25.1 ± 4.8	0.33
Medical history								
Myocardial infarction	32 (57%)	80 (46%)	76 (49%)	0.35	153 (46%)	252 (38%)	121 (29%)	<0.001
Coronary revascularization*	10 (18%)	35 (20%)	63 (41%)	<0.001	68 (20%)	115 (17%)	99 (23%)	0.046
Heart surgery (not CAGB)	3 (5%)	16 (9%)	19 (12%)	0.30	49 (15%)	87 (13%)	63 (15%)	0.64
Heart transplantation	0 (0%)	0 (0%)	1 (0.6%)	0.55	1 (0.3%)	5 (0.7%)	1 (0.5%)	0.73
Waiting for heart transplantation	1 (2%)	0 (0%)	3 (2%)	0.12	8 (2%)	14 (2%)	9 (2%)	0.90
Heart failure	23 (41%)	82 (47%)	79 (51%)	0.41	165 (50%)	321 (48%)	218 (51%)	0.58
Rhythm- or conduction disorder	11 (20%)	30 (17%)	42 (27%)	0.08	79 (24%)	152 (23%)	131 (31%)	0.01
Hypertension	19 (34%)	85 (49%)	80 (52%)	0.07	72 (22%)	190 (28%)	144 (34%)	0.001

	Patients with diabetes				Patients without diabetes			
Heart failure								
Aetiology of heart failure				>0.05				>0.05
Ischemic origin	35 (62%)	107 (61%)	97 (63%)		162 (49%)	276 (41%)	168 (40%)	
Non-ischemic origin	21 (38%)	67 (39%)	57 (37%)		171 (51%)	392 (59%)	257 (60%)	
Atrial fibrillation at admission	9 (16%)	37 (21%)	29 (19%)	0.67	70 (21%)	144 (22%)	102 (24%)	0.54
Left ventricular ejection fraction				>0.05				>0.05
Good	20 (35%)	54 (31%)	48 (31%)		93 (28%)	198 (30%)	110 (26%)	
Moderate	9 (15%)	47 (27%)	36 (23%)		71 (21%)	161 (24%)	104 (24%)	
Poor	28 (50%)	73 (42%)	70 (46%)		169 (51%)	309 (46%)	212 (50%)	

CABG, coronary artery bypass graft; *Percutaneous coronary intervention and/or CABG

CHAPTER 5

Renal function and anemia in relation to short- and long-term prognosis of patients with acute heart failure in the period 1985-2008: A clinical cohort study.

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Abstract

Background: Renal dysfunction and anaemia are common in patients with acute heart failure (HF). It is not known whether their combined presence has additive prognostic value. We investigated their prognostic value separately and in combination, on prognosis in acute HF patients. Furthermore, we examined whether the improvement in prognosis was comparable between patients with and without renal dysfunction.

Methods and Results: This prospective registry includes 1783 patients admitted to the (Intensive) Coronary Care Unit for acute HF in the period of 1985-2008. The outcome measure was the composite of all-cause mortality, heart transplantation and left ventricular assist device implantation. In patients without renal dysfunction, anemia was associated with worse 30-day outcome (HR 2.91; [95% CI 1.69-5.00]), but not with 10-year outcome (HR 1.13 [95% CI 0.93-1.37]). On the contrary, anemia was found to influence prognosis in patients with renal dysfunction, both at 30 days (HR 1.93 [95% CI 1.33-2.80]) and at 10 years (HR 1.27 [95% CI 1.10-1.47]). Over time, the 10-year survival rate improved in patients with preserved renal function (HR 0.73 [95% CI 0.55-0.97]), but not in patients with renal dysfunction.

Conclusion: The long-term prognosis of acute HF patients with a preserved renal function was found to have improved significantly. However, the prognosis of patients with renal dysfunction did not change. Anemia was a strong prognosticator for short-term outcome in all patients. In patients with renal dysfunction, anemia was also associated with impaired long-term prognosis.

Introduction

Acute heart failure (HF) is commonly accompanied by various non-cardiovascular comorbidities. Renal dysfunction is among one of the most common although its exact prevalence has varied between studies.[1, 2] Renal dysfunction in acute HF is associated with various adverse outcomes: longer hospital stay, higher re-hospitalization rate, and higher mortality.[1, 2] Of note, the follow-up period in most of these studies is restricted to only 1 year after the initial hospitalization.

In the last decades, an improvement in long-term outcome has been observed among patients with acute HF in several cohorts.[3-5] New therapeutic options and an increased understanding of the pathophysiology of HF are most likely responsible for this trend. Importantly, renal dysfunction is a (relative) contra-indication for some of the new therapeutic modalities[6]. As of yet, it has not been established whether the improvement in prognosis over time of patients with acute HF is modified by the presence of renal dysfunction.

Anemia is another important and common comorbidity in patients with acute HF, with a prevalence up to almost 60%.[7-12] There is conflicting data regarding the prognostic impact of anemia in patients with acute HF.[10-13] Moreover, the combination of HF, renal dysfunction and anemia carries an incremental negative prognostic impact in patients with *chronic* HF.[14] However, the additive prognostic value of anemia in patients with *acute* HF with and without renal dysfunction remains scarce.

Therefore, the aims of the present study were (1) to examine the impact of renal function on short- and long-term prognosis of patients with acute HF, (2) to determine whether the improvement in prognosis of patients with acute HF and renal impairment was comparable to that of patients with normal renal function, and (3) to study the impact of anemia, alone or in combination with renal dysfunction, on prognosis of patients with acute HF.

Materials and Methods

Patients

This prospective registry was carried out among patients who were admitted with acute HF at the Intensive Coronary Care Unit (ICCU) in our hospital during the period from 1985 until 2008. The study design and inclusion have been described previously.[5] Briefly, consecutive patients aged 18 years and older were included when they were diagnosed with acute HF or cardiogenic shock at admission. Both patients with de novo HF and patients with worsening symptoms of chronic HF were included. Patients could only contribute once to the database, and if patients were admitted more than once with acute HF during the inclusion period, only the first admission was included for analyses.

This was a prospective cohort registry. For analyses, we used completely anonymized data. During the enrolment of the patients, approval from the research ethics committee of the Erasmus MC to conduct this study was not required. At a later stage, the committee confirmed that we did not need their approval to conduct this study. Furthermore, there was no requirement for patients' informed consent. The study was conducted according to the Declaration of Helsinki.[15]

Endpoints

The outcome measure was the composite of all-cause mortality, heart transplantation and left ventricular assist device (LVAD) implantation at 30 days, 1 year and 10 years after the initial hospitalization.

Survival status was assessed by using the Municipal Civil Registries in January 2017 and was available for 98% of the included patients. To determine whether patients received an LVAD or underwent heart transplantation, we used prospectively collected data from our hospital information system.

Variables and definitions

Baseline variables were derived from patient records and discharge letters. We collected the following variables: age, gender, Body Mass Index (BMI), cardiac history, etiology of HF, left ventricular ejection fraction (LVEF) and treatment at the ICCU. Furthermore, the results of the following laboratory tests were collected: sodium (mmol/L), potassium (mmol/L), creatinine (μmol/L), urea (mmol/L) and hemoglobin (mmol/L).

Diabetes mellitus was considered to be present when patients received antidiabetic therapy. The LVEF was classified into the following qualitative categories: good, moderate and poor. If quantitative outcome for the LVEF was used, we applied the following cut-offs: >45%, 30-44% and <30% for good, moderate and poor LVEF, respectively.[5] The etiology of HF was categorized into ischemic cause versus non-ischemic cause of HF. For all laboratory tests, the first measured value during hospitalization was taken into account. The estimated glomerular filtration rate (eGFR) was estimated by using the Modification of Diet in Renal Disease (MDRD) equation for serum creatinine (μmol/L): eGFR = 30849 × serum creatinine $^{-1.154}$ × age $^{-0.203}$ × 0.742 (if female) [eGFR in mL/min/1.73 m^2].[16] In line with the most recent HF guideline of the European Society of Cardiology,[6] renal function was categorized as follows: preserved renal function: eGFR ≥60 mL/min/1.73 m^2; moderately impaired renal function eGFR 30-59 mL/min/1.73 m^2; severely impaired renal function eGFR <30 mL/min/1.73 m^2. We used the definition of the World Health Organization to define anemia: hemoglobin <7.5 mmol/L in women and <8.2 mmol/L in men. Hyponatremia was defined as a serum sodium level ≤135 mmol/L. For the definition of hypo- and hyperkalemia the following cut-off values were applied: serum potassium <3.5 mmol/L and >5.0 mmol/L, respectively.

Statistical analysis

Categorical variables are presented as frequencies and percentages. The χ^2 test and the Fisher-Freeman-Halton exact test were used to compare categorical variables. Normally distributed, continuous data are presented as mean values with standard deviation and were compared using the one-way ANOVA. Continuous data that were not normally distributed are presented as median and interquartile range (IQR). The Mann-Whitney U test or the Kruskal-Wallis H test was used to compare these data.

Since data for LVEF and etiology were incomplete for, respectively, 28% and 12% of the patients, multiple imputation was performed by using baseline characteristics as predictors. Pooled means are given for LVEF and etiology.

The Kaplan-Meier method was used for presenting the cumulative event curves and they were compared using the log-rank test. Secondary analyses were carried out among the 30-day event-free survivors. Logistic regression for 30-day outcome and the Cox proportional hazard method for long-term outcome were applied in order to examine the independent association between renal function and the composite endpoint of all-cause mortality, heart transplantation and LVAD implantation, as well as between anemia and the composite endpoint. Adjustments were made for age, gender, history of HF, diabetes, hypertension, etiology of HF, atrial fibrillation at admission, LVEF, renal function and anemia.

All tests were two-tailed and p-values <0.05 were considered statistically significant. Results of logistic regression and the Cox proportional hazard model were reported as odds ratios (ORs) and hazard ratios (HRs), respectively, with their corresponding 95% confidence interval (95% CI). All statistical analyses were carried out using SPSS software (SPSS 21.0, IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

In total, 1810 patients were admitted with acute HF in the period 1985-2008. Of these, 1783 (99%) patients had at least one creatinine measurement and they constitute the present study population. Over half of the patients were found to have renal dysfunction, which was severely impaired in 18%. The proportion of patients with severe renal impairment remained stable over time, whereas the number of patients with preserved renal function increased and moderately impaired renal function became less prevalent ($p<0.001$; Figure 1).

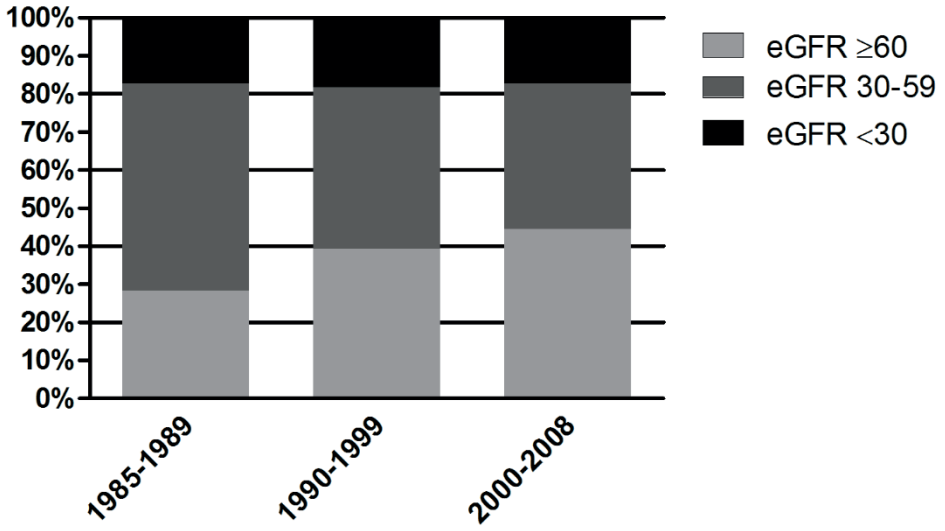

Figure 1. Distribution of the study population according to the renal function and the admission period. eGFR, estimated glomerular filtration rate in mL/min/1.73 m^2

Compared to patients with renal dysfunction, patients with preserved renal function were on average 6 years younger (Table 1). In addition, they less often had prior myocardial infarction and coronary revascularization. With decreasing renal function, the prevalence of prior HF, diabetes and hypertension increased. Hyponatremia was also more common in patients with renal dysfunction, as was anemia.

Table 1. Baseline characteristics and therapy according to renal function

	eGFR ≥60	eGFR 30-59	eGFR <30	p-value*
No. of patients	688 (39%)	778 (44%)	317 (18%)	
Baseline				
Age (mean, y)	59.7 ± 16.3	66.1 ± 13.2	65.9 ± 12.9	<0.001
Male	458 (67%)	475 (61%)	201 (63%)	0.09
BMI	25.4 ± 5.2	24.9 ± 4.8	25.0 ± 4.7	0.57
Medical history				
Myocardial infarction	237 (34%)	347 (45%)	120 (38%)	<0.001
Coronary revascularization†	124 (18%)	187 (24%)	75 (24%)	0.01
Heart surgery (not CABG)	111 (16%)	87 (11%)	36 (11%)	0.01
Heart transplantation	2 (0.3%)	1 (0.1%)	6 (2%)	0.002
Waiting for heart transplantation	16 (2.3%)	11 (1.4%)	8 (2.5%)	0.33

	eGFR ≥60	eGFR 30-59	eGFR <30	p-value*
Heart failure	300 (44%)	390 (50%)	188 (59%)	<0.001
Rhythm- or conduction disorder	157 (23%)	210 (27%)	73 (23%)	0.14
Diabetes	132 (19%)	168 (22%)	81 (26%)	0.07
Hypertension	194 (28%)	257 (33%)	133 (42%)	<0.001
Heart failure				
Etiology of heart failure				<0.05
Ischemic origin	302 (44%)	392 (50%)	140 (44%)	
Non-ischemic origin	386 (56%)	386 (50%)	177 (56%)	
Atrial fibrillation at admission	159 (23%)	178 (23%)	49 (16%)	0.01
Left ventricular ejection fraction				<0.05
Good	199 (29%)	225 (29%)	91 (29%)	
Moderate	187 (27%)	156 (20%)	76 (24%)	
Poor	302 (44%)	396 (51%)	149 (47%)	
Laboratory values				
Sodium	137 ± 5	137 ± 6	135 ± 6	<0.001
Potassium	4.0 ± 0.6	4.2 ± 0.7	4.6 ± 0.9	<0.001
Urea (median, IQR)	7.2 (5.7-9.3)	10.6 (8.2-14.4)	23.5 (17.5-30.8)	<0.001
eGFR (median, IQR)	75 (66-89)	47 (39-53)	20 (14-25)	<0.001
Creatinine (median, IQR)	80 (71-96)	123 (109-142)	258 (215-346)	<0.001
Hemoglobin	8.3 ± 1.3	8.1 ± 1.4	6.9 ± 1.5	<0.001
Hyponatremia	221 (32%)	224 (29%)	151 (48%)	<0.001
Hypokalemia	106 (15%)	98 (13%)	23 (7%)	<0.001
Hyperkalemia	38 (6%)	81 (10%)	85 (27%)	<0.001
Anemia	262 (38%)	334 (43%)	244 (77%)	<0.001
Therapy during ICCU hospitalization				
Intubation	69 (10%)	117 (15%)	57 (18%)	0.001
Resuscitation	19 (3%)	36 (5%)	15 (5%)	0.13
Mechanical circulatory support‡	34 (5%)	41 (5%)	29 (9%)	0.02
Inotropics	196 (29%)	253 (33%)	123 (39%)	0.01
Beta-blocker	146 (21%)	111 (14%)	47 (15%)	0.001
Antiarrhythmics	115 (17%)	154 (20%)	45 (14%)	0.06
Calcium antagonist	77 (11%)	102 (13%)	72 (23%)	<0.001
Digitalis	300 (44%)	347 (45%)	87 (27%)	<0.001
ACE-inhibitor or ARB	422 (61%)	430 (55%)	113 (36%)	<0.001

	eGFR ≥60	eGFR 30-59	eGFR <30	p-value*
Diuretics	640 (93%)	718 (92%)	257 (81%)	<0.001
Nitrates	234 (34%)	289 (37%)	121 (38%)	0.24
Nitroprusside	46 (7%)	74 (10%)	39 (12%)	0.01
Antiplatelet agents	200 (29%)	189 (24%)	71 (22%)	0.04
Oral anticoagulant	351 (51%)	406 (52%)	136 (43%)	0.02

ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blocker; BMI, Body Mass Index; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; ICCU, intensive cardiac care unit; IQR, interquartile range; *p for any difference; †Percutaneous coronary intervention and/or CABG; ‡Intra-aortic balloon pump and/or left ventricular assist device and/or extracorporeal membrane oxygenation

Regarding therapy, patients with renal impairment were more frequently treated with intubation and mechanical ventilation, mechanical circulatory support and inotropic agents (Table 1). Moreover, the degree of renal impairment was associated with lower in-hospital usage of beta-blockers, ACE-inhibitors and diuretics.

Renal function and outcome

The median survival of patients with a severely impaired, moderately impaired and preserved renal function was 1.0, 2.1 and 4.4 years, respectively. The impact of renal function on outcome is shown in Figure 2 and Table 2. Patients with a severely impaired renal function had the worst prognosis both at short- and long-term.

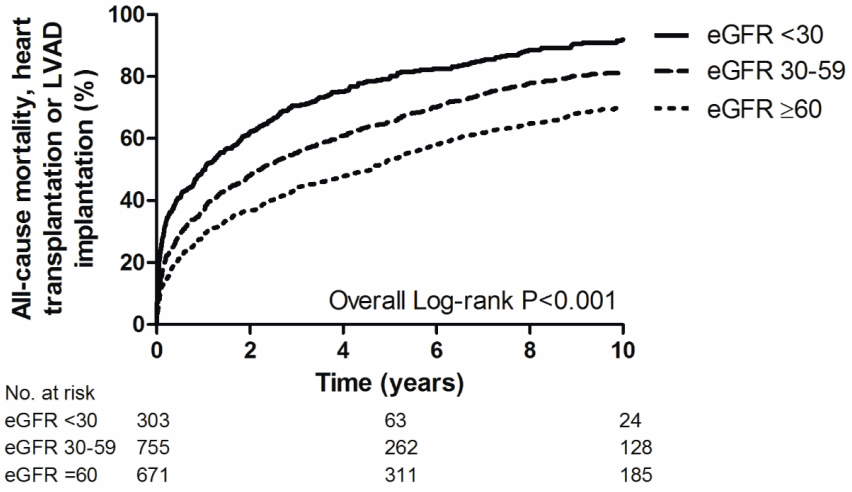

Figure 2. Kaplan-Meier curve of patients with acute heart failure according to the renal function. eGFR, estimated glomerular filtration rate in mL/min/1.73 m^2; LVAD, left ventricular assist device

Table 2. Prognosis at different follow-up moments according to renal function

	All-cause mortality, heart transplantation or LVAD implantation	Univariable analysis*	Multivariable analysis*
30 days			
eGFR ≥60	10%	Reference	Reference
eGFR 30-59	14%	1.51 (1.10-2.08)	1.50 (1.06-2.11)
eGFR <30	24%	2.85 (1.99-4.08)	2.32 (1.55-3.47)
1 year			
eGFR ≥60	28%	Reference	Reference
eGFR 30-59	36%	1.41 (1.17-1.69)	1.34 (1.11-1.62)
eGFR <30	50%	2.21 (1.79-2.73)	1.81 (1.44-2.28)
10 years			
eGFR ≥60	69%	Reference	Reference
eGFR 30-59	81%	1.42 (1.33-1.51)	1.24 (1.09-1.40)
eGFR <30	92%	2.14 (1.99-2.31)	1.68 (1.43-1.96)

eGFR, estimated glomerular filtration rate in mL/min/1.73 m2; LVAD, left ventricular assist device; *Odds ratio with 95% confidence interval (CI) for 30-day outcome, hazard ratio with 95% CI for 1-year and 10-year outcome

These findings remained unchanged after multivariable adjustment for other prognostic factors. Although the influence of renal function on prognosis became less prominent with longer duration of follow-up, renal function still remained a strong predictor of the composite endpoint of all-cause mortality, heart transplantation and LVAD implantation.

Over time, the 10-year outcome of patients with a preserved renal function improved significantly, both unadjusted (HR 0.70 [95% CI 0.61-0.81] for most recent period versus first period) and after adjustment for confounding variables (adjusted HR 0.73 [95% CI 0.55-0.97]; Figure 3A). This improvement was more pronounced among the 30-day survivors (adjusted HR 0.65 [95% CI 0.48-0.88]; Figure 3B). In contrast, this pattern was not present in patients with renal dysfunction. Consequently, the prognosis of these patients did not improve over time.

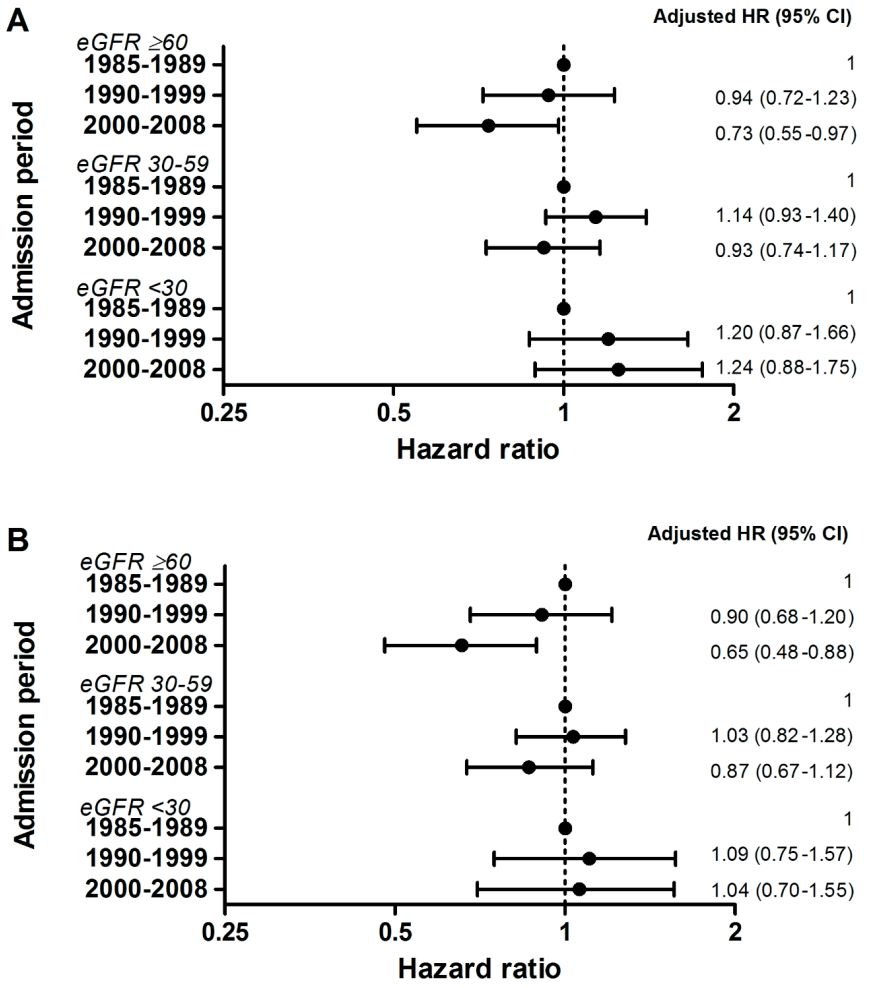

Figure 3. Prognosis over time among (A) the total population and (B) the 30-day survivors of patients with acute heart failure.
Results were divided into three groups according to the renal function. CI, confidence interval; eGFR, estimated glomerular filtration rate in mL/min/1.73 m^2; HR, hazard ratio

Anemia and outcome

Almost 50% of the patients were found to have anemia. The characteristics of these patients differed in some aspects from those without anemia (Table 3). Anemic patients more frequently had previous HF and atrial fibrillation at admission. Importantly, they more often had impaired renal function.

Table 3. Baseline characteristics and therapy of patients with and without anemia

	Anemia +	Anemia -	p-value
No. of patients	850 (48%)	919 (52%)	
Baseline			
Age (mean, y)	63.1 ± 14.5	64.1 ± 15.0	0.15
Male	565 (67%)	560 (61%)	0.02
BMI	24.8 ± 4.8	25.4 ± 5.2	0.20
Medical history			
Myocardial infarction	336 (40%)	362 (39%)	0.95
Coronary revascularization*	199 (23%)	183 (20%)	0.07
Heart surgery (not CABG)	131 (15%)	102 (11%)	0.01
Heart transplantation	8 (0.9%)	1 (0.1%)	0.02
Waiting for heart transplantation	22 (2.6%)	12 (1.3%)	0.05
Heart failure	440 (52%)	425 (46%)	0.02
Rhythm- or conduction disorder	215 (25%)	218 (24%)	0.44
Diabetes	199 (23%)	181 (20%)	0.06
Hypertension	271 (32%)	308 (34%)	0.47
Heart failure			
Etiology of heart failure			>0.05
Ischemic origin	387 (45%)	438 (48%)	
Non-ischemic origin	463 (55%)	481 (52%)	
Atrial fibrillation at admission	141 (17%)	243 (26%)	<0.001
Left ventricular ejection fraction			>0.05
Good	260 (31%)	250 (27%)	
Moderate	192 (23%)	227 (25%)	
Poor	399 (47%)	442 (48%)	
Laboratory values			
Sodium	136 ± 6	138 ± 5	<0.001
Potassium	4.3 ± 0.8	4.1 ± 0.7	0.001
Urea (median, IQR)	12.6 (8.3-20.4)	8.4 (6.6-11.6)	<0.001
eGFR (median, IQR)	47 (26-64)	57 (43-73)	<0.001
Creatinine (median, IQR)	123 (94-200)	102 (82-130)	<0.001
Hemoglobin	6.7 ± 0.9	9.0 ± 0.8	<0.001
Hyponatremia	359 (42%)	233 (25%)	<0.001
Hypokalemia	100 (12%)	125 (14%)	0.28
Hyperkalemia	122 (14%)	85 (9%)	0.001

	Anemia +	Anemia -	p-value
Therapy during ICCU hospitalization			
Intubation	151 (18%)	92 (10%)	<0.001
Resuscitation	36 (4%)	34 (4%)	0.56
Mechanical circulatory support†	80 (9%)	23 (3%)	<0.001
Inotropics	329 (39%)	238 (26%)	<0.001
Beta-blocker	128 (15%)	174 (19%)	0.03
Antiarrhythmics	143 (17%)	165 (18%)	0.53
Calcium antagonist	130 (15%)	123 (13%)	0.25
Digitalis	305 (36%)	419 (46%)	<0.001
ACE-inhibitor or ARB	417 (49%)	540 (59%)	<0.001
Diuretics	747 (88%)	854 (93%)	<0.001
Nitrates	295 (35%)	342 (37%)	0.27
Nitroprusside	73 (9%)	86 (9%)	0.57
Antiplatelet agents	238 (28%)	224 (24%)	0.08
Oral anticoagulant	383 (45%)	497 (54%)	<0.001

ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blocker; BMI, Body Mass Index; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; ICCU, intensive cardiac care unit; IQR, interquartile range; *Percutaneous coronary intervention and/or CABG; †Intra-aortic balloon pump and/or left ventricular assist device and/or extracorporeal membrane oxygenation

The prognosis of patients with anemia was worse than of patients without anemia (Figure 4). After adjustment for confounders, anemia remained significantly associated with increased for reaching the composite endpoint of all-cause mortality, heart transplantation and LVAD implantation at 30 days, 1 year and 10 years (HR 2.23 [95% CI 1.64-3.03], HR 1.58 [95% CI 1.33-1.87] and HR 1.24 [1.11-1.39], respectively; Table 4).

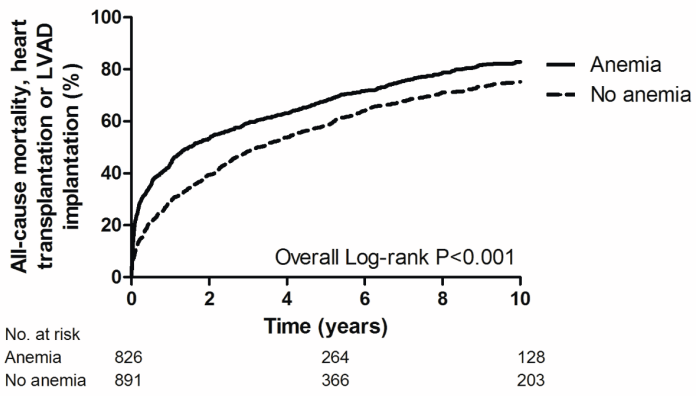

Figure 4. Kaplan-Meier curve of acute heart failure patients with and without anemia.
LVAD, left ventricular assist device

Table 4. Prognosis at different follow-up moments according to the presence of anemia

	All-cause mortality, heart transplantation or LVAD implantation	Univariable analysis*	Multivariable analysis*
30 days			
No anemia	9%	Reference	Reference
Anemia	20%	2.55 (1.92-3.38)	2.23 (1.64-3.03)
1 year			
No anemia	28%	Reference	Reference
Anemia	43%	1.75 (1.49-2.05)	1.58 (1.33-1.87)
10 years			
No anemia	75%	Reference	Reference
Anemia	83%	1.35 (1.28-1.43)	1.24 (1.11-1.39)

LVAD, left ventricular assist device; * Odds ratio with 95% confidence interval (CI) for 30-day outcome, hazard ratio with 95% CI for 1-year and 10-year outcome

Since anemia was a predictor of poor outcome in the total population of acute HF patients, we separately analyzed whether anemia had incremental prognostic value independent from renal dysfunction (Figure 5). Among patients with a preserved renal function, anemia proved to be a strong predictor for 30-day outcome, but its prognostic value decreased with longer duration of follow-up. In contrast, anemia was associated with worse outcome both during short- and long-term follow-up among patients with renal dysfunction. This relationship persisted after the exclusion of patients who died within 30 days after admission.

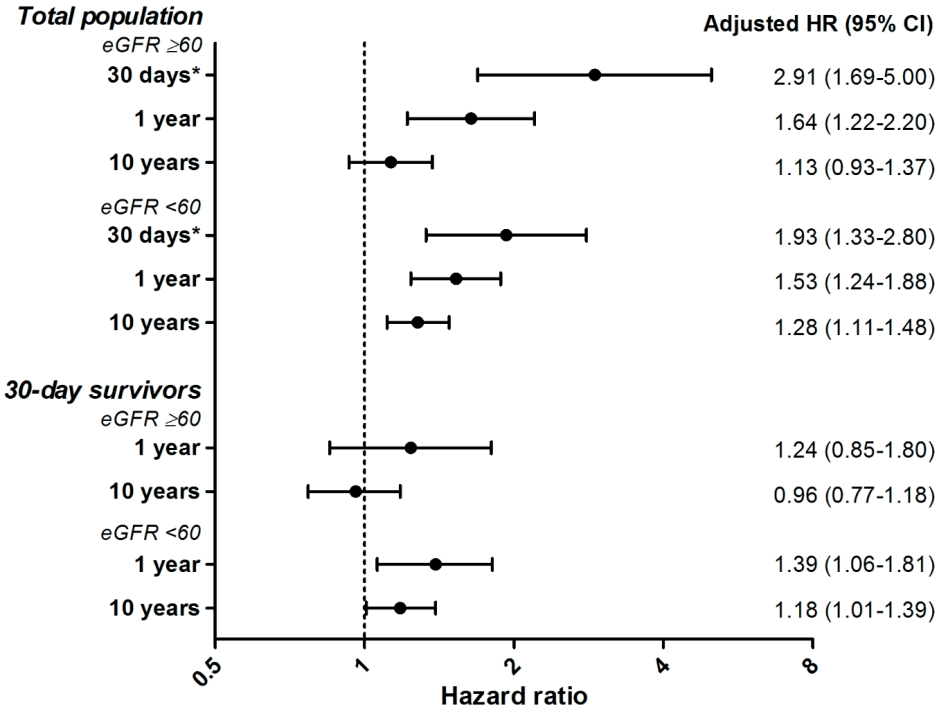

Figure 5. Prognostic impact of anemia at different follow-up moments in the total population and 30-day survivors. Analyses were separately done for renal impairment whether or not. CI, confidence interval; eGFR, estimated glomerular filtration rate in mL/min/1.73 m^2; HR, hazard ratio; *outcome at 30 days was reported as odds ratio with 95% CI.

Discussion

In this prospective registry of patients with acute HF, we found that renal dysfunction was a strong predictor for poor outcome (i.e. the composite of all-cause mortality, heart transplantation and LVAD implantation) up to 10 years following initial hospitalization. Importantly, this study is the first to show that patients with acute HF and an impaired renal function had no improvement in prognosis that occurred in the last three decades. This contrasts findings in patients with a preserved renal function. Furthermore, we found that the prognostic impact of anemia was dependent on the presence of renal function. Anemia had no impact on the long-term prognosis of patients with a preserved renal function. On the other hand, anemia was associated with impaired prognosis among patients with renal dysfunction.

Renal function and prognosis

Renal dysfunction proved to be a strong predictor of a poor outcome: the poorer the renal function, the poorer the prognosis. Among studies that demonstrated the adverse association between renal dysfunction and poor survival,[1, 2] most only used a short follow-up period, usually up to 1 year after hospitalization. Our results support and extend these findings by demonstrating that renal dysfunction continued to be a strong predictor for long-term outcome (i.e. 10 years).

It is generally assumed that the new therapeutic options for the treatment of HF developed during the last decades are responsible for the prognostic improvement in the total population of patients acute HF. Our finding that only patients with a normal renal function experienced an improved long-term prognosis in the most recently study period is novel. This contrasts with the findings currently obtained among patients with renal dysfunction. Their prognosis remained stable over time. So far, the temporal trends in prognosis have not been studied separately for patients with and without renal dysfunction. Two potential mechanisms may explain this finding. First, some of the new therapeutics, like ACE inhibitors, ARBs and MRAs, that are considered to be responsible for the prognostic improvement of patients with HF over the last decades, interact with the renal function.[6] Moreover, patients with lower eGFR were also less frequently treated with diuretics during ICCU admission. Therefore, it is plausible that patients with renal dysfunction were less frequently treated with these drugs and that, in case they were treated, the optimal dose was not achieved. Indeed, we found that ACE inhibitors were less frequently prescribed during admission in patients with renal dysfunction. Although data on medical therapy during follow-up were not included in this registry, it can be assumed that this pattern of prescription continued after discharge. Another possible explanation for the disparity in temporal trends between patients with and without renal dysfunction may be the grade of their illness. Patients with renal dysfunction had more comorbidities and were more frequently treated with intubation, mechanical circulatory support and inotropics than patients with preserved renal function. This suggests that patients with renal dysfunction were more critically ill as compared to those with a preserved renal function, and they might thus experience a more progressive course of their disease and, therefore, a poorer prognosis.

Anemia and prognosis

The second result of our study was the finding that anemia was associated with both an impaired short- and long-term prognosis among patients with acute HF. The relation between anemia and adverse outcome in patients with acute HF has been published previously, although the data are not consistent.[10-13] Two studies that did not report anemia to be a prognosticator of poor outcome had study populations with quite different characteristics than ours.[10, 13]

When we studied the prognostic value of anemia in more detail, we found that anemia was an independent predictor of short-term outcome in all patients, irrespective of renal function. However, while anemia also was independently associated with an impaired

outcome during long-term follow-up in patients with renal dysfunction, its presence had no incremental long-term prognostic impact in patients with a preserved renal function. The reasons for this difference are not totally clear. A possible explanation may be the actual cause of the anemia. However, as we were not able to assess the exact etiology of the anemia, the following hypothesis should be studied further in the future.

Anemia in patients with HF is well known, and has been attributed to multiple factors including iron deficiency, renal dysfunction, HF as a chronic disease and hemodilution.[14] The iron status was not assessed in our patients so we cannot make any conclusions as whether there was a difference in iron status between patients with and without renal dysfunction. The fact that anemia was associated with impaired long-term outcome in patients with renal dysfunction but not in patients with a preserved renal function might be due to the fact that patients with renal dysfunction more frequently had 'true anemia'.

Hemodilution is one of the potential causes of anemia in patients with HF.[17] The causal factor in that case is a low hemoglobin level caused by an increased extracellular volume. When the extracellular volume decreases, for example by diuretic therapy, the hemoglobin level will increase and the patient will no longer be classified as having anemia. Therefore, in case of hemodilution anemia should be seen as a marker of fluid retention, just as sodium level. We hypothesize that hemodilution as the only cause of anemia was more frequent in patients without renal dysfunction than in those with renal dysfunction. Probably, patients with an impaired renal function had also anemia based on hemodilution but in addition, could also have suffered from 'true anemia'. There are several reasons for such a phenomenon. First, it is well known that renal failure is associated with anemia.[14] Second, in our study, chronic HF was more common among patients with renal dysfunction than among those without renal dysfunction. Since chronic HF has been associated with elevated plasma levels of cytokines,[18] chronic HF can cause anemia of chronic diseases. These cytokines suppress the erythropoietic stem cells in the bone marrow and reduce the release of iron form the reticulo-endothelial system, resulting in anemia.[19]

The so-called cardiorenal anemia syndrome has not been investigated extensively in patients with acute HF. Investigators form the ATTEND registry also found anemia to be a strong predictor of in-hospital mortality both among patients with and without renal dysfunction.[20] Furthermore, their results with respect to the 1-year outcome were consistent with our data. In addition, these authors also showed that anemia had additive prognostic value for increased 1-year mortality only in the patients with renal dysfunction but not in those with a preserved renal function.[21] Because these investigators used anemia at discharge as predictor, and thus made hemodilution less likely as cause from anemia, this supports our hypothesis of 'true anemia' among patients with renal dysfunction. Our data provide new evidence on the very long-term prognosis of patients with acute HF since we found that anemia, even after 10 years of follow-up, continued to have additive prognostic value among patients with renal dysfunction.

Strengths and limitations

The unique strength of our study is the duration of the follow-up of 10 years after the initial hospitalization. This enabled us to investigate the prognostic impact of renal dysfunction, anemia, as well as their interrelationship on short- en (very) long-term. Research covering three decades with such a long follow-up time is quite unique in this research field.

Despite these strengths, some limitations should be considered in the interpretation of the results of this study. Since our study was done in a tertiary referral hospital, external validity could have been affected. However, despite the fact that our hospital was a tertiary referral center, a significant part of our patients still were primary and secondary referrals. Therefore, our population consisted of patients within the whole, broad range of patients admitted with acute HF. Second, analyses were made on a composite outcome and therefore caution is needed when interpreting the estimates of the covariates, since these are estimates on the composite outcome only and not on the separate outcomes. Third, we were not able to identify the cause of anemia in all patients, nor were we always able to assess whether patients had chronic or acute renal dysfunction. Furthermore, while it has been suggested that changing hemoglobin and creatinine levels during admission may influence prognosis,[2, 22] the design of our study did not allow us to assess trends in hemoglobin and creatinine levels. Finally, since we had no data on the ethnicity of our patients, we could not multiply for black race in the MDRD formula. Therefore, the eGFR that we employed might be an underestimation of the real renal function. However, such misclassification could have only led to underestimation of the effects observed.

Conclusions

We found renal dysfunction to be a strong predictor of both short- and long-term composite endpoint of all-cause mortality, heart transplantation and LVAD implantation among patients with acute HF. In addition, we established that the long-term prognosis of patients with a preserved renal function significantly improved over the last decades. However, in patients with renal dysfunction, the prognosis did not improve over the last decades. These findings emphasize the importance of renal dysfunction as comorbidity in patients with HF and underscore the need for new therapeutic modalities, especially for patients with renal dysfunction. Furthermore, we established anemia as a prognosticator of short-term outcome both among acute HF patients with and without renal dysfunction. Among patients with renal dysfunction, the presence of anemia was also associated with impaired long-term prognosis. Anemia did not influence the long-term prognosis of patients with preserved renal function. Further research should be undertaken to investigate the pathogenesis of the prognostic impact of anemia and renal dysfunction among patients with acute HF.

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CHAPTER 6

Relative conditional survival analysis provides additional insights into the prognosis of heart failure patients

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Heart failure (HF) entails high mortality rates.[1] Mortality rates presented in literature are usually based on cumulative probabilities, providing statistical estimates for the entire duration of the follow-up period. Presented this way, aspects of prognosis in HF are missed that may contain important information for the patient or treating physician. Additional insights into prognosis may be gained by using relative and conditional survival analysis, approaches commonly used and proven highly useful in oncology research.[2] We explored these measures of survival in a large cohort of patients with acute HF.

We used a consecutive single-center cohort of acute HF patients with long-term follow-up.[3] Briefly, 1810 patients admitted with acute HF to Erasmus MC, Rotterdam, the Netherlands, were included in a prospective registry between 1985-2008 (baseline characteristics: Supplemental Table 1). We calculated cumulative survival rates for 10 years, stratified by age in four equal groups, using the Kaplan-Meier method (Figure, Panel A; Supplemental Table 2). As expected, one- and ten-year survival rates were low (between 56%-65% at one year and 9%-35% at ten years). Overall, younger patients had better survival than older patients.

The steep decline in survival in the first year attenuated during subsequent follow-up. This became even more evident when one-year conditional survival rates were calculated, which indicate the probability of surviving one year, given that the patient had already survived up to that time, and show how a patient's estimated survival changes over time (Panel B). For example, patients aged 55 or younger had a cumulative survival probability of 56% at one year and of 50% at two years of follow-up. However, if those patients survived the first year, survival probability of also surviving the second year increased to 89%. These much higher one-year survival rates persisted throughout the remainder of the follow-up (panel B). A similar pattern was seen in the other age groups. Younger patients had higher one-year conditional survival rates than older patients.

How much of the all-cause mortality in this cohort can be attributed to HF is shown by relative or relative conditional survival (RCS). Relative survival directly compares a patient's survival to the survival of a person in the general population with the same age and gender, retrieved from Statistics Netherlands.[4] RCS demonstrates at which point in time the survival of a patient becomes similar to that of the general population (RCS=1).[5] Panel C shows the one-year RCS estimates. For example, if patients aged 75 or older survive the first year, their survival is 79%, This corresponds to a prognosis that is 85% of the general population. The RCS probability lines never reach the value of one, indicating that during the entire 10 year follow-up period, all patients continue to have an increased mortality rate compared to the general population. Relative survival rates show more overlap for the different patient groups than in the conditional analysis. So, although younger patients have better prognosis than older patients, compared to their peers survival remains suboptimal and increased HF mortality persists throughout follow-up.

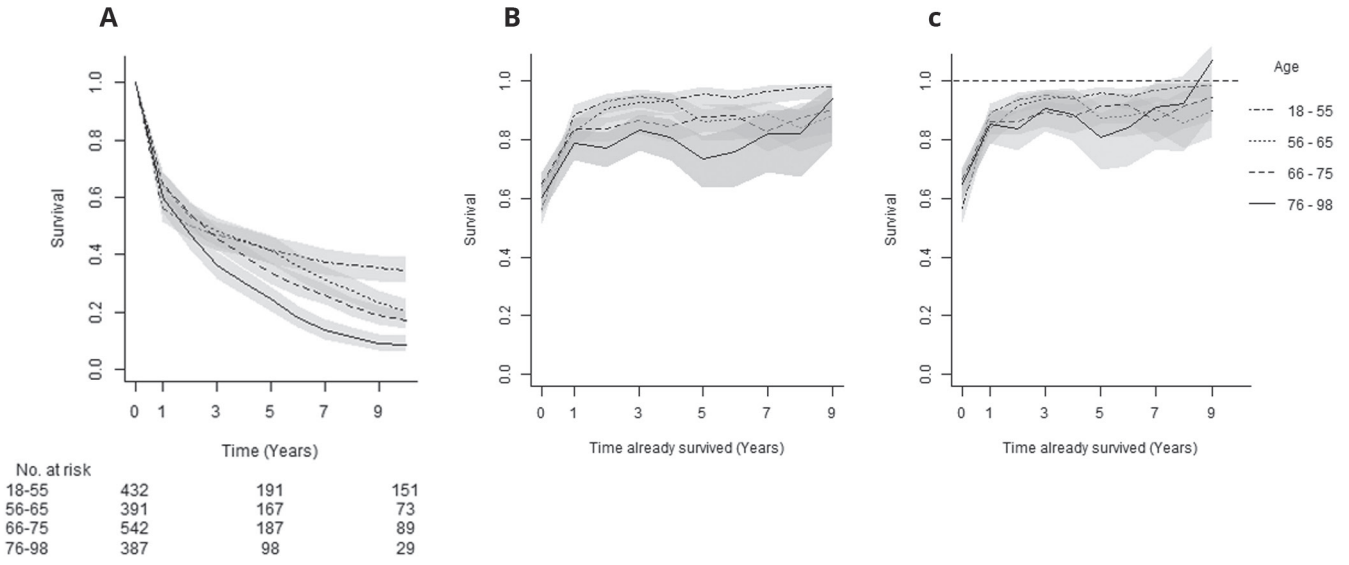

Figure. Cumulative, conditional and relative conditional survival curves. Panel A shows cumulative survival in years (with 95% confidence intervals) for four age groups and the number of patients still at risk at 0, 5, and 10 years. Panel B shows 1-year survival estimates, conditional on surviving the number of years indicated on the x-axis. Panel C shows the 1-year conditional survival relative to the general population. The estimates at year 0 in Panel B and C correspond to (relative) survival estimate at one year. The dashed line in panel C indicates survival equal to the general population (relative survival=1).

We repeated the analyses stratifying on sex, left ventricular ejection fraction (LVEF), etiology, diabetes, hypertension and kidney function (results: Supplemental material). For patients with a poor LVEF, survival was lower in the first year compared to the other patients. Interestingly, this difference disappeared when patients with poor LVEF survived the first period, as demonstrated by RCS. Patients with severe kidney dysfunction similarly showed lower survival rates. This difference persisted, although less pronounced, when calculating (relative) conditional survival. For the other factors and comorbidities differences were less evident, but in line with previous literature. For every stratifying factor, all patient groups showed excess mortality compared to the general population. A multivariable relative regression model was estimated (details in Supplemental material). In short, the first follow-up period, age, LVEF, eGFR, diabetes, and hypertension were significantly independently associated with relative excess risk, in line with results of the stratified analyses.

In conclusion, acute HF entails high mortality. (Relative) conditional survival can be used to gain additional insights into the disease course and communicate this more clearly to patients. Using these measures, we found that mortality occurs largely in the first period, and there is substantial improvement thereafter. Thus the first period after hospitalization is crucial. Cardiologists could use conditional survival to update patient prognosis during each visit and show higher survival probabilities to patients once they survive the first year. The RCS estimates however show that, for these acute HF patients, survival never becomes 'normal' again. This also holds for younger patients, patients without specific comorbidities, and with ejection fraction≥45%. This notion is particularly important for young patients, who will carry the burden of their disease for the rest of their lives.

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Supplemental material

Supplemental Table 1. Baseline characteristics

Variable	n = 1810
Age, mean (sd)	63.5 (14.8)
Gender (Male), n (%)	1153 (64%)
Etiology (Ischemic), n (%)	740 (47%)
Left ventricular function, n (%)	
Good (ejection fraction≥45%)	381 (29%)
Moderate (ejection fraction 30%-44%)	312 (24%)
Poor (ejection fraction <30%)	620 (47%)
eGFR, n (%)	
>60 (Mildly reduced/normal kidney function)	665 (41%)
30-60 (Moderately reduced kidney function)	653 (40%)
<30 (Severely reduced kidney function)	308 (19%)
Diabetes, n (%)	384 (21%)
Hypertension, n(%)	590 (33%)

eGFR; estimated glomerular filtration rate

Supplemental Table 2. Cumulative, conditional and relative conditional survival estimates

	Cumulative survival at:				Conditional Survival (95% CI) 1y survival, conditional on surviving:				Relative Conditional Survival (95% CI) 1y survival, conditional on surviving:			
Age	**1y**	**2y**	**5y**	**10y**	**0y**	**1y**	**4y**	**9y**	**0y**	**1y**	**4y**	**9y**
18 - 55	56%	50%	41%	35%	56%	89%	94%	98%	57%	89%	94%	99%
	(51%-1%)	(45%-5%)	(37%-6%)	(30%-9%)	(51%-61%)	(84%-92%)	(89%-96%)	(94%-99%)	(52%-61%)	(84%-92%)	(60%-97%)	(95%-100%)
56 - 65	64%	53%	42%	21%	64%	83%	93%	88%	65%	84%	95%	90%
	(59%-69%)	(48%-58%)	(37%-47%)	(17%-25%)	(59%-69%)	(78%-87%)	(89%-96%)	(79%-94%)	(60%-70%)	(79%-88%)	(90%-97%)	(81%-95%)
66 - 75	65%	55%	34%	17%	65%	84%	85%	90%	67%	86%	88%	95%
	(61%-69%)	(50%-59%)	(30%-38%)	(14%-20%)	(61%-69%)	(80%-87%)	(79%-89%)	(83%-95%)	(62%-71%)	(82%-90%)	(82%-92%)	(87%-99%)
76 - 98	60%	47%	25%	9%	60%	79%	81%	94%	65%	85%	89%	107%
	(55%-65%)	(42%-52%)	(21%-29%)	(6%-12%)	(55%-65%)	(73%-83%)	(73%-87%)	(78%-98%)	(59%-70%)	(79%-90%)	(80%-95%)	(89%-112%)

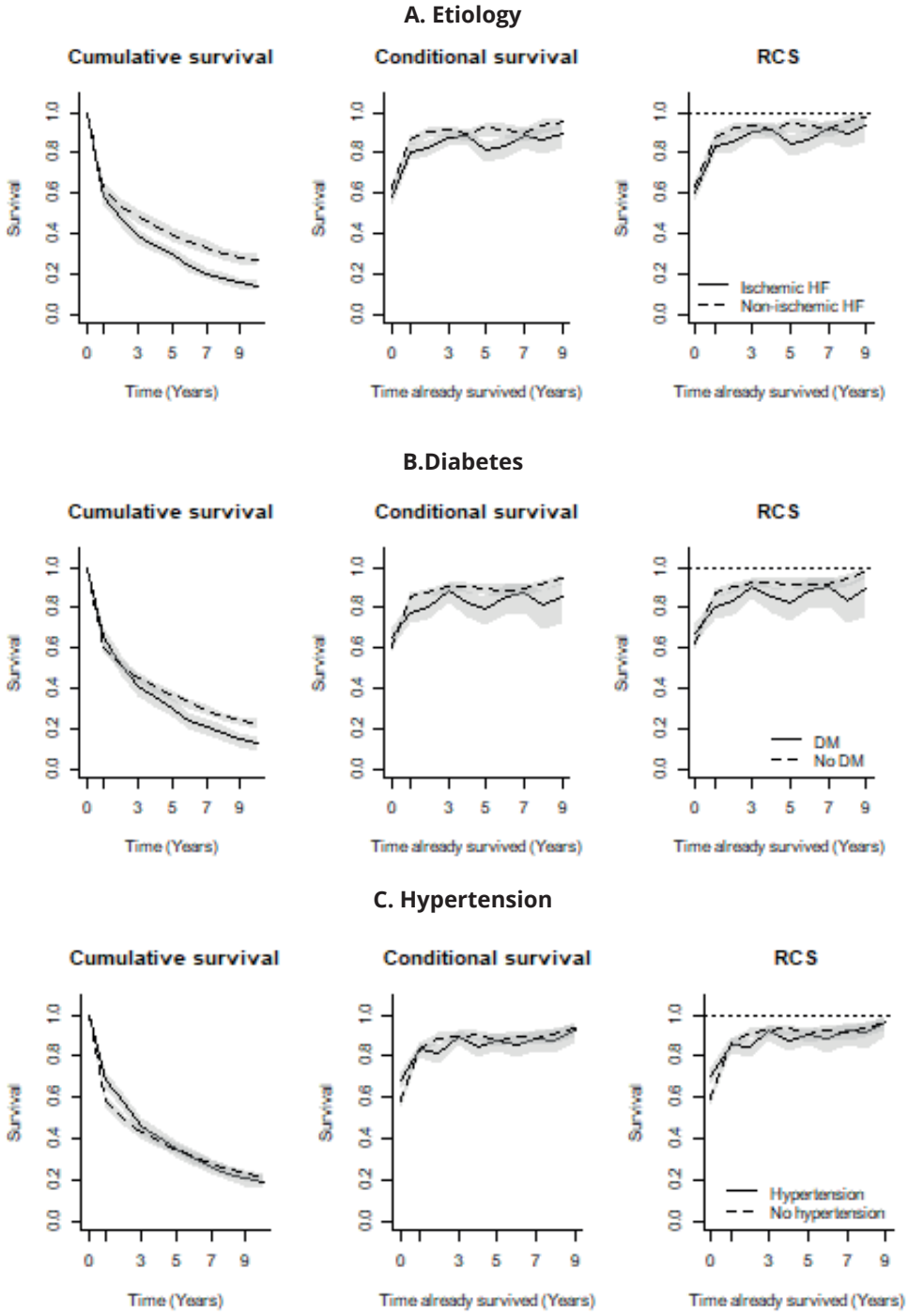
The three types of survival measures calculated at selected points during follow-up. Cumulative survival is the standard survival method calculated using the Kaplan-Meier method. One year conditional survival estimated are conditional on having survived the previous period. Relative conditional survival estimates related the survival to a comparable person from the general population. Survival estimates include the 95% confidence interval

Stratified analyses

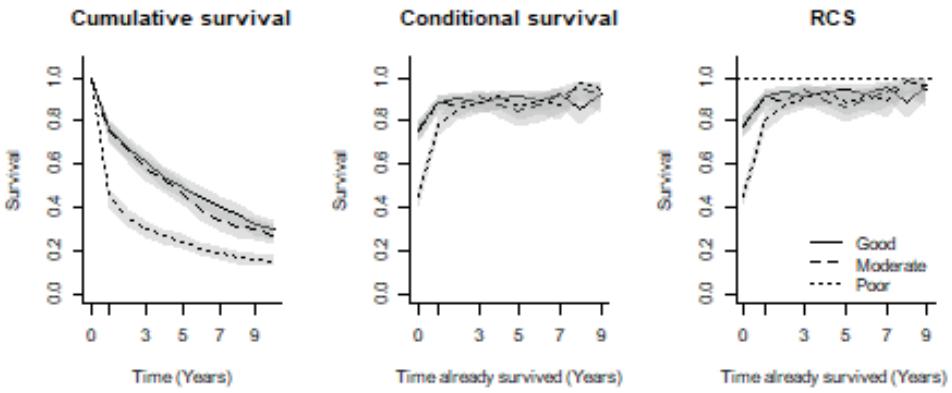
Supplemental figure 1 shows the results for the cumulative survival, one-year conditional and one-year relative conditional survival (RCS) analyses, stratified on different factors: left ventricular ejection fraction (LVEF), kidney function (assessed by estimated glomerular filtration rate (eGFR)), sex, etiology (ischemic or non-ischemic), diabetes and hypertension. In general, all stratified analyses illustrate the steep decline in cumulative survival in the first year, and low cumulative survival at ten years. The conditional survival curves demonstrate improved and stable one-year survival estimates for the patients that survive the first period. The RCS panels demonstrate however, that for all patient groups survival never reaches the level of the general population (RCS < 1).

The results of the stratification on LVEF and eGFR are discussed in the main manuscript and the cumulative survival findings are in line with previous literature.[1, 2] In Supplemental Figure 1C, women appear to have slightly higher survival rates coinciding with the survival benefit shown in prior heart failure studies.[3] This difference in survival is no longer present in the patients that survive the first period. Patients with ischemic heart failure (Supplemental Figure 1D) have higher mortality rates than patients with non-ischemic heart failure. The differences between ischemic and non-ischemic patients are not present early during follow-up, but appear after surviving the first year. This difference in survival was previously shown by Gajanna et al (2016).[4] Similar, although less pronounced, results are found for diabetes (Supplemental Figure 1E). Patients with diabetes have lower survival rates than patients without diabetes, as expected[5], although this difference is not present in the first period. Survival seems slightly better for patients with hypertension in the first period (Supplemental Figure 1F). This paradoxical association has been identified previously.[6] For patients surviving the first year, this difference disappears and the conditional survival curves become similar for patients with or without hypertension

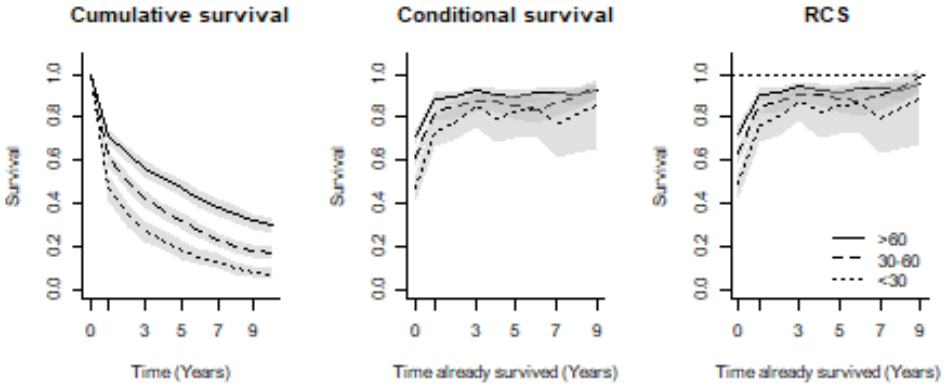
Supplemental Figure 1. Cumulative, conditional and relative conditional survival estimates stratified on patient characteristics



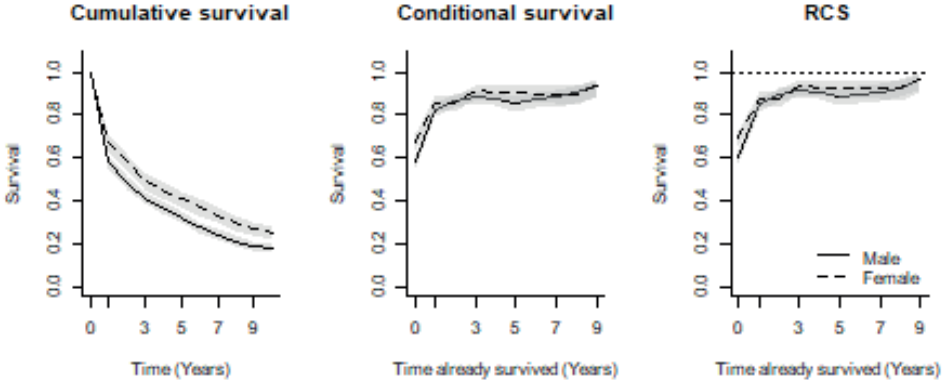
D. Left ventricular ejection fraction



E. Estimated glomerular filtration rate (eGFR)



F. Sex



The first panel in each graph shows cumulative survival in years (with 95% confidence intervals) for different groups. The second panel shows the 1-year survival estimates, conditional on surviving the number of years indicated on the x-axis. Panel C shows the 1-year conditional survival relative to the general population. The estimates at year 0 in Panel B and C correspond to (relative) survival estimate at one year since hospitalization. Additionally in panel C, the dashed line indicates a survival equal to that of the general population (relative survival=1).

Relative survival regression model

Due to the relatively limited number of patients in the cohort, simultaneous stratification on multiple variables and applying the current method is not feasible. Alternatively, a multivariable relative survival regression model can be estimated to account for multiple variables. Briefly, this model estimates the number of deaths in each time interval (every year of follow-up), assuming a Poisson distribution.[7] The model estimates the relative excess risk (RER) per variable (i.e., the difference between the observed and expected risk). The results can be found in Supplemental Table 3. The model includes the stratification factors as in the stratified analyses, age as continuous variable and an indicator for the first year of follow-up. The RER of the first year compared to the remainder of follow-up of 4.69 means that the excess risk of mortality (compared to the general population) in the first year is almost five times higher than in the remainder of the follow-up. This corresponds to the lower relative survival at time 0 in the figures. In the relative survival model the first year of follow-up, age, LVEF, eGFR, and diabetes are independently significantly related to higher excess risk. Hypertension shows a lower excess risk, in line with the findings in the stratified analysis.

Supplemental Table 3. Results from the Poisson relative survival model

Parameter	Relative Excess Risk (estimated)	95 % CI	p-value
Follow-up *First year vs remainder*	4.69	(3.98 – 5.52)	<0.001
Sex *Female vs Male*	0.94	(0.79 – 1.11)	0.454
Age (*per year*)	1.01	(1.001 – 1.02)	0.018
Etiology *Ischemic vs Non-Ischemic*	1.15	(0.96 – 1.37)	0.124
LVEF *Poor vs Good*	1.72	(1.40 – 2.10)	<0.001
LVEF *Moderate vs Good*	0.98	(0.76 – 1.26)	0.876
Diabetes *Yes vs No*	1.30	(1.08 – 1.57)	0.007
Hypertension *Yes vs No*	0.82	(0.69 – 0.98)	0.032
eGFR *Severe vs Mild-Normal*	2.13	(1.71 – 2.65)	<0.001
eGFR *Moderate vs Mild-Normal*	1.45	(1.20 – 1.75)	<0.001

Parameter estimates are interpreted as relative excess risk estimates. The estimate for follow-up of 4.69 indicates that the excess risk of mortality (compared to the general population) in the first year is almost five times higher than in the remainder of the follow-up. LVEF; Left ventricular ejection fraction, eGFR; estimated glomerular filtration rate

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CHAPTER 7

Left ventricular remodeling and prognosis after discharge in new-onset acute heart failure with reduced ejection fraction

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Abstract

Aims: To investigate the left ventricular (LV) remodeling and long-term prognosis of patients with new-onset acute heart failure (AHF) with reduced ejection fraction (HFrEF) who were pharmacologically managed and survived until hospital discharge. We compared patients with ischaemic and non-ischaemic aetiology.

Methods and Results: This cohort study consisted of 111 patients admitted with new-onset AHF in the period 2008-2016 (62% non-ischaemic aetiology, 48% supported by inotropes, vasopressors or short-term mechanical circulatory devices, left ventricular ejection fraction [LVEF] at discharge 28% [IQR 22-34]). LV dimensions, LVEF and mitral valve regurgitation were used as markers for LV remodeling during up to 3 years of follow-up. Both patients with non-ischaemic and ischaemic HF had significant improvement in LVEF ($p<0.001$ and $p=0.004$, respectively) with significant higher improvement in those with non-ischaemic HF (17% vs. 6%, $p<0.001$). Patients with non-ischaemic HF had reduction in LV end-diastolic and end-systolic diameters (6mm and 10mm, both $p<0.001$) but this was not found in those with ischaemic HF (+3mm [$p=0.09$] and +2mm [$p=0.07$], respectively). During a median follow-up of 4.6 years, 98 patients (88%) did not reach the composite end-point of left ventricular assist device implantation, heart transplantation or all-cause mortality, with no difference between with ischaemic and non-ischaemic HF (HR 0.69 [95% CI 0.19-2.45]).

Conclusion: Patients with new-onset acute HFrEF discharged on optimal medical treatment have a good prognosis. We observed a considerable LV remodeling with improvement in LV function and dimensions, starting already at 6 months in patients with non-ischaemic HF but not in their ischaemic counterparts.

Introduction

Hospitalisation for new-onset heart failure (HF) often indicates a severe HF phenotype, in which introduction and titration of medication may be difficult and the response to treatment is influenced by the severity of EF impairment.(1) Less is known about the natural course of patients with new-onset acute HFrEF who can be medically managed, but in whom the severity of left ventricle (LV) dysfunction raises the question whether advanced treatment is indicated. A too early decision for left ventricular assist device (LVAD) or heart transplantation (HT) in patients with first admission for new-onset HF with reduced ejection fraction (HFrEF) and who tolerate HF medication may have a heavy impact on the morbidity and mortality risks of the individual patients as well as on health care resources, as LV function may recover in some of these patients.(2)

In the current study, we aimed to investigate the LV remodeling and long-term prognosis of patients with new-onset acute HFrEF who were pharmacologically managed and survived to hospital discharge. We designed this study in patients with new-onset acute HF in order to evaluate the effect of HF medication in a formerly non-exposed patient with HF. Because the remodeling is dependent on the HF aetiology, we compared the LV remodeling between patients with ischaemic and non-ischaemic aetiology of acute HFrEF.

Methods

Study population

This retrospective cohort study consisted of patients admitted with acute HF to the Erasmus Medical Center in the period January 2008 until December 2016. The inclusion criteria were (1) a diagnosis of acute HF at admission, (2) no history of chronic HF or any other structural heart disease and (3) an left ventricular ejection fraction (LVEF) <40% at admission. Patients were excluded if they received an LVAD, underwent HT or died before discharge and in case of limited or no follow-up in our hospital.

Our hospital is a tertiary referral centre and serves as one of the national referral centres for patients with advanced HF with need for mechanical circulatory support or HT for a significant part of the Netherlands. This study was conducted in accordance to the declaration of Helsinki.(3) Our local research ethics committee has given approval for this study.

Data collection

We extracted the variables from patients' records and discharge letters. Data collection started at day of admission for new-onset acute HF. Follow-up was considered complete after approximately 3 years. Variables were collected during admission (i.e. baseline), at 6 months, and at 1, 2 and 3 years after admission (all ±3 months). Data collection ended when patients died, received an LVAD, underwent HT or moved to another hospital's outpatient clinic.

In addition to the variables age and sex, we collected body mass index, medical history and aetiology of HF. At baseline and during follow-up moments, we gathered systolic and diastolic blood pressure, heart rate, rhythm on electrocardiogram, medical and device therapy and a selection of laboratory parameters.

We also collected a number of echo parameters with transthoracic echocardiography. These included left ventricular end-diastolic (LVED) diameter, left ventricular end-systolic (LVES) diameter and LVEF. The LVEF was determined by using the Simpson method with software Image-Com 5.5 (TomTec Imaging Systems GmbH, Unterschleissheim, Germany). If available, we measured the following parameters of diastolic function: E/A ratio, mitral valve deceleration time and E/e' ratio. The severity of mitral valve regurgitation and tricuspid valve regurgitation were classified into absent, mild, moderate or severe. Mitral and tricuspid valve regurgitation was defined by using the qualitative and semiquantitative criteria as defined in the ESC guideline about valvular heart disease.(4) Grading the severity of mitral and tricuspid valve regurgitation was done according to the guidelines of the European Association of echocardiography.(5) Right ventricular function was quantified with the TAPSE. Lastly, we measured the inferior caval vein's diameter.

Definitions

We defined the recovery of the LV as an LVEF of at least of 50% in a patient with previously HFrEF as this definition has been used in several other studies.(6, 7) Furthermore, in the TRED-HF trial on withdrawal of HF medication after recovery of dilated cardiomyopathy, an improvement of LVEF to 50% was required before withdrawal was attempted.(8) Furthermore, we used an increase of > 10% of LVEF as a measure of significant LV reverse remodeling.

Endpoint

The primary endpoint of our study was the LV remodeling during up to 3 years of follow-up. LVED diameter, LVES diameter and LVEF were used as markers for LV remodeling. Next to those markers, we analysed the pattern of mitral valve regurgitation.

We also studied the patient's prognosis (up to 10 years) using the composite of all-cause mortality, HT and LVAD implantation. We also analysed the HF rehospitalisation according to aetiology. The Municipal Civil Registries were consulted to assess the survival status of the included patients.

Statistical analyses

Continuous variables were presented as median with interquartile range (IQR) and categorical variables as numbers and percentages. The Mann-Whitney U test and $\chi 2$ test were used to compare continuous and categorical variables, respectively.

We used the Kaplan-Meier method in order to estimate the cumulative event rates. Cox proportional hazard models were applied to evaluate the difference in the composite endpoint between patients with ischaemic and non-ischaemic HF. The results are presented as hazard ratio (HR) with their 95% confidence interval (95% CI).

Linear mixed-effects models were fitted for LVEF, LVED diameter and LVES diameter (dependent) to assess remodeling. To compare remodeling between ischemic HF and non-ischemic HF patients, we calculated the delta remodeling by subtracting the baseline measurement from the measurements taken at least 6 months after inclusion per patient, as we expected that most remodeling will have occurred within the first six months after admission. Subsequently, these deltas were used as dependent in the adjusted linear mixed-effects models. Lastly, Cox proportional hazard regression was used to relate the repeated LVEF, LVED and LVES measurements to outcome. To avoid bias, parameters of the linear mixed-effects models and Cox regression models were combined in a joint-model.

All tests were two-tailed and $p<0.05$ were considered as statistically significant. SPSS software (SPSS 24.0, IBM Corp., Armonk, NY, USA) was used for the descriptive statistical analyses and the survival analyses. R statistical software (version 3.4.3) was used for the linear mixed-effects models and joint-models, in particular the packages *nlme* and *JMbayes*.

Results

Baseline characteristics

During the inclusion period, 141 patients admitted with acute HF potentially qualified for inclusion. Of these, 17 patients were excluded because they died or received an LVAD before discharge and 13 patients were excluded due to limited follow-up in our hospital. Consequently, we included 111 patients admitted with new-onset acute HF (Figure 1).

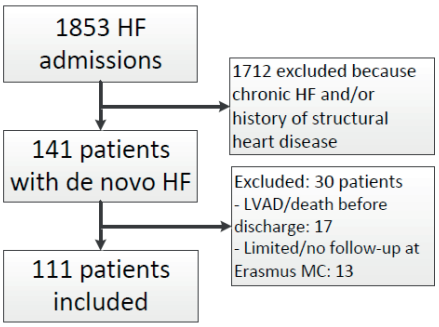

Figure 1. Flow chart of patient selection
HF, heart failure; LVAD, left ventricular assist device

The included patients had a median age of 50.0 (IQR 38.6-60.3) years, almost half were men and 38% of the patients had ischaemic HF (Table 1). Non-ischaemic HF was predominately diagnosed as idiopathic dilated cardiomyopathy (n=27), toxic cardiomyopathy (n=13) and myocarditis (n=11). During admission, 48% of the patients required inotrope and/or vasopressor support and 23% needed in addition short-term mechanical circulatory support by ECMO and/or IABP. Of the patients with ischaemic HF, 33 had a percutaneous coronary intervention and 1 underwent coronary artery bypass grafting during the initial hospitalisation. At discharge, NYHA class and HF treatment were comparable between patients with ischaemic and non-ischaemic HF.

Table 1. Baseline characteristics of patients with ischaemic and non-ischaemic HF

	Total population (n=111)	**Ischaemic HF (n=42)**	**Non-ischaemic HF (n=69)**	**p-value**
Demographics				
Age	50.0 (38.6-60.3)	58.9 (50.3-64.9)	43.8 (32.9-54.7)	<0.001
Male	62 (56%)	26 (62%)	36 (52%)	0.32
Body mass index	24.9 (22.3-27.3)	24.9 (22.7-27.2)	24.9 (21.8-28.0)	0.91
Aetiology heart failure				<0.001
Ischaemic				
STEMI	31 (28%)	31 (74%)		
Non STEMI	3 (3%)	3 (7%)		
Stable coronary artery disease	8 (7%)	8 (19%)		
Idiopathic dilated cardiomyopathy	27 (24%)		27 (39%)	
Non-compaction cardiomyopathy	5 (5%)		5 (7%)	
Hypertensive cardiomyopathy	5 (5%)		5 (7%)	
Immune-mediated cardiomyopathy	2 (2%)		2 (3%)	
Toxic cardiomyopathy	13 (12%)		13 (20%)	
Peri-partum cardiomyopathy	4 (4%)		4 (6%)	
Myocarditis	11 (10%)		11 (16%)	
Tako-tsubo cardiomyopathy	2 (2%)		2 (3%)	
Medical history				
Atrial fibrillation	2 (2%)	1 (2%)	1 (1%)	1.00
Diabetes	8 (7%)	7 (17%)	1 (1%)	0.008
Hypertension	27 (24%)	19 (45%)	8 (12%)	<0.001
Hypercholesterolemia	11 (10%)	9 (21%)	2 (3%)	0.007
Smoker				0.82
Current smoker	35 (32%)	16 (38%)	19 (28%)	
Former smoker	17 (15%)	7 (17%)	10 (15%)	

	Total population (n=111)	Ischaemic HF (n=42)	Non-ischaemic HF (n=69)	p-value
Renal dysfunction	3 (3%)	2 (5%)	1 (1%)	0.57
Anaemia	2 (2%)	0 (0%)	2 (3%)	0.51
Chronic obstructive pulmonary disease	2 (2%)	1 (2%)	1 (1%)	1.00
Malignancy	8 (7%)	1 (2%)	7 (10%)	0.13
Depression	5 (5%)	1 (2%)	4 (6%)	0.39
Advanced therapy during admission				
IABP treatment	24 (22%)	21 (50%)	3 (4%)	<0.001
ECMO treatment	3 (3%)	1 (2%)	2 (3%)	1.00
Inotrope/vasopressor support	53 (48%)	25 (60%)	28 (41%)	0.05
Characteristics at discharge				
Systolic blood pressure (mmHg)	103 (90-115)	105 (88-116)	103 (93-115)	0.53
Diastolic blood pressure (mmHg)	63 (55-75)	65 (55-75)	62 (56-75)	0.85
Heart rate (bpm)	74 (65-83)	76 (69-84)	72 (63-82)	0.19
Sinus rhythm	101 (92%)	40 (95%)	61 (90%)	0.48
Bundle branch block				0.67
Left bundle branch block	5 (5%)	1 (2%)	4 (6%)	
Right bundle branch block	6 (5%)	2 (5%)	4 (6%)	
Therapy at discharge				
Beta-blocker	103 (93%)	36 (86%)	67 (97%)	0.05
ACE inhibitor or ARB	106 (96%)	41 (98%)	65 (94%)	0.65
Mineralocorticoid receptor antagonist	67 (60%)	24 (57%)	43 (62%)	0.59
Diuretics	97 (87%)	36 (86%)	61 (88%)	0.68
Digoxin	55 (50%)	16 (38%)	39 (57%)	0.06
Statin	45 (41%)	39 (93%)	6 (9%)	<0.001
(Direct) oral anticoagulant	78 (70%)	27 (64%)	51 (74%)	0.28
Thrombocyte aggregation inhibitor	36 (32%)	30 (71%)	6 (9%)	<0.001
Pacemaker	1 (1%)	0 (0%)	1 (1%)	1.00
ICD	26 (23%)	7 (17%)	19 (28%)	0.19
CRT	4 (4%)	0 (0%)	4 (6%)	0.16
Laboratory values at discharge				
Creatinine (µmol/L)	91 (76-116)	94 (80-129)	89 (72-112)	0.22
eGFR (ml/min)	64 (54-83)	60 (48-80)	67 (56-86)	0.11
Sodium (mmol/L)	139 (137-141)	139 (137-141)	139 (137-141)	0.86
Potassium (mmol/L)	4.5 (4.2-4.8)	4.5 (4.2-4.8)	4.5 (4.2-4.8)	0.85

	Total population (n=111)	Ischaemic HF (n=42)	Non-ischaemic HF (n=69)	p-value
Urea (mmol/L)	9.2 (6.8-12.3)	9.3 (6.7-12.3)	9.2 (7.0-12.3)	0.82
ASAT (U/L)	29 (23-38)	26 (19-33)	31 (25-43)	0.06
ALAT (U/L)	35 (24-60)	26 (19-43)	39 (29-70)	0.02
Haemoglobin (mmol/L)	7.6 (6.7-8.6)	7.0 (6.3-7.8)	8.2 (7.0-9.7)	<0.001
Haematocrit (L/L)	0.38 (0.33-0.41)	0.35 (0.31-0.38)	0.39 (0.36-0.43)	0.001
NT-proBNP (pmol/L)	251 (100-577)	577 (392-738)	234 (87-401)	0.02

Results depicted as N (%) or median (interquartile range)

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; CRT, cardiac resynchronization therapy; ECMO, extra-corporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; HF, heart failure; IABP, intra-aortic balloon pump; ICD, implantable cardioverter defibrillator; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; STEMI, ST-elevated myocardial infarction

Left ventricular remodeling

At discharge, both the LVED and LVES diameter were significantly larger in patients with non-ischaemic HF than in those with ischaemic HF (Table 2). In addition, patients with non-ischaemic HF had lower LVEF than patients with ischaemic HF (26% [IQR 21-33] and 32% [IQR 25-36], respectively). The prevalence of poor LVEF (i.e. LVEF ≤30%) at discharge was higher in patients with non-ischaemic HF than in those with ischaemic HF (67% versus 48%, p=0.047). Furthermore, 44% of the patients exhibited moderate to severe mitral valve regurgitation and 26% moderate to severe tricuspid valve regurgitation.

Table 2. Echocardiography parameters at discharge of patients with ischaemic and non-ischaemic HF

	Total population	Ischaemic HF	Non-ischaemic HF	p-value
LVED diameter (mm)	58 (53-66)	54 (52-62)	60 (56-68)	0.001
LVES diameter (mm)	48 (39-56)	43 (36-49)	52 (46-59)	<0.001
LVEF (%)	28 (22-34)	32 (25-36)	26 (21-33)	0.03
Mitral valve regurgitation				0.80
Absent	22 (21%)	10 (25%)	12 (18%)	
Mild	37 (35%)	12 (30%)	25 (37%)	
Moderate	24 (22%)	9 (23%)	15 (22%)	
Severe	24 (22%)	9 (23%)	15 (22%)	
E/A ratio	1.6 (1.0-2.3)	1.4 (0.9-2.2)	1.7 (1.1-2.3)	0.29
Deceleration time mitral valve (ms)	158 (123-190)	171 (136-201)	151 (113-181)	0.06
E/E'	14.7 (10.2-19.8)	13.9 (10.1-23.1)	14.7 (10.3-19.4)	0.70

	Total population	Ischaemic HF	Non-ischaemic HF	p-value
Tricuspid valve regurgitation				0.95
Absent	44 (43%)	16 (41%)	28 (44%)	
Mild	32 (31%)	13 (33%)	19 (30%)	
Moderate	17 (17%)	7 (18%)	10 (16%)	
Severe	9 (9%)	3 (8%)	6 (10%)	
Tricuspid insufficiency gradient (mmHg)	27 (21-36)	36 (26-43)	25 (21-29)	0.002
Diameter inferior caval vein (mm)	16 (13-19)	17 (13-18)	16 (13-20)	0.79
TAPSE (mm)	18 (16-22)	19 (16-22)	18 (16-22)	0.59

Results depicted as N (%) or median (interquartile range)
LVED, left ventricular end-diastolic; LVEF, left ventricular ejection fraction; LVES, left ventricular end-systolic

During 3 years of follow-up, LVEF recovered in 10% of the patients with ischaemic HF and in 39% of those with non-ischaemic HF ($p<0.001$). Of the patients with LVEF recovery, recovery was already present in half of the patients during the echocardiographic assessment at 6 months after discharge. In total 26% of the patients with ischaemic HF had a significant (at least 10%) improvement of LVEF, compared to 72% of those with non-ischaemic HF ($p<0.001$). The LVEF recovery and significant improvement of LVEF was comparable between patients with an LVEF ≤30% and LVEF >30% ($p=0.06$).

Figure 2 presents the time-dependent changes in LVED diameter, LVES diameter and LVEF after discharge (see Supplemental Table 1 for fitting values). Both patients with non-ischaemic and ischaemic HF had significant improvement in LVEF ($p<0.001$ and $p=0.004$, respectively). This improvement was significant higher in those with non-ischaemic HF (17% vs. 6%, $p<0.001$). Furthermore, while patients with non-ischaemic HF had a significant reduction in LVED and LVES diameters (6mm and 10mm, both $p<0.001$), these diameters did not change in those with ischaemic HF (+3mm [$p=0.09$] and +2mm [$p=0.07$], respectively). In addition to the above mentioned parameters of LV remodeling, we also found that the severity of mitral valve regurgitation decreased during the first 6 months ($p=0.02$) in patients with non-ischaemic and not in those with ischaemic HF (Figure 3). Furthermore, the NT-proBNP levels decreased in both ischaemic and non-ischaemic HF patients during follow-up, especially in the first 6 months (Table 3).

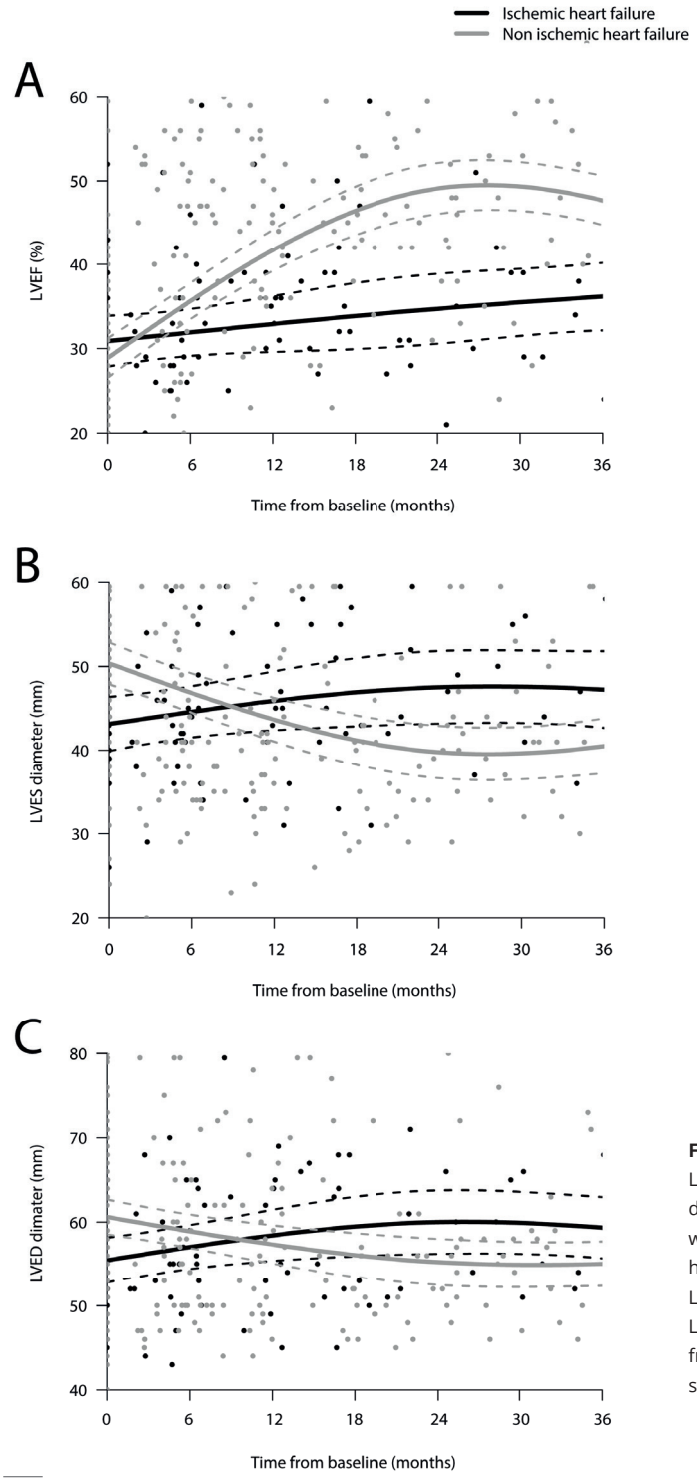

Figure 2. Changes in LVEF (**A**), LVES diameter (**B**) and LVED diameter (**C**) over time in patients with ischaemic and non-ischaemic heart failure

LVED, left ventricular end-diastolic; LVEF, left ventricular ejection fraction; LVES, left ventricular end-systolic

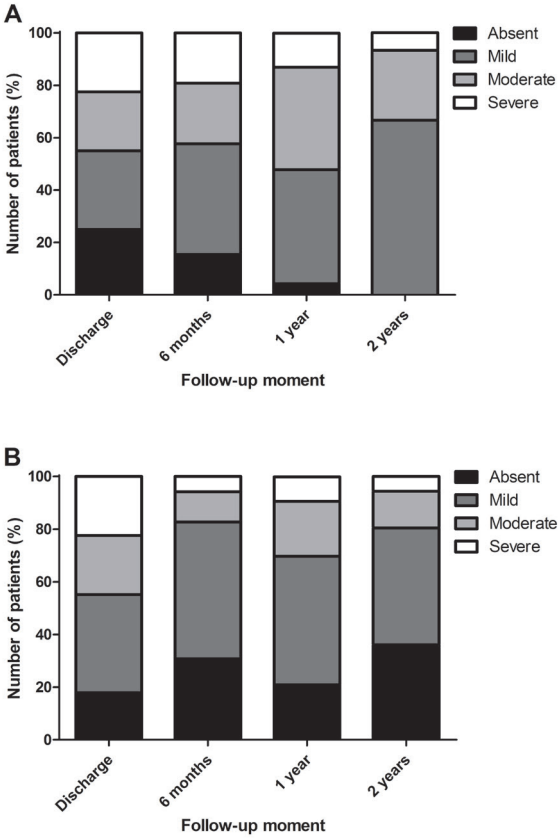

Figure 3. Severity of mitral valve regurgitation in patients with ischaemic (**A**) and non-ischaemic (**B**) HF

Table 3. NT-proBNP during follow-up in patient with ischaemic and non-ischaemic HF

	Ischaemic HF	Non-ischaemic HF	p-value
Baseline	577 (392-738)	234 (87-401)	0.02
6 months	237 (101-514)	48 (22-114)	<0.001
1 year	170 (80-285)	38 (18-81)	0.004
2 years	137 (79-294)	22 (12-95)	0.008
3 years	74 (41-151)	16 (6-124)	0.17

Results depicted as median (interquartile range)
HF, heart failure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide

Since there was no consistent policy on the interval between the echocardiograms, we had missing values in LVED diameter, LVES diameter, LVEF and mitral valve regurgitation during the 3 years of follow-up (Supplemental Table 2). Nevertheless, the median number of repeated measurements for LVED diameter, LVES diameter and LVEF was 3 (IQR 2-4).

Prognosis

During a median follow-up time of 4.6 years, 13 patients (12%) reached the composite end-point of all-cause mortality, HT and LVAD implantation. Prognosis was comparable between patients with ischaemic and non-ischaemic HF (HR 0.69 [95% CI 0.19-2.45]; Figure 4). Eleven patients died during follow-up; 3 patients received an LVAD and 2 underwent HT. Thirteen patients (12%) needed rehospitalisation for HF during the follow-up, with no difference between patients with and without ischaemic aetiology (HR 2.02 [95% CI 0.68-6.02]).

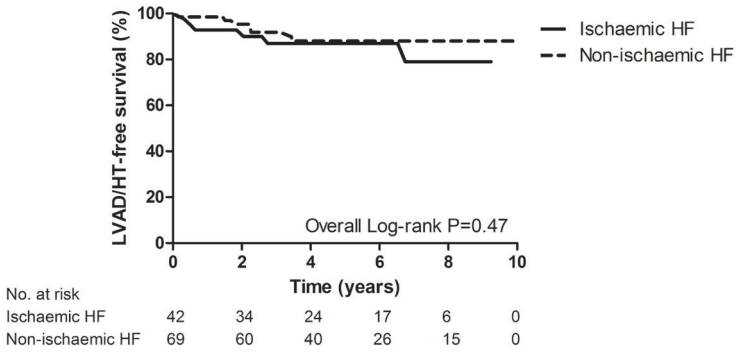

Figure 4. LVAD/HT-free survival curve of patients with ischaemic and non-ischaemic heart failure
HF, heart failure; HT, heart transplantation; LVAD, left ventricular assist device

Furthermore, we found that higher increase in LVEF was associated with better prognosis (HR per 5% increase 1.13 [95% CI 1.10-1.43]). In contrast, decreases in LVED diameter and LVES diameter were not associated with better outcome (HR per 1 mm decrease in LVED diameter 1.002 [95% CI 0.93-1.07] and HR per 1 mm decrease in LVES diameter 1.00 [95% CI 0.92-1.06]). Adjustment for HF aetiology did not change these associations.

Among the patients with clinical follow-up until 3 years (n= 58), 28 patients received an ICD and 5 patients of them a CRT device. During up to 3 years of clinical follow-up, 8 patients had 9 shock events. Of these, 4 shocks were inappropriate.

After the initial hospitalisation, 4 patients underwent cardiac surgery (3 coronary artery bypass grafting and 1 mitral valve replacement) and 8 patients received catheter based therapy (8 percutaneous coronary interventions, 1 mitraclip implantation, 1 transcatheter aortic valve implantation).

Discussion

This study describes the LV remodeling and long-term prognosis in a cohort of patients with new-onset severe HFrEF, who required admission and in many cases needed inotropes (48% of the patients) and short-term mechanical support (23% of the patients), but who were eventually successfully weaned from support and discharged with medication. The improvement in LVEF was already present at 6 months in the patients with non-ischemic aetiology and increased exponentially up to 2 years of follow-up, which mirrored the decrease of LV diameters, both end-diastolic and end-systolic. Furthermore, in these patients the severity of mitral regurgitation significantly decreased at 6 months. On the contrary, in their ischaemic counterparts, the LVEF modestly increased linearly during follow-up, while LV diameters and the severity of mitral regurgitation did not change. The prognosis of this subpopulation of patients discharged on medication after the first episode of severe acute HFrEF is much better as compared with other studies on large cohorts with acute decompensated HF.

Indeed, it is not very unique to study recovery of LVEF and its relation with prognosis.(9-12) However, our study has some unique strengths. First, we included a less heterogenic population than others. Although other studies did not include de novo heart failure patient specifically, in our opinion, left ventricular remodeling should be studied in an early stage of HF because of recovery of the LVEF takes place early. Further, compared to other studies, echocardiography in our study was repeated after a relatively short period. This enables us to say something about the trend in remodeling. Last, we included clinical variables that are missing from other studies.

Left ventricular remodeling

Improvement of LVEF in a minority of patients with dilated cardiomyopathy within 6 months and therefore deferral of listing for HT was already reported in 1994, before the introduction of beta-blocker therapy.(13) However, after the introduction of beta-blockers and aldosterone-antagonists in HF treatment a significant improvement of LVEF was shown in one-third of patients with recently diagnosed HFrEF, and in half of them this improvement already occurred at 6 months.(14) More studies have investigated improvement of LVEF and prognosis in outpatients with recent onset dilated cardiomyopathy.(15) To the best of our knowledge, our study is the first to investigate the LV remodeling in a subpopulation of severe new-onset HFrEF that required admission.

A large proportions of our patients received digoxin (57% of the patients with non-ischemic HF). The beneficial properties of digoxin in acute HF syndromes have been attributed to the improvement of hemodynamics by attenuating tachycardia without negative inotrope effects and to the absence of side effects at lower dosages.(16) The inotropy-dependent low-output patients in our cohort could be immediately treated with digoxin, while introduction of beta-blocker was postponed until the relief of congestion and achievement of euvolemia, according to a previously published protocol from our center.(1) At discharge > 90% of patients were treated by beta-blockers in combination

with ACE-inhibitors or angiotensin-receptor blockers. The patients were followed weekly thereafter at our outpatient clinic and the medication has been up titrated till maximum tolerated dosage according to the ESC heart failure guidelines.(17)

We found a clear difference in LV remodeling between patients with non-ischaemic HF and those with ischaemic HF. This difference can primarily be explained by the aetiology of HF. To qualify for LV remodeling, there should be limited replacement fibrosis and enough viable myocardium.(18) Patients with ischaemic HF are less potential to develop LV remodeling because ischaemic myocardium is more extensively and irreversibly damaged. In contrast, patients with non-ischaemic HF may have more viable myocytes.(7, 18) Indeed, it has been observed that some specific non-ischaemic causes like myocarditis and peripartum cardiomyopathy have a relatively high chance to recover.(6) However, optimal HF treatment may be another explanation for LV remodeling. HF treatment and in particular neurohumoral blockers have been associated with LV remodeling.(19, 20) Optimal therapy with beta-blockers, ACE-inhibitors, angiotensin receptor blockers and MRAs is of great importance.

In literature, several other factors, besides optimal medical treatment, have been found to be associated with LVEF improvement.(9-12, 14) In several studies, female sex has been associated with improvement of LV function.(9-12) In our study, the distribution of sex was not different between the ischaemic and non-ischaemic HF, and we found no difference in the outcomes. However, the size of our cohort may be too small to assess the effect of sex on top of the medical treatment. The presence of hypertension and diabetes have also been correlated with LVEF changes. Furthermore, it has been reported that LVEF improvement was more common in patients with HF with non-ischaemic cause than in subjects with ischaemic HF. However, so far, the time-dependent evolution of LV remodeling including LVEF, LV dimensions and mitral valve regurgitation has never been compared in patients with ischaemic and non-ischaemic HF.

Further, we also found a decrease in severity of mitral valve regurgitation. Decrease in mitral valve regurgitation has found to be associated with better prognosis and symptom relieve.(21, 22) Our study showed that LV remodeling by medical treatment also leads to reduction of mitral valve regurgitation, which is consistent with other reports.(21-23)

Prognosis

The prognosis of patients with acute HF has been studied extensively. Mortality rates of up to 35% at 1 year(24-28) and up to 75% at 5 years follow-up(25, 27) are reported. These cohorts included acute HF patients of the whole broad range: both new-onset acute HF and decompensated chronic HF, with and without cardiac history, patients admitted to secondary and tertiary hospitals. Notably, our patients had a more favourable prognosis with an LVAD/HT-free survival of 88% during a follow-up of up to 10 years. The better prognosis in our study can be explained by the specific inclusion of new-onset HF in patients without a history of HF or any structural heart disease and exclusion of patients

who could not be weaned from advanced support and received a permanent LVAD or died in hospital. Furthermore, we included patients in a more recent era than previous studies and, hence, our patients were treated with the broad range of guideline based HF medication, including a large number of patients using beta-blocker therapy.

Furthermore, we found that improvement in LVEF was associated with a better prognosis. This was in accordance with a recent meta-analysis by Jorgensen et al.(29) who showed that patients in whom LVEF improved were found to have a better prognosis consisting of both improved survival rate and lower risk of appropriate ICD shocks.

Implications for clinical practice

As already mentioned, patients with HFrEF should be treated according to the guidelines with optimal dosage of beta-blocker, renin angiotensin aldosterone system inhibition and MRAs.(17) Recently, data from the PIONEER-HF trial show that introduction of angiotensin-receptor neprilysin inhibitor (ARNI) during hospitalisation for acute heart failure significantly improved the clinical outcome as compared to ACE-inhibitors.(30) Although not investigated in our study, replacing ACE-inhibitor by ARNI should be considered before discharge or at the outpatient clinic. Optimal medical treatment does not only carry prognostic benefit but it may also contribute to the LV remodeling. Since we found that remodeling may occur until 2 years after the initial event mainly in non-ischaemic HF, clinicians should optimize medication and give time to remodel before concluding that LVAD or HT is necessary.(2)

Since almost half of our study patients needed inotrope and/or vasopressor support and almost a quarter of the patients received mechanical circulatory support, this indicates that we included very ill HF patients. Despite this adverse clinical presentation, we found remodeling in a significant part of these patients. Since we included patients with severe HFrEF with or without cardiogenic shock at presentation, part of them may currently qualify for LVAD or HT. Indeed, LVAD therapy also leads to cardiac remodeling. However, LVAD therapy has several potential complications like stroke, pump thrombosis, bleeding and infection.(31) Therefore, we propose persuasion of the attempts to wean the support in patients with the first hospitalisation for new-onset HFrEF during concomitant optimization of HF medication. Only under the condition that patients remain inotrope-dependent, one should proceed to urgent LVAD or HT.

It still remains uncertain how patients with recovered LVEF should be treated in the long-term. Indeed, patients with recovered LV function may have abnormal biomarker levels and may still have an adverse long-term prognosis.(32) Recently, the TRED-HF trial has shown that withdrawal of pharmacological treatment negatively influenced the course of dilated cardiomyopathy.(8) In our hospital, patients with completely recovered LVEF and without HF symptoms are continued to be treated with beta-blocker and ACE-inhibitor or angiotensin receptor blocker. Basuray and Fang(6) also advocated continuation of HF medication after recovered LVEF in patients with several different aetiologies.

Limitations

Several study limitations should be acknowledged. First and foremost, the retrospective nature of this study resulted into a significant number of missing LVED diameters, LVES diameters, LVEF, mitral valve regurgitation and NT-proBNP measurements during follow-up. However, we used the delta remodeling in the linear mixed-effects models in order to make optimal use of all the available measurements. Secondly, despite the long inclusion period, we had a relatively small number of patients. This is suggesting that there are only a limited number of patients with severe new-onset HFrEF without any previous structural heart disease requiring hospitalisation. Thirdly, since we are a tertiary referral centre, part of our patients initially presented in another hospital. Consequently, there may be a bias since a number of patients were not referred to our hospital which may reduce the external validity. Next, we excluded patients who died or received an LVAD during the initial hospital admission, because we designed this study to investigate the LV remodeling in patients treated with medical HF therapy. However, this may have influenced the prognostic end-point of this study. Furthermore, there were low implantation rates of ICD and CRT. This could be explained by the LVEF improvement during follow-up and therefore the lack of indication for ICD. Also, the low number of events did not allow a proper multivariable analysis, because the event-per-variable ratio would lead to significant overfitting in the model and a high risk of statistical error. Lastly, we did not measure LV volumes which could give additional information regarding LV remodeling.

We also acknowledge the lack of treatment with ARNIs and SGLT2-inhibitors, which were not available at the moment of our study, but nevertheless may present a limitation for extrapolation of our results to the modern clinical practice.

Conclusion

This study investigated LV remodeling and prognosis in patients with new-onset acute severe HFrEF. There was no difference in prognosis between patients with ischaemic and non-ischaemic HF, although the LV remodeling differed considerably between these two patient groups. In contrast to those with ischaemic HF, patients with non-ischaemic HF showed significant LV remodeling already at 6 months, which progressed exponentially in the first 2 years of medical treatment. Hence, our study emphasizes the importance of optimal medical treatment at discharge, as this is a determinant of LV remodeling and a good long-term prognosis.

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Supplemental material

Supplemental Table 1. Fitting values belonging to Figure 2

Left ventricular ejection fraction				
	Estimates	95% confidence interval		P-value
Ischaemic HF	0.988	0.331	1.644	0.004
Non-ischaemic HF	2.864	2.234	3.494	<0.001
Left ventricular end-diastolic diameter				
	Estimates	95% confidence interval		P-value
Ischaemic HF	0.529	-0.073	1.131	0.09
Non-ischaemic HF	-0.958	-1.342	-0.575	<0.001
Left ventricular end-systolic diameter				
	Estimates	95% confidence interval		P-value
Ischaemic HF	0.576	-0.046	1.195	0.072
Non-ischaemic HF	-1.616	-2.161	-1.071	<0.001

Estimates are per 6 months
HF, heart failure

Supplemental Table 2. Number of missing values

	LVED diameter	LVES diameter	LVEF	MVR	NT-proBNP
Baseline	5	5	0	4	84
6 months	35	36	32	33	58
1 year	48	48	45	45	73
2 years	63	64	60	60	82
3 years	79	80	76	76	86

LVED, left ventricular end-diastolic; LVEF, left ventricular ejection fraction; LVES, left ventricular end-systolic; MVR, mitral valve regurgitation; NT-proBNP, N-terminal prohormone of brain natriuretic peptide

CHAPTER 8

Preventive ICD-therapy in Contemporary Clinical Practice

More stringent selection criteria long overdue

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ESC Heart Failure: accepted for publication

Abstract

While the efficacy of the intracardiac defibrillators (ICDs) for primary prevention is not disputed, the relevant studies were carried out a long time ago. Most pertinent trials, including MADIT-II, SCD-Heft and DEFINITE, recruited patients more than 20 years ago. Since then, improved therapeutic modalities including, in addition to cardiac-resynchronization therapy, mineralocorticoid-receptor antagonists, angiotensin receptor-neprisylin inhibitors and, most recently, inhibitors of sodium-glucose cotransporter 2, have lowered present-day rates of mortality and of sudden cardiac death. Thus, nowadays, ICD therapy may be less effective than previously reported, and not as beneficial as many people currently believe. However, criteria for ICD-implantation remain very inclusive. The patient must (only) be symptomatic and have ejection fraction (EF) ≤35%. The choice of EF 35% is notable because the average EF in all large trials was much lower, and clinical benefit was mainly limited to EF ≤30%. This EF cut-off value defines a substantial portion of potential ICD recipients. It seems therefore reasonable to limit ICD eligibility criteria in the EF range 30 to 35% to patients at highest risk only. We discuss and present some rational criteria to assist the clinician in improving risk stratification for preventive ICD implantation.

Introduction

Each month, over 10,000 cardioverter-defibrillators (ICDs) are being implanted in the US alone, while the overall volume of worldwide implantations continues to increase as well.(1-3) Most devices are implanted in patients at high risk of sustained ventricular tachycardia or fibrillation.(2) While the efficacy of the ICDs for this indication - primary prevention – is not disputed, it is fair to say that the relevant studies were carried out a long time ago.(4-10) Most trial reports date from early this century, implying that their results were obtained in – and in theory thus only applicable to - patients treated over twenty years ago. Since then, the principle of electric shock for life-threatening arrhythmias has not changed much, while other therapeutic options have progressed and rates of sudden cardiac death have decreased.(11) Thus, present-day ICD therapy may be less effective than previously reported, and not as beneficial as many people currently believe. This assessment is validated by the results of the most recent and large study on preventive ICD-implantation, which reported only a minor survival advantage of ICD-placement compared to usual clinical care in individuals with a cardiomyopathy of non-ischemic origin.(12) Admittedly, patients with ischemic heart disease (IHD) are at higher risk of sudden cardiac death, but their recruitment in the applicable trials also dates back two decades, and the therapy that they received reflects that. Therefore, time has come for an updated qualitative assessment of current indications for preventive ICD-therapy, and that is the aim of our paper.

The trails

In ischemic heart disease

Preventive ICD-implantation in IHD has been investigated in seven randomized trials.(4-10) MADIT I and MUSTT started enrolment in 1990 (see Table 1 for characteristics of both studies). Electrophysiological investigation (EP) was needed prior to inclusion in both, a requirement that has been abandoned in subsequent trials.(4, 6) In fact, MUSTT was a comparison of EP guided versus "conventional" therapy and, among the 351 randomized to EP guided therapy, 161 (46%) patients initially received defibrillators. Two "negative" trials – DINAMIT and IRIS - took place shortly (within 40 days) after myocardial infarction (MI), and resulted in the contra-indication of ICD-implantation in early post-MI survivors.(8, 10) The CABG Patch trial was done in patients undergoing surgical coronary revascularization, but found no benefit of ICD-insertion in that population.(5) Thus, MADIT II and SCD-HeFT comprise the most recent trials favouring ICD implantation in IHD.(7, 9) Because of their significance, both – so-called landmark – trials are described in some detail. Additional details are presented in Table 1.

Table 1. Characteristics and outcome of randomized trials of ICD-implantation and novel pharmacotherapies in ischemic and non-ischemic heart disease.

Trial name	Intervention	Year of publication	Num-ber[1]	Number with IHD[1]	Annual death rate	Inclusion EF	Mean EF	Mortality reduction	ACE-Inhibition	Beta-blockers	MRAs
MADIT-I	ICD in IHD	1996	93	93	12%	≤35%	26%	54%	54%	23%	unk
MUSTT	EP guided therapy	1999	351	351	10%	≤40%	30%	60%	unk	40%	unk
MADIT-II	ICD in IHD	2002	742	742	9%	≤30%	23%	31%	70%	70%	unk
SCD-Heft	ICD "mixed"	2005	829	431	10%	≤35%	25%	23%	94%	69%	20%
DEFINITE	ICD dilated CM	2004	229	NA	6%	≤35%	21%	35%	84%	85%	unk
Danish trial[2]	ICD dilated CM	2016	556	NA	4%	≤35%	25%	13%	97%	92%	57%
EPHESUS[3]	MRA	2003	3319	3319	8%	<40%	33%	15%	87%	75%	100%[5]
EMPHASIS	MRA	2011	1364	951	7%	≤30%	26%	22%	94%	87%	100%[5]
PARADIGM	LCZ696	2014	4187	2506	7%	≤35%[4]	30%	16%	100%[5]	93%	54%
DAPA-HF	SGLT2	2019	2373	1316	7%	≤40%	31%	17%	95%	96%	71%

ACE, Angiotensin-converting enzyme; CM, cardiomyopathy; EF, ejection fraction; ICD, intracardiac defibrillator; IHD, ischaemic heart disease; MRA, mineralocorticoid receptor antagonist; NA, not applicable; SGLT2, Sodium-glucose co-transporter-2 inhibitor; Unk, unknown

1. Number of patients in the active treatment arm
2. Cardiomyopathy of non-ischemic origin
3. Early post MI patients, high initial mortality
4. After protocol modification
5. By trial design

Starting in July 1997, MADIT II randomized 1232 post-MI patients with advanced left ventricular (LV) dysfunction, defined as LV ejection fraction (EF) ≤30% (Table 1).(7) The hazard ratio for mortality was 0.69, but the plausible effect range was wide (95% confidence interval (CI) 0.51 – 0.93).

From September 1997 onwards, SCD-HeFT evaluated prophylactic ICD-therapy versus placebo (as well as versus amiodarone) in three groups each of about 840 patients with symptomatic congestive heart failure and EF ≤35%.(9) The cardiomyopathy was of ischemic origin in approximately 50% of the patients. Compared to placebo, ICD-implantation was associated with a 23% (95% CI 4% to 38%) reduction in mortality. The largest survival benefit was observed in patients with NYHA class II heart failure and with LVEF ≤30%, characteristics present in 70 to 80% of patients included.

In non-ischemic cardiomyopathy

As described above, SCD-Heft was a mixed trial of patients with ischemic as well as non-ischemic heart disease. Randomized trials of preventive ICD therapy in patients with exclusively non-ischemic heart disease include – in chronological order - CAT, AMIOVIRT, DEFINITE and the DANISH study.(12-15). Both CAT and AMIOVIRT were quite small, each including about 100 patients. Enrolment in CAT began in 1991 and required – amongst others - EF ≤ 30%.(13) The number of deaths in patients randomized to ICD (n=13) or medical therapy (n=17) was not different, the main predictor of mortality was low EF. Recruitment in AMIOVIRT commenced in August 1996 and was completed by September 2000, with the purpose to compare total mortality during therapy with amiodarone or ICD.(14) The inclusion EF was ≤35%, but the mean EF of the included patients was much lower, namely 23%. Survival at three years was similar among patients treated with ICD (88%) and amiodarone (87%).

DEFINITE randomized 458 symptomatic patients with LVEF ≤35% and ambient arrhythmias.(15) The first patient was randomized in 1998, mean EF was 21%. With 28 and 40 deaths in the ICD and control group, respectively, the point estimate of the difference in mortality was sizeable (hazard ratio 0.65, 95% CI 0.40 to 1.06), although not statistically significant.

The DANISH study is the most recent and largest trial in non-ischemic cardiomyopathy. (12) This study randomized 556 patients with symptomatic systolic heart failure and EF ≤35% to ICD, and 560 to usual clinical care. After a median follow-up of almost 6 years, 120 patients in the ICD and 131 patients in the control groups had died (HR 0.87, 95% CI 0.68 to 1.12, p =0.28). Although ICD placement was effective in lowering the rate of sudden cardiac death - from 8.2% to 4.3%, the authors concluded that prophylactic ICD implantation did not reduce long-term mortality.

When the data from the various trials are combined, the mortality benefits associated with preventive ICD-insertion in non-ischemic disease typically range from 19% to 25%.(16-19) Details of the two largest trials, DEFINITE and the DANISH study, are presented in Table 1.

Current therapeutic options

Medical treatment in the two first landmark trials in ischemic heart disease, MADIT-II and SCD-Heft, was probably standard for that time period, although usage of beta-blockers and mineralocorticoid receptor antagonists was relatively modest while, as a reflection of previous clinical practice, digoxin was used frequently. But in the next twenty years, further therapeutic advancements have become available for patients with LV dysfunction, with significant bearing on their outcome.

One relevant development in the treatment of patients with heart failure includes the introduction of cardiac-resynchronization therapy (CRT) and with or without ICD. The COMPANION investigators established the worth of this treatment modality in 1520 patients with advanced (NYHA class III and IV) heart failure, 57% of them with IHD. Most patients, with mean EF of 22%, received contemporary medical treatment. One-year mortality, almost 20%, was very high. The combination of CRT and defibrillator was successful in reducing all-cause mortality with 34%.(16) CRT has since become recommended standard therapy in patients with symptomatic heart failure in sinus rhythm and with EF ≤35%, QRS duration ≥150 msec and left bundle branch block QRS morphology.(17)

The most relevant developments in the medical treatment of patient with symptomatic heart failure include the mineralocorticoid-receptor antagonists, the angiotensin receptor-neprisylin inhibitors and, most recently, inhibitors of sodium-glucose cotransporter 2 (SGLT2).(18-21) Both eplerenone and spironolactone – not separately reported in DEFINITE, infrequently used in MADIT-II and SCD-Heft and employed in about 60% of patients in the DANISH trial - were found to lower mortality with 20% in advanced heart failure.(18, 19) Neprisylin inhibition with LCZ696 *in lieu* of ACE-inhibition, and associated with a relative and absolute reduction in mortality of 16% and 1.8%, respectively, was not used in any of the preventive ICD trials.(20) And neither was the SGLT2 inhibitor, a relatively novel drug that lowered mortality with (relative) 17% and (absolute) 2.8% compared to recommended therapy in symptomatic patients with heart failure.(21) The main characteristics of the largest modern-day heart failure drug trials are also given in Table 1.

The data in Table 1 illustrate the limited use of currently available optimal medical treatment in the early trials, just as the – probably partly ensuing - high event rates of the early studies compared to the more recent. In addition, it is obvious that event rates in non-ischemic cardiomyopathy are lower than in IHD. The data in Table 1 make it also clear that the benefits of each of the new therapeutic modalities clearly fall within the plausible effect ranges of the most recent ICD trials (while their combined effects could be larger).

Complications and costs

Immediately after their introduction, controversy about the costs and complications associated with ICD-implantation was unleashed.(7, 22) This debate has continued ever since. The ICD implantation itself carries approximately 9% peri-procedural risk of complication.(23-26) During follow-up, in addition to the regular device interrogations, inappropriate shocks and re-hospitalizations are not uncommon, while generator replacement every 4 to 7 years carries a risk of minor and major complications.(27) A list of short- and long-term ICD complications is summarized in Table 2.

Table 2. Short, medium and long-term complication rates of ICD implantation

Early (peri- implant)(23, 24)	
Any	9%
Mortality	0.5%
Pneumothorax	1%
Bleeding	1%
Infection	2%
Other	4%

During 3 to 4 years follow-up(25, 26)	
Inappropriate ICD shock	12%
Device malfunction or lead failure	6%
Device or lead infection	2%
Hospitalization (for other reasons)	3%

Device replacement related(27)	
Any	4%
Stroke	0.5%
Infection/ inflammation	2%
Hematoma requiring intervention	2%

As it currently stands, 25 ICD's are required to save one life.(17, 28) In view of their high levels of current employment, the financial burden of preventive ICD-implantation apparently seems to be acceptable at individual levels in rich countries. However, this is much less the case from a societal point of view. Rising numbers of implantations and the prospect of even larger numbers of future patients with heart failure in aging populations are unwelcome from that perspective. It is thus logical that measures have been taken in some countries to minimize the rate of implantations, for instance by limiting the number of implanting centres. It is unknown whether this has been effective.

ICD cost-effectiveness decreases when event rates decline. There can be no doubt that – in addition to the observed decrease in overall mortality observed in the pharmacological trials depicted in Table 1 – the risk of sudden death has also decreased substantially, reportedly by 44%, in the last decades.(11) Importantly, the absolute rate of sudden death was found to be lower among patients with a recent diagnosis of heart failure, consistent with the cumulative benefit of evidence-based medication on this mode of death. These findings can probably be extrapolated to the population at large.(29) In our region, we have witnessed a reduction of about 40% in the rate of sudden cardiac death in middle aged and elderly men and women, a much larger decrease than the observed decline in overall mortality in the same population.(30)

Ejection fraction and icd selection criteria

Historically, when new and – in their early phase - expensive pharmaceutical agents were introduced, for instance with the early clinical introduction of ACE-inhibitors, statins and - now - PCSK9-inhibitors, their clinical application has been tailored to men and women at highest risk.(31-33) But this has not been the practice for preventive ICD's. Despite many attempts to identify specific patient groups in whom the devices would be more (cost) effective, such efforts have not resulted in modification of guidance on their use in clinical practice. In fact, with time, the criteria for ICD-implantation have only become more inclusive and lenient. Both the European and American guidelines currently state that the patient (only) needs to be symptomatic (NYHA class II or III) and have an ejection fraction ≤35% (while receiving "optimal" medical treatment).(17, 34) In patients with a non-ischemic cardiomyopathy, treatment with "optimal" medical treatment for three months is additionally advised, although improvement in LV function ("remodeling") may happen after longer period of times.(35, 36)

The cut-off value of EF 35% is important because this criterion identifies and defines a large group of potential ICD recipients. For example, exactly 50% of the patients in PARADIGM-HF had an ejection fraction between 30 and 35%.(20) Of note, the EF inclusion criterion in SCD-Heft was ≤35% and ≤30% in MADIT-II, but the average EF in both trials, 25% and 23% respectively, was much lower, just as in the DANISH study and in DEFINITE. The evidence of ICD benefit in the low EF range is considerable, but this is much less the case when LV function is better preserved. For instance, the positive effects of ICD-implantation in SCD-Heft were only observed in patients with EF ≤30%, who – importantly - comprised 80% of the study population.(9) In MUSTT, with EF ≤40% as LV function inclusion criterion, the relation between ejection fraction and event rates was highly significant whether EF was treated as continuous or dichotomized variable, and total mortality in patients with EF ≤30% was more than 50% higher compared to EF between 30 and 40%.(37)

Of course, sudden arrhythmic death will continue to occur, but - given the currently available therapeutic options - at a much lower rate than observed in the landmark and other trials.(11) The conclusion that this affects ICD-therapy effectiveness is not new, and has led to multiple attempts to identify patients at highest risk. But individualized

prediction of sudden cardiac death remains notoriously difficult(38-42) and, despite the development of innovative clinical risk models, the continuing increase in ICD insertions as well as the unchanged guidance in their use indicate that such methods of selection have not been successful.(43, 44)

There can be little doubt that, within the EF range between 30 and 35%, the evidence for ICD benefit in primary prevention is limited. This is in particular true in non-ischemic cardiomyopathy where event rates are lower than in IHD. Of note, the risk of arrhythmic endpoints is reportedly larger in the presence of myocardial fibrosis assessed with late gadolinium enhancement.(45, 46) And the finding of such fibrosis, although its relevance has not yet been confirmed in randomized comparisons, may tip the balance in favouring ICD implantation in non-ischemic cardiomyopathy. In patients with myocarditis, longer duration of medical therapy than 3 months may be necessary to establish improvement of LV function.(35, 36) Lastly, patients with normal QRS duration have often been reported to be at relatively low risk, and ICD implantation may be deferred in such instances.(40) Table 3 provides a summary of these recommendations.

Summary and Conclusions

Findings from the landmark ICD-trials, interpreted in combination with the clinical evidence and effective therapeutic options since accumulated, and set against the costs and the potential complications of ICD implantation, now demand and allow for better and more stringent ICD implant selection criteria in primary prevention. Moreover, while it must be acknowledged that the relationship between LVEF and ICD effectiveness is not straightforward – benefit is both low in those at extremely high and at very low risk – LV function is a major determinant of prognosis in all studies of patients with heart failure, regardless of their cause.(17, 47, 48) In the most recent and largest trials, ICD benefit was mainly confined to patients with LVEF ≤30%. At this moment, it seems reasonable to limit the ICD eligibility criteria in the EF range 30 to 35% to patients at highest risk only, and to defer ICD implantation in subjects within this EF range without features suggesting high risk. In Table 3, such criteria have been presented. We realize that these cover only a limited selection of risk categories, and will only be applicable to a limited number of patients and implant decisions. Nevertheless, we hope that the rational and considerations presented in this paper will gain following and will encourage modifications in clinical practice as well as in future guidance.

Table 3. Factors associated with ICD benefit or harm in EF range 30 to 35%

Factors favouring ICD implant
Ischemic heart disease
QRS width ≥150 msec and LBBB*
Presence of fibrosis on MRI
Factors not favouring ICD implant
Limited life-expectancy
Myocarditis < 6 months
QRS width <120 msec

EF, ejection fraction; ICD, intracardiac defibrillator; LBBB, left bundle branch block; MRI, magnetic resonance imaging

* with cardiac resynchronization therapy

It goes without saying that a proper assessment of the contemporary benefit of preventive ICD in patients with relatively mild LV dysfunction, with or without CRT, will require a new randomized clinical trial. The study should include symptomatic patients with heart failure of any cause with an EF above the range currently debated, thus with LVEF over 30%, and must employ baseline imaging techniques detailed enough to establish their worth in subsequent clinical risk stratification. Given the current ICD implantation rates, the recruitment of such patients should be relatively straightforward.

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PART II

Patient reported outcomes in acute heart failure

CHAPTER 9

Determinants of quality of life in acute heart failure patients with and without comorbidities

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Abstract

Background: The relation between non-cardiac comorbidities and health-related quality of life (HRQoL) in patients with heart failure (HF) has been studied to a limited extent.
Aim: To investigate the HRQoL and their determinants among HF patients with and without comorbidities.

Methods: TRIUMPH (TRanslational Initiative on Unique and novel strategies for Management of Patients with Heart failure) is a Dutch prospective, multicenter study enrolling 496 acute HF patients between 2009 and 2014. We included 334 patients who had completed the HRQoL questionnaires at baseline. The HRQoL was measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) en EuroQuality-of-life 5 Dimensions (EQ-5D). Comorbidity was defined as having a history of at least one of the following comorbidities: chronic kidney disease, diabetes mellitus, chronic obstructive pulmonary disease (COPD) and/or cerebrovascular accident (CVA).

Results: Patients with comorbidity (n=205, 61%) had lower scores on the physical limitation scale and clinical summary score of the KCCQ (p=0.03 and p=0.01, respectively). Female sex, COPD, previous HF, increasing BMI, elevated NT-proBNP, high systolic blood pressure and the presence of anxiety and/or depression negatively influenced the HRQoL among HF patients with comorbidity. Besides anxiety and depression, we hardly found any other determinant of HRQoL in patients without comorbidity.

Conclusion: HF patients without comorbidity had better HRQoL than patients with comorbidity. Sex, previous HF, BMI, COPD, systolic blood pressure, NT-proBNP levels and also anxiety and depression were determinants of HRQoL in patients with comorbidity. In those without comorbidity, apart from anxiety and depression, no further determinants of HRQoL were found.

Introduction

Heart failure (HF) is a clinical syndrome that is frequently accompanied by non-cardiac comorbidities such as renal dysfunction, chronic obstructive pulmonary disease (COPD), diabetes, cerebrovascular accident (CVA) and anemia. Some of these comorbidities may be a result of HF, whereas other diseases may be associated with the development of HF.[1, 2]

It has also been established that among patients with HF, those with one or more comorbidities have a worse prognosis when compared with those without comorbidities.[2] Besides a poor prognosis, HF patients also have an impaired health-related quality of life (HRQoL).[3] The HRQoL among patients with HF has not only been found to be worse than that in the general population, but it is even worse than that of patients with other chronic conditions.[4, 5] Moreover, an impaired HRQoL is a driver of adverse outcome in HF.[6] Also from a patient's perspective, HRQoL is very important. Some studies have found that patients value quality of life at least as important as longevity.[7, 8] Therefore, HRQoL is an interesting and important topic from a clinical and research perspective.

The relation between non-cardiac comorbidities and HRQoL in patients with HF has been studied to a limited extent. The relative few studies available have shown a relation between comorbidities and HRQoL,[3, 9-11] but there is inconsistency among the different studies.[12] However, there have been no studies reporting on differences in determinants of HRQoL between patients with and without (multi-)comorbidity. Therefore, we aimed to investigate the HRQoL and their determinants among HF patients with and without somatic comorbidities based on data from the TRIUMPH study (TRanslational Initiative on Unique and novel strategies for Management of Patients with Heart failure [TRIUMPH]: NTR1893).

Methods

Study population and procedures

The design of the TRIUMPH study has been described previously.[13, 14] In short, this study is a prospective, observational study performed in 14 hospitals in the Netherlands. In the period of September 2009 until December 2013, patients aged 18 years and older hospitalized with acute HF were enrolled. Acute HF was defined as either new onset HF or worsening symptoms of chronic HF. We included patients admitted with acute HF with evidence of sustained systolic of diastolic dysfunction. Additionally, patients were included if their natriuretic peptide level should be at least three times higher than the upper limit of normal and they should be treated with intravenous diuretics during the hospitalization. We obtained written informed consent from all patients. All participating center's ethical committees have given approval for the study. The investigation conforms with the principles outlined in the Declaration of Helsinki.[15]

The primary aim of the TRIUMPH study was to investigate the clinical value of repeated measurements of several biomarkers in patients with acute HF. One of the secondary aims was to study HRQoL in patients with acute HF.

During hospitalization, patients were visited three times: at admission, at day 2 to 4 following admission and on the day of discharge. After hospital discharge, four follow-up moments were planned: at 2 to 4 weeks, 3 months, 6 months and 9 to 12 months. At each measurement moment, patients underwent physical examination (including blood pressure, heart rate and weight measurement), blood sampling and patients were scored according to the New York Heart Association (NYHA) classification. Patients were treated in accordance to the European Society of Cardiology Guidelines[16] by their treating physician. The TRIUMPH study did not intervene in the usual care.

Quality of life measurement

Patients were asked to complete several questionnaires before hospital discharge and at the last follow-up visit. HRQoL was measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) en EuroQuality-of-life 5 Dimensions (EQ-5D). Symptoms of anxiety and depression were measured by the Hospital Anxiety and Depression Scale (HADS).

The KCCQ is a disease-specific questionnaire to measure the HRQoL of patients with HF. This 23-item questionnaire covers the following six domains: physical limitation (KCCQ-PL), symptom stability, total symptom score (combination of symptom frequency and symptom burden), self-efficacy score, quality of life score and social limitation. Two summary scores can be computed from these domains: the clinical summary score (KCCQ-CS) comprising the domains physical limitation and total symptom score, and the overall summary score (KCCQ-OS) which captures the domains physical limitation, total symptom score, quality of life and social limitation. Each domain and summary score has been transformed into a 0 to 100 scale. Higher scores indicate better HRQoL.[17]

The EQ-5D is a general, non-disease-specific HRQoL questionnaire that consists of two components. The first component is the health state description and the second component is the health state evaluation. We used the 3-level version of the EQ-5D for health state description. The three levels were: (1) no problems, (2) some problems, and (3) extreme problems. A total of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) were scored according to these three levels. For each dimension, patients were asked to choose the statement which best described their health status that day. In the second part (i.e. health state evaluation) patients were asked to score their health status by using a visual analogue scale within a range of 0 (worst imaginable health status) to 100 (best imaginable health status).[18]

The HADS has been shown a valid and reliable instrument to assess symptoms of anxiety and depression. Patients were asked to answer fourteen questions. Seven items contribute to each of the two subscales (anxiety and depression, respectively) and

were answered on a 4-point Likert scale from 0 to 3, which implies a total score range per subscale of 0-21.[19, 20] A score of ≥8 points on the subscale anxiety as well as on the subscale depression was used to determine whether patients had an anxiety disorder and/or depression.[19]

Definitions

To answer our research question, analyses were stratified by comorbidity. Comorbidity was defined as having a history of at least one of the following significant, non-cardiac comorbidities: chronic kidney disease, diabetes mellitus, COPD and/or CVA. The presence of the comorbidities was according to the investigator's statement of the medical history in the case report form. These four comorbidities were chosen because of their high prevalence in HF and because there is evidence that they may influence HRQoL and/or the presence of anxiety and depression.

HF with reduced ejection fraction was defined as a left ventricular ejection fraction below 50%. During admission, NYHA classification was determined at three time points. Since the NYHA classification at discharge was considered the most stable of these three, this measurement was used as the baseline NYHA classification.

Statistical analyses

Categorical variables are presented as numbers and percentages. The $\chi 2$ test was used to compare categorical variables. Continuous variables are given as median with interquartile range (IQR) and were compared with the Mann-Whitney U test.

The determinants of HRQoL (based on the EQ-5D and KCCQ) were analyzed by using linear regression models and logistic regression, respectively. First, we performed univariable analyses in the total study population with all baseline characteristics. Anxiety and depression were included as predictors, using the HADS model to define whether there was anxiety and/or depression or not. Then, all determinants with $p<0.2$ in the univariable analyses were included in the multivariable analyses (forward step method) in order to search for determinants of HRQoL in the total population. Further, the significant (i.e. $p<0.05$) determinants of HRQoL in the total population plus age and sex were included in the multivariable analyses (enter method) to test determinants of HRQoL in patients with and without comorbidity. Finally, we tested for interaction between comorbidity and the determinants of HRQoL.

All tests were two-tailed and p-values <0.05 were considered statistically significant. We used SPSS software (SPSS 24.0, IBM Corp., Armonk, NY, USA) for all statistical analyses.

Results

Baseline characteristics

In total, 496 patients were enrolled in the TRIUMPH study. Three patients withdrew their informed consent. Another 18 patients were excluded from statistical analyses because of inclusion violation since they had no evidence of sustained systolic or diastolic dysfunction. Of the 475 remaining patients, we included the 334 patients (70%) who had completed the HRQoL questionnaires at baseline into the analyses set. Besides higher occurrence of comorbidity and higher levels of NT-proBNP, the baseline characteristics of the 141 patients (74% with comorbidity) who did not complete the HRQoL questionnaires were almost comparable with that of the patients in the analyses set (see Supplemental Table 1).

The included patients consisted of 219 men (66%), the median age was 74 years (IQR 65-81) and 205 patients (61%) had at least one of the comorbidities diabetes mellitus, chronic kidney dysfunction, COPD or prior CVA (Table 1). Almost half of the patients had ischemic HF and 85% had HF with reduced ejection fraction.

Table 1. Baseline characteristics of patients with and without comorbidity

	Overall sample **n=334**	**Comorbidity +** **n=205**	**Comorbidity -** **n=129**	**p-value**
Demographics				
Age, years	74 (65-81)	76 (66-81)	73 (60-80)	0.04
Male	219 (66%)	145 (71%)	74 (57%)	0.01
Caucasian	319 (96%)	196 (96%)	123 (95%)	0.59
Medical history				
Previous heart failure	215 (65%)	144 (71%)	71 (55%)	0.004
Previous heart failure hospitalization within last 6 months	69 (21%)	49 (24%)	20 (16%)	0.06
Ischemic heart failure	158 (47%)	115 (56%)	43 (33%)	<0.001
Heart failure with reduced ejection fraction	228 (85%)	134 (82%)	94 (89%)	0.15
Hypertension	166 (50%)	119 (58%)	47 (36%)	<0.001
Atrial fibrillation	143 (43%)	94 (46%)	49 (38%)	0.16
Diabetes mellitus	118 (35%)	118 (58%)	0 (0%)	<0.001
Chronic obstructive pulmonary disease	65 (20%)	65 (32%)	0 (0%)	<0.001
Chronic kidney dysfunction	55 (17%)	55 (27%)	0 (0%)	<0.001
Cerebrovascular accident	52 (16%)	52 (25%)	0 (0%)	<0.001
Baseline measurements				
Body mass index, kg/m^2	28 (25-31)	28 (25-32)	26 (24-30)	0.004
Systolic blood pressure, mmHg	125 (110-148)	125 (110-148)	124 (110-145)	0.53
Diastolic blood pressure, mmHg	74 (64-85)	70 (65-82)	78 (64-89)	0.049

	Overall sample n=334	Comorbidity + n=205	Comorbidity - n=129	p-value
Heart rate, bpm	85 (72-100)	84 (70-99)	90 (76-105)	0.02
Kreatinin, umol/L	122 (100-158)	134 (106-181)	111 (95-140)	<0.001
NT-proBNP, pg/ml	3738 (1928-8601)	3726 (1928-9381)	3738 (2072-6816)	0.79
Left ventricular ejection fraction, %	30 (21-40)	30 (22-42)	30 (20-39)	0.09
NYHA classification				0.29
I	35 (13%)	20 (12%)	15 (14%)	
II	127 (47%)	71 (43%)	56 (52%)	
III	98 (36%)	65 (39%)	33 (31%)	
IV	12 (4%)	9 (6%)	3 (3%)	

Results depicted as median (interquartile range) or N (%)
NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association
Comorbidity defined as presence of one or more of the following: diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease and/or prior cerebrovascular accident
P-value for comparison between patients with and those without comorbidity

On average, patients with comorbidity were 3 years older, more frequently male, and more often had a history of HF and an ischemic cause of HF. Of the patients with comorbidity, 135 patients (65%) had only one of the four comorbidities and 14 patients (7%) had three or more. The most common comorbidity was diabetes mellitus. Notably, indicators of cardiac function like left ventricular ejection fraction, NT-proBNP en NYHA class did not differ between patients with and without comorbidity.

Differences in HRQoL according to comorbidity

The NYHA classification at discharge of patients with and without comorbidity was comparable (Table 2). Furthermore, the EQ-5D score neither did differ between patients with and without comorbidity (p=0.16). In contrast, the HRQoL measured by the disease-specific questionnaire (i.e. KCCQ) showed that patients with comorbidity had a significant lower KCCQ-PL and KCCQ-CS (p=0.03 and p=0.01, respectively). Lastly, patients with comorbidity had more depressive symptoms than those without comorbidity (42% vs. 30%, p=0.03).

Table 2. HRQoL, anxiety and depression in patient with and without comorbidity

		Baseline			1 year follow-up		
		Comorbidity +	**Comorbidity -**	**p value**	**Comorbidity +**	**Comorbidity -**	**p value**
NYHA	I	20 (12%)	15 (14%)	0.29	10 (12%)	23 (37%)	0.002
	II	71 (43%)	56 (52%)		55 (65%)	24 (39%)	
	III	65 (39%)	33 (31%)		19 (22%)	14 (23%)	
	IV	9 (6%)	3 (3%)		1 (1%)	1 (2%)	
EQ-5D	EQ-5D score	0.68 (0.34-0.81)	0.69 (0.43-0.86)	0.16	0.81 (0.65-0.89)	0.86 (0.77-1.00)	0.04
	EQ-5D VAS	60 (49-70)	60 (50-70)	0.33	70 (55-80)	70 (60-80)	0.19
KCCQ	KCCQ-PL	33 (13-63)	42 (21-71)	0.03	58 (33-82)	75 (44-96)	0.01
	KCCQ-CS	31 (16-54)	35 (25-61)	0.01	69 (41-88)	77 (50-96)	0.05
	KCCQ-OS	30 (18-51)	35 (21-56)	0.14	65 (40-85)	77 (49-91)	0.06
HADS	Anxiety	63 (32%)	46 (36%)	0.41	17 (19%)	12 (20%)	0.8
	Depression	83 (42%)	38 (30%)	0.03	24 (26%)	10 (17%)	0.19

Results depicted as median (interquartile range) or N (%)

CS, clinical summary score; EQ-5D, EuroQuality-of-life 5 Dimensions; HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; OS, overall summary score; PL, physical limitation; VAS, visual analogue scale

A total of 154 of the 334 included patients (46%) also completed the HRQoL questionnaires after 9-12 months of follow-up. This response rate was comparable between patients with and without comorbidity (p=0.43). After 1 year follow-up, the NYHA classification was worse in patients with comorbidity (Table 2). Both the generic (i.e. EQ-5D) and disease-specific (i.e. KCCQ) questionnaires measured a worse HRQoL in patients with comorbidity after 9-12 months of follow-up.

Determinants of HRQoL

The studied comorbidities (i.e. COPD, CVA, chronic kidney dysfunction and diabetes mellitus) were found to be modest predictors of the HRQoL in the total study population. After multivariable adjustment, COPD was the only of these comorbidities that was found to be a significant determinant, namely for KCCQ-PL and KCCQ-CS (β -10.439 [95% CI -18.721 - -2.157], β -7.815 [95% CI -14.527 - -1.103], respectively; Table 3).

Table 3. Multivariable adjusted determinants of HRQoL in the total population

	β	95% CI lower bound	95% CI upper bound
EQ-5D score			
Age (per 10 years increase)	-0.038	-0.061	-0.015
Male	0.109	0.046	0.172
NYHA class III/IV	-0.081	-0.143	-0.02
Anxiety	-0.150	-0.221	-0.079
Depression	-0.244	-0.314	-0.174
EQ-5D VAS			
Age (per 10 years increase)	-0.093	-2.978	0.471
Male	3.820	-0.868	8.508
Previous HF	-5.051	-9.646	-0.456
LVEF (per % increase)	0.252	0.095	0.409
Anxiety	-8.342	-13.589	-3.094
Depression	-5.803	-10.963	-0.644
KCCQ-PL			
Age (per 10 years increase)	-0.382	-2.939	2.175
Male	13.607	6.977	20.238
Previous HF	-9.090	-15.686	-2.494
Chronic obstructive pulmonary disease	-10.439	-18.721	-2.157
BMI (per 1 point increase)	-0.845	-1.429	-0.262
NT-proBNP (per 100 points increase)	-0.063	-0.107	-0.020
Depression	-15.179	-21.841	-8.517
KCCQ-CS			
Age (per 10 years increase)	-0.526	-2.635	1.583
Male	10.185	4.749	15.621
Previous HF	-7.133	-12.643	-1.622
Chronic obstructive pulmonary disease	-7.815	-14.527	-1.103
BMI (per 1 point increase)	-1.047	-1.527	-0.567
Systolic blood pressure (per 10 points increase)	1.143	0.209	2.077

	β	95% CI lower bound	95% CI upper bound
NT-proBNP (per 100 points increase)	-0.058	-0.094	-0.022
Depression	-13.677	-19.142	-8.212
KCCQ-OS			
Age (per 10 years increase)	0.441	-1.511	2.393
Male	7.167	2.183	12.151
Previous HF	-5.872	-10.907	-0.836
Ischemic HF	-6.009	-10.904	-1.115
BMI (per 1 point increase)	-0.718	-1.150	-0.285
Systolic blood pressure (per 10 points increase)	1.034	0.184	1.884
NT-proBNP (per 100 points increase)	-0.052	-0.084	-0.019
Anxiety	-7.463	-12.945	-1.981
Depression	-14.279	-19.695	-8.864

BMI, body mass index; CI, confidence interval; CS, clinical summary score; EQ-5D, EuroQuality-of-life 5 Dimensions; HADS, Hospital Anxiety and Depression Scale; HF, heart failure; HRQoL, health-related quality of life; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OS, overall summary score; PL, physical limitation; VAS, visual analogue scale

Besides the studied comorbidities, other factors were associated with HRQoL. Increasing age, female sex, increasing BMI and higher NT-proBNP were the major determinants of an adverse score on the KCCQ. Furthermore, depression (as measured with the HADS) was also associated with lower HRQoL scores, both on the EQ-5D (β -0.244 [95% CI -0.314 - -0.174]) and on the KCCQ (PL: β -15.179 [95% CI -21.841 - -0.8517]; CS: β -13.677 [95 CI -19.142 - -8.212]; OS: -14.279 [95% CI -19.695 - -8.864]).

The determinants of HRQoL differed considerably between patients with and without comorbidity (Figure 1). Sex, previous HF, BMI, NT-proBNP and systolic blood pressure at discharge were determinants of HRQoL among HF patients with comorbidity. The presence of anxiety and/or depression also negatively influenced the HRQoL of patients with and without comorbidity. Besides anxiety and depression, we hardly found any other determinant of HRQoL in patients without comorbidity.

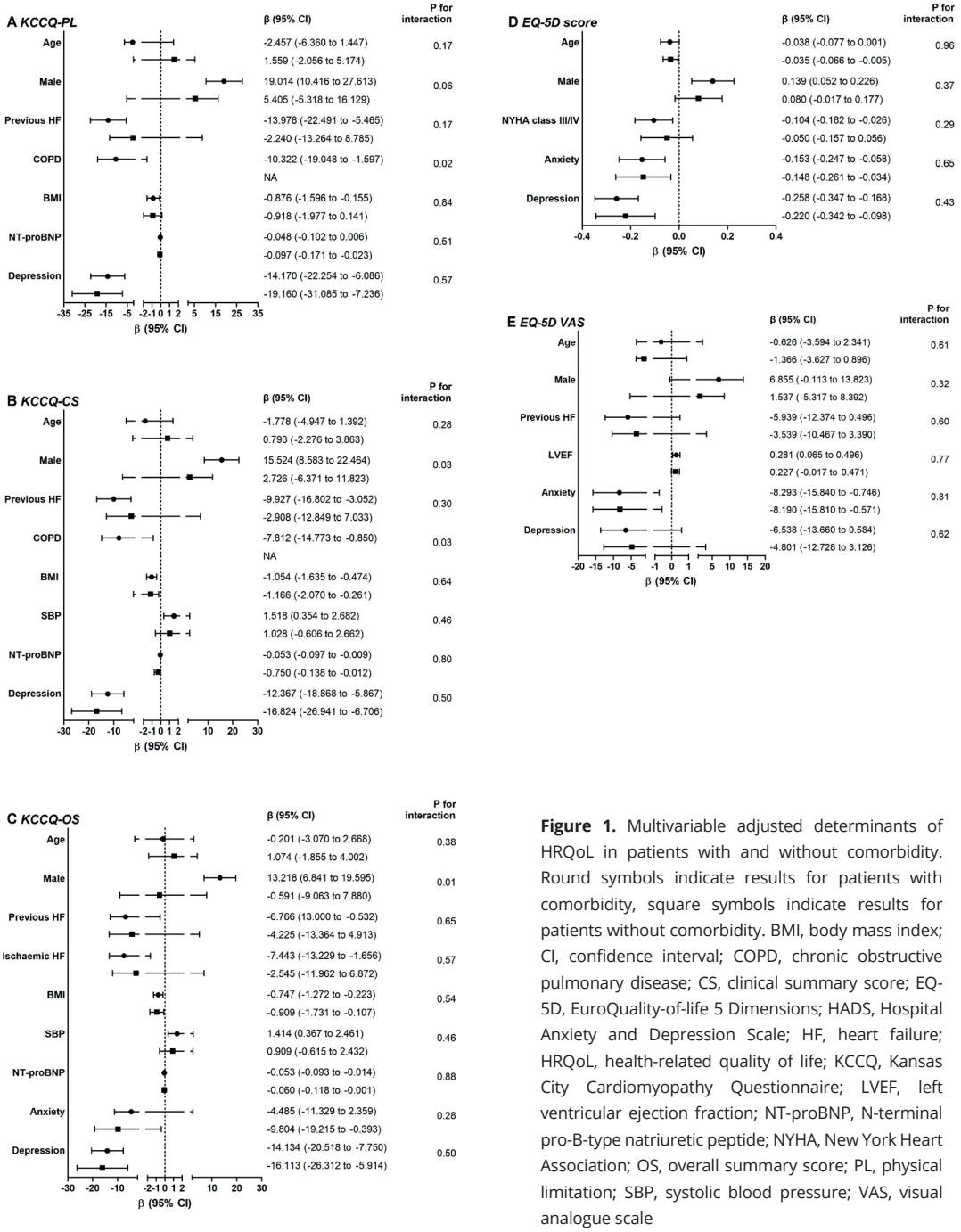

Figure 1. Multivariable adjusted determinants of HRQoL in patients with and without comorbidity. Round symbols indicate results for patients with comorbidity, square symbols indicate results for patients without comorbidity. BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CS, clinical summary score; EQ-5D, EuroQuality-of-life 5 Dimensions; HADS, Hospital Anxiety and Depression Scale; HF, heart failure; HRQoL, health-related quality of life; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OS, overall summary score; PL, physical limitation; SBP, systolic blood pressure; VAS, visual analogue scale

Discussion

In this prospective, multi-center study, we found that patients with one or more of the four investigated comorbidities (i.e. COPD, diabetes mellitus, chronic kidney disease and/or prior CVA) had a higher prevalence of depression at baseline than patients without comorbidity. Of the four comorbidities, only COPD was modestly associated with worse HRQoL. Important determinants of HRQoL in our population were sex, history of HF, BMI, NT-proBNP at admission, systolic blood pressure at discharge and the presence of a depression. Most of these characteristics were also associated with HRQoL in the subgroup of patients with comorbidity. In contrast, besides anxiety and depression, we hardly found any other determinant of HRQoL in patients without comorbidity.

Differences in HRQoL

To the best of our knowledge, this study is the first investigating differences in HRQoL between HF patients with and without a cluster of four selected non-cardiac comorbidities. Despite a comparable severity of HF (indicated by equal NT-proBNP levels and comparable NYHA classification) in patients with and without comorbidity, we found lower HRQoL and higher prevalence of depression in HF patients with comorbidity. A possible explanation of this might be that patients with comorbidity already had a worse HRQoL pre-admission. This potential lower HRQoL pre-admission may not only be due to the comorbidities for which was stratified in this study (i.e. prior CVA, chronic kidney dysfunction, diabetes and COPD), but we also found other factors that may cause lower HRQoL in patient with comorbidity, like higher BMI, more frequent a history of HF before inclusion and hypertension.[9]

Question remains why there was a difference in HRQoL measured with the KCCQ questionnaire between patients with and without comorbidity and no difference in the EQ-5D score despite the fact that there is some overlap in the questions among both questionnaires.[17, 18] This inconsistency may be due to the fact that two questionnaires consist of different questions on different aspects of HRQoL and, hence, may give different outcome. Further, the KCCQ questionnaire is disease-specific and the EQ-5D is short and very generic. On the other hand, we think that the difference in way of asking the questions may also be responsible for this difference. In the EQ-5D questionnaire, patients were asked about their functioning at that day.[18] However, the KCCQ questionnaire specifically asked to complete the questions about their functioning and to compare it with their functioning two weeks ago.[17] This explicitly stated two-week time frame may cause that patients answer the questions in a different way.

Determinants of HRQoL

A unique aim of this study was to investigate the determinants of HRQoL in patients with and without comorbidity. Female sex, previous HF, COPD, increasing BMI and higher NT-proBNP levels at admission were found to be important determinants of worse HRQoL in patients with comorbidity. Those determinants were also associated with HRQoL in

studies that did not investigate differences in determinants of HRQoL in patients with and without comorbidity.[21, 22] Furthermore, female patients, patients with a history of CVA and patients with worse NYHA classification at discharge were at higher risk for depression. A striking finding was that we, apart from depression, hardly found any determinant of HRQoL in patients without comorbidity. A possible explanation for this might be that HF itself is by far the most important determinant of the reduced HRQoL in patients without comorbidity. Another possible explanation might be that there are other determinants of HRQoL in patients without comorbidity that we did not measure (e.g. patients' illness knowledge, patients' coping strategy[23] and socioeconomic status[24]). Indeed, these determinants may also influence the HRQoL of patients with comorbidity and not only in those without comorbidity.

Besides the above-mentioned demographic and clinical factors, we also found psychosocial determinants of HRQoL: presence of anxiety and depression negatively influenced HRQoL. This may have important clinical implications for both patients with and without comorbidity.

Clinical implication

Our opinion is that HRQoL should get more attention among clinicians. Prognosis should not be the only therapeutic goal. Since HF patients value HRQoL at least as important as longevity,[7, 8] clinicians should strive for better HRQoL instead of focusing on survival per se. Indeed, in our study, we only found a limited number of determinants of HRQoL that may be influenced by clinicians, although we think that optimal HF treatment in accordance with the guidelines is an important intervention for improving HRQoL.[25] Also, optimal treatment of comorbidities like diabetes mellitus, chronic kidney disease and COPD, and managing the risk factors BMI and systolic blood pressure may improve HRQoL. This is in line to what Lawson et al. recently stated based on data of the Swedish Heart Failure Registry, namely that in order to improve HRQoL, HF guideline-driven care needs to include optimal management of the most prevalent non-cardiovascular comorbidities.[9] Furthermore, psychosocial interventions to intervene with depressive and anxiety symptoms may also break the vicious circle of anxiety/depression and HRQoL. The last, but very important and maybe a 'bit forgotten' intervention we would like to emphasize, is cardiac rehabilitation. Cardiac rehabilitation should at least consist of exercise therapy and patient education.[25-27] Besides improving HRQoL, cardiac rehabilitation in patients with HF has proven to be favorable for other endpoints like rehospitalization and probably (long-term) mortality.[28] Despite the proven effectiveness and the strong recommendations in the HF guidelines,[25] the number of referrals to cardiac rehabilitation[29] and patients' adherence[30] may be increased enormously.

Strengths and limitations

This study is the first reporting HRQoL and their determinants in HF patients with and without comorbidity. Moreover, we used a set of different questionnaires to get an impression of a patient's QoL, namely EQ-5D, KCCQ and HADS. However, some limitations should be mentioned. First, this study was designed as a sub study of the TRIUMPH study. Therefore, results of this sub study may be underpowered. Another limitation is that the choice for the comorbidities CVA, chronic kidney disease, COPD and diabetes was relatively arbitrary. Indeed, we have chosen common HF non-comorbidities that may influence HRQoL[9] but others may have chosen other comorbidities. However, as there were no previous studies investigating this topic, we should make a selection. Finally, 70% of the initial study population completed the baseline questionnaires. Part of the patients who could not complete the questionnaires at discharge were those who died during admission. The other part of the 30% non-responders were patients who have not completed the questionnaires for reasons unknown or who may have not received the questionnaires from their caregivers. Anyway, the baseline characteristics of the responders and non-responders were largely comparable so the missing seems to be at random.

Conclusions

In conclusion, HF patients without comorbidity had better HRQoL and less depression than patients with comorbidity. Sex, previous HF, COPD, BMI, NT-proBNP levels and presence of anxiety and depression were determinants of HRQoL in patients with comorbidity. In contrast, we have found hardly any demographic or clinical determinants of HRQoL in those without comorbidity. In clinical practice, in addition to aiming for improved survival, physicians may pay greater attention to improving HRQoL of HF patients both with and without comorbidity.

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Supplemental material

Supplemental Table 1. Baseline characteristics of patients who completed the HRQoL questionnaires and those who did not

	Responders n=334	Non-responders n=141	p-value
Demographics			
Age, years	74 (65-81)	72 (64-80)	0.42
Male	219 (66%)	79 (56%)	0.049
Caucasian	319 (96%)	130 (92%)	0.18
Medical history			
Previous heart failure	215 (65%)	86 (62%)	0.58
Previous heart failure hospitalization within last 6 months	69 (21%)	25 (18%)	0.5
Ischemic heart failure	158 (47%)	71 (51%)	0.47
Heart failure with reduced ejection fraction	228 (85%)	80 (78%)	0.11
Hypertension	166 (50%)	76 (55%)	0.32
Atrial fibrillation	143 (43%)	55 (40%)	0.51
Diabetes mellitus	118 (35%)	54 (39%)	0.44
Chronic obstructive pulmonary disease	65 (20%)	27 (20%)	0.98
Chronic kidney dysfunction	55 (17%)	36 (26%)	0.02
Cerebrovascular accident	52 (16%)	29 (21%)	0.16
Comorbidity	205 (61%)	102 (74%)	0.009
Baseline measurements			
Body mass index, kg/m^2	28 (25-31)	27 (25-32)	0.83
Systolic blood pressure, mmHg	125 (110-148)	130 (110-147)	0.53
Diastolic blood pressure, mmHg	74 (64-85)	75 (66-89)	0.32
Heart rate, bpm	85 (72-100)	82 (70-99)	0.21
Kreatinin, umol/L	122 (100-158)	133 (103-170)	0.18
NT-proBNP, pg/ml	3738 (1928-8601)	5658 (2781-10085)	0.005
Left ventricular ejection fraction, %	30 (21-40)	35 (25-47)	0.045
NYHA classification			0.92
I	35 (13%)	10 (12%)	
II	127 (47%)	42 (51%)	
III	98 (36%)	27 (33%)	
IV	12 (4%)	4 (5%)	

Results depicted as median (interquartile range) or N (%)

HRQoL, health-related quality of life; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association

CHAPTER 10

Symptoms and depression in acute heart failure patients

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Abstract

Objective: There is lack of research regarding the occurrence and burden of symptoms in acute heart failure (HF) patients in relation to depression. We investigated the impact of depression on symptom occurrence and symptom burden in acute HF patients.

Methods: TRIUMPH (TRanslational Initiative on Unique and novel strategies for Management of Patients with Heart failure) is a Dutch prospective, multicenter study enrolling acute HF patients. We included the 325 patients who completed the Hospital Anxiety and Depression Scale (HADS) at hospital discharge. Patients were then also asked to complete the Kansas City Cardiomyopathy Questionnaire (KCCQ), EuroQol 5 Dimensions (EQ-5D) and a questionnaire regarding the presence and burden of HF-related symptoms. In patients who were still alive, all questionnaires were repeated at 1-year follow-up.

Results: A total of 121 patients (37%) had depression according to the HADS definition. Patients with depression were found to have worse health-related quality of life on both the KCCQ and the EQ-5D ($p<0.001$). Furthermore, symptom occurrence and symptom burden were higher in patients with depression than in those without depression. We did not only find this at discharge but also after 1 year of follow-up.

Conclusions: Both at discharge and after 1-year follow-up, acute HF patients with depression reported a significantly higher symptom occurrence and burden of HF-related symptoms than those without depression. Therefore, besides depression, symptom management deserves to get attention in clinical practice.

Introduction

Heart failure (HF) is a clinical syndrome characterized by typical signs and symptoms.[1] Previous research showed that patients with HF reported a high number of different symptoms. Depending on the methods used, the mean number of symptoms ranged from 7 until 19.[2-5] Obviously, several symptoms are directly related to the underlying HF phenotype, including dyspnea, orthopnea and edema, while other symptoms are associated with medication or comorbidities, including dry mouth, cough and loss of appetite. It is important to emphasize that these symptoms negatively influence the prognosis and health-related quality of life (HRQoL) of HF patients,[2, 4-8] and are an important reason for healthcare utilization.[9]

It is important to know what the cause of the symptoms is in HF patients. First, HF itself may be the cause of many symptoms. Therefore, HF treatment should be optimized in order to reduce symptoms. Second, side effects related to the use of medication can also contribute to the symptoms. Finally, many HF patients also have comorbidities that may also be (partly) responsible for one or more symptoms like dyspnea in patients with HF en COPD.

Depression is one of the comorbidities that frequently accompany HF. With a prevalence of 21.6% (range 9% to 60%) in HF patients, it is far more common than in the general population.[10] Bekelman et al.[2] studied 60 chronic HF patients, and has found that the presence of depression was associated with higher number of symptoms as well as higher symptom distress. We studied a much larger series of 325 acute HF patients, and particularly investigated the influence of depression on symptom occurrence and symptom burden. Furthermore, we analyzed the HRQoL in patients with and without depression.

Methods

Study population and procedures

The design of the TRIUMPH (TRanslational Initiative on Unique and novel strategies for Management of Patients with Heart failure) study has been described in detail previously.[11, 12] In brief, this prospective, observational study included patients aged 18 years and older hospitalized with acute HF. Acute HF was defined as new onset HF or decompensation of known chronic HF. The study was performed in 14 hospitals in the Netherlands between of September 2009 end December 2013. In order to be enrolled in this study, patients had to fulfill all of the following three inclusion criteria: (1) natriuretic peptide level at admission of at least three times the upper limit of normal, (2) treatment with intravenous diuretics during the hospitalization and (3) evidence of sustained systolic of diastolic dysfunction. All included patients gave written informed consent. The ethical committees of each participating center have given approval for the study. The study has been registered in the Dutch Trial Register (NTR 1893).

During one year of follow-up, there were seven assessment moments: at admission, at day 2 to 4 of admission, at discharge, at 2 to 4 weeks after discharge, as well as after 3, 6 and 9 to 12 months. At each assessment moment, patients underwent physical examination (including blood pressure, heart rate and weight measurement), blood samples were obtained and patients were scored according to the New York Heart Association (NYHA) classification. The TRIUMPH study did not intervene in the usual care and treatment of patients was in accordance with the guidelines of the European Society of Cardiology on acute and chronic HF.[13]

The primary aim of the TRIUMPH study was to evaluate the clinical value of repeated measurements of several biomarkers in patients with acute HF. Consequently, TRIUMPH was powered for this purpose. However, several questionnaires were added in order to give the opportunity to perform sub-studies to evaluate HRQoL and HF-related symptoms.

Questionnaires

At discharge and after 9-12 months of follow-up, patients were asked to complete four questionnaires: (1) Hospital Anxiety and Depression Scale (HADS) questionnaire, (2) Kansas City Cardiomyopathy Questionnaire (KCCQ), (3) EuroQuality-of-life 5 Dimensions (EQ-5D) questionnaire and (4) a specific HF-related questionnaire about symptom occurrence and symptom burden.

Hospital Anxiety and Depression Scale

The presence of anxiety and depression was measured with the HADS questionnaire. The HADS has shown to be valid and reliable for this purpose. The HADS consists of fourteen questions which are to be answered. Seven items contribute to each of the two subscales and were answered on a 4-point Likert scale from 0 to 3 (score range per subscale, 0-21).[14, 15] A score of ≥8 points on the anxiety subscale and depression subscale was used as cut-off to determine whether patients had an anxiety disorder and/or depression.[14] In this study, we only used the depression subscale.

Kansas City Cardiomyopathy Questionnaire

The disease-specific KCCQ was used to assess the HF-related HRQoL. This questionnaire consists of 23 questions and covers six domains: physical limitation, symptom stability, total symptom score (combination of symptom frequency and symptom burden), self-efficacy score, quality of life score and social limitation. Two summary scores can be computed from these domains: (1) the clinical summary score contains the domains physical limitation and total symptom score, and (2) the overall summary score captures physical limitation, total symptom score, quality of life and social limitation. Each domain and summary score is transformed into a 0 to 100 scale. Higher scores indicate better HRQoL.[16]

EuroQuality-of-life 5 Dimensions

The EQ-5D is a non-disease specific HRQoL questionnaire and has two components: health state description and health state evaluation. The 3-level version of the EQ-5D was used for health state description. The three levels were: (1) no problems, (2) some problems, and (3) extreme problems. Three statements that correspond with the three levels were made for each of the five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, patients were asked to choose the statement which best described their health status that day. In the second part (i.e. health state evaluation) patients were asked to score their health status by using a visual analogue scale (VAS) within a range of 0 (worst imaginable health status) to 100 (best imaginable health status).[17]

Symptom occurrence and symptom burden

Finally, patients were asked to complete a questionnaire about 11 HF-related symptoms (see Supplemental Data for questionnaire translated in English). Patients were asked about the presence of edema, sleep disturbance, loss of appetite, fatigue, dyspnea and cough. Further, patients were asked to score the burden for each of the present symptoms (score range 1-10). This questionnaire has been developed by the investigators of the COACH trial.[18]

Definitions

HF with reduced ejection fraction was defined as a left ventricular ejection fraction below 50%.

During admission, NYHA classification was determined at three moments. Since the NYHA classification at discharge is considered the most stable of the three, this measurement was used as the baseline NYHA classification.

Statistical analyses

We presented categorical variables as numbers with percentages and used $\chi 2$ test to compare these variables. Continuous variables are given as median with interquartile range (IQR) and were compared with the Mann-Whitney U test.

We analyzed whether there were differences in symptom occurrence and symptom burden between patients with and without depression. Therefore, for comparison, we used the $\chi 2$ for symptom occurrence and the Mann-Whitney U test for symptom burden. Further, the results of the KCCQ and EQ-5D were also compared with the Mann-Whitney U test in order to determine difference in HRQoL between patients with depression and those without depression.

The symptom occurrence and burden and HRQol after 1 year of follow-up was performed in those patients who also completed the questionnaires at hospital discharge.

All tests were two-tailed and p-values <0.05 were considered statistically significant. We used SPSS software (SPSS 24.0, IBM Corp., Armonk, NY, USA) for all statistical analyses.

Results

Baseline characteristics

Of the 496 patients enrolled in the TRIUMPH study, 21 patients were subsequently excluded: 3 patients withdrew their informed consent and 18 patients turned out to have no sustained systolic or diastolic dysfunction. Of the 475 remaining patients, 325 patients completed the HADS questionnaire at discharge. These patients constitute the study population for the present analysis. Besides a higher NT-proBNP level at admission and a higher prevalence of chronic kidney dysfunction, patients who did not complete the HADS questionnaire at discharge were comparable on medical variables with those who completed the HADS questionnaire (Supplementary Table 1).

Our study population was predominantly male (65%) with a median age of 74 years (IQR 65-81) and a reduced ejection fraction (85%). Almost half of the patients had ischemic HF (Table 1). At discharge, 37% of the patients fulfilled the criteria for depression according to the HADS definition. Patients with depression differed considerably from those without depression (Table 1): patients with depression had more frequently an ischemic cause of HF and a history of previous HF, COPD and CVA. Also, patients with depression had more frequently NYHA class III/IV than patients without depression (57% vs. 32%, p<0.001), although NT-proBNP level, renal function and left ventricular ejection fraction did not differ between both groups.

Table 1. Baseline characteristics

	Total population n=325	Depression + n=121	Depression - n=204	p-value
Demographics				
Age, years	74 (65-81)	74 (64-81)	75 (65-80)	0.53
Male	212 (65%)	86 (71%)	126 (62%)	0.088
Caucasian	310 (95%)	112 (93%)	198 (97%)	0.15
Medical history				
Previous heart failure	209 (65%)	91 (76%)	118 (58%)	0.001
Previous heart failure hospitalization within last 6 months	66 (20%)	24 (20%)	42 (21%)	0.90
Ischemic heart failure	153 (47%)	69 (58%)	84 (41%)	0.004
Heart failure with reduced ejection fraction	223 (85%)	85 (84%)	138 (85%)	0.82
Hypertension	160 (49%)	59 (49%)	101 (50%)	0.90
Diabetes mellitus	112 (35%)	47 (39%)	65 (32%)	0.20

	Total population n=325	Depression + n=121	Depression - n=204	p-value
Atrial fibrillation	141 (43%)	56 (46%)	85 (42%)	0.42
COPD	64 (20%)	32 (26%)	3 (2%)	0.018
Chronic kidney dysfunction	54 (17%)	22 (18%)	32 (16%)	0.56
CVA	51 (16%)	29 (24%)	22 (11%)	0.002
Depression	25 (8%)	13 (11%)	12 (6%)	0.11
Baseline measurements				
Body mass index, kg/m^2	28 (25-31)	28 (25-34)	27 (25-30)	0.042
Systolic blood pressure, mmHg	125 (110-145)	120 (109-142)	125 (113-149)	0.031
Diastolic blood pressure, mmHg	74 (64-85)	70 (61-80)	76 (65-90)	0.002
Heart rate, bpm	85 (73-100)	80 (70-96)	90 (76-103)	0.003
Creatinine, umol/L	122 (100-158)	125 (102-160)	122 (98-158)	0.58
NT-proBNP, pg/ml	3738 (1928-8601)	3696 (1930-8965)	3746 (1928-8381)	0.77
Left ventricular ejection fraction, %	30 (21-40)	30 (20-40)	30 (22-40)	0.64
NYHA classification				0.001
I	32 (12%)	8 (9%)	24 (14%)	
II	125 (47%)	32 (34%)	93 (54%)	
III	98 (37%)	48 (51%)	50 (29%)	
IV	12 (5%)	6 (6%)	6 (4%)	
Depression*	121 (37%)	121 (100%)	0 (0%)	<0.001

Results depicted as n (%) or median (interquartile range)

*Depression according to the HADS criteria

COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association

Depression and symptom occurrence and symptom burden at discharge

The specific questionnaire on the HF-related symptoms provided additional information on the symptom occurrence and the symptom burden of HF patients with and without depression (Table 2). Overall, all of the eleven symptoms had a prevalence above 50% at discharge. Further, almost all of the eleven symptoms more frequently occurred in patients with depression than those without depression. For example, patients with depression more frequently had ankle edema during the day (72% vs. 57%, p=0.009) and orthopnea (71% vs. 57%, p=0.01). Moreover, when the symptoms were present, the symptom burden for most of the symptoms was also significantly higher in patients with depression (Table 2 and Supplemental Figure 1).

Table 2. Symptom occurrence and symptom burden at baseline in heart failure patients with and without depression

	Symptom occurrence			Symptom burden		
	Depression +	**Depression -**	**p-value**	**Depression +**	**Depression -**	**p-value**
1. Ankle edema when you got out of bed	82 (71%)	104 (52%)	0.001	7 (5-8)	6 (4-8)	0.09
2. Ankle edema during the day	82 (72%)	114 (57%)	0.009	7 (6-8)	6 (5-8)	0.026
3. Troubles with falling asleep	73 (62%)	113 (57%)	0.30	8 (7-9)	7 (6-8)	<0.001
4. Troubles with sleeping trough	100 (85%)	138 (69%)	0.002	8 (6-9)	7 (6-8)	<0.001
5. Decreased appetite	75 (64%)	87 (44%)	0.001	7 (6-8)	6 (6-8)	0.17
6. More fatigue than before	111 (95%)	162 (81%)	0.001	8 (7-9)	7 (6-8)	<0.001
7. Shortness of breath at rest	80 (68%)	99 (50%)	0.002	8 (6-9)	7 (6-8)	0.067
8. Dyspnea d'effort	114 (97%)	182 (92%)	0.047	9 (8-10)	8 (6-9)	<0.001
9. Orthopnea	84 (71%)	115 (57%)	0.010	8 (7-9)	7 (6-9)	0.041
10. Cough	83 (71%)	129 (64%)	0.22	7 (6-9)	7 (5-8)	0.009
11. Dry cough	66 (57%)	91 (45%)	0.046	8 (6-9)	7 (5-8)	0.009

Results of symptom occurrence depicted as n (%); results of symptom burden depicted as median (IQR)

Depression and HRQoL at discharge

Patients with depression according to the HADS reported a worse HRQoL than those without depression (Table 3). When using the non-disease-specific HRQoL questionnaire, the EQ-5D, patients with depression were found to have lower scores (0.40 [IQR 0.20-0.66] vs. 0.78 [IQR 0.56-0.89], p<0.001)and a lower self-reported VAS score (50 [IQR 40-60] vs. 60 [IQR 50-70], p<0.001) than those without depression. Also, the KCCQ (as a disease-specific HRQoL questionnaire) showed that patients with depression had a lower HRQoL on all subdomains and on both the clinical summary score (24 [IQR 13-42] vs. 44 [IQR 26-66], p<0.001) and overall summary score (22 [IQR 11-35] vs. 41 [IQR 27-61], p<0.001). Notably, patients without depression had a more favorable symptom stability, symptom frequency, symptom burden and total symptom score. Social limitation is another domain with great differences between patients with and without depression (13 [IQR 0-31] vs. 42 [IQR 18-67], p<0.001).

Table 3. Health-related quality of life at baseline in patients with and without depression

	Depression +	Depression -	p-value
EQ-5D			
EQ-5D score	0.40 (0.20-0.66)	0.78 (0.56-0.89)	<0.001
EQ-5D VAS	50 (40-60)	60 (50-70)	<0.001
KCCQ			
Physical limitation	25 (13-50)	50 (25-71)	<0.001
Symptom stability	25 (0-50)	25 (0-75)	0.008
Symptom frequency	25 (8-38)	42 (22-67)	<0.001
Symptom burden	25 (8-33)	33 (25-67)	<0.001
Total symptom score	23 (13-36)	41 (21-68)	<0.001
Self-efficacy score	63 (50-88)	75 (50-100)	0.005
Quality of life score	17 (8-33)	42 (25-58)	<0.001
Social limitation	13 (0-31)	42 (18-67)	<0.001
Clinical summary score	24 (13-42)	44 (26-66)	<0.001
Overall summary score	22 (11-35)	41 (27-61)	<0.001

EQ-5D, EuroQuality-of-life 5 Dimensions; KCCQ, Kansas City Cardiomyopathy Questionnaire; VAS, visual analogue scale

HRQoL and symptoms in relation to depression at follow-up

Of the initially included patients, 257 patients were alive after 1 year of follow-up. Of these, 147 patients (57%) completed the follow-up HADS questionnaire. In these patients, we found a higher symptom occurrence for a significant part of the symptoms in patients with depression (Supplemental Table 2). We also observed a worse HRQoL (both on the EQ-5D and the KCCQ) in patients with depression as compared to those without depression (Supplemental Table 3).

Discussion

In this prospective, multicenter study using general, as well as disease specific questionnaires on symptoms, depression and HRQoL in patients admitted with acute HF, we found that patients reported a high number and wide variety of HF-related symptoms, especially those identified as having depression according to the self-reported HADS. Importantly, patients with depression not only had a significantly higher number of symptoms but also a substantially higher symptom burden than patients without depression. Moreover, patients with depression had a markedly worse HRQoL than those without depression. Lastly, we showed that the worse outcome as described above of patients with depression with respect to symptom occurrence, symptom burden and HRQoL was not only present at discharge but persisted during the more chronic phase until 1-year follow-up.

HF-related symptoms in HF patients

This study found that patients with acute HF, especially those with depression according to the HADS at discharge, suffered from a substantial number of HF-related symptoms in the preceding days or weeks. We speculate that there may be enough room for improvement in symptom management. Indeed, after the acute phase of HF, patients should be adjusted to optimal treatment. But, also in de chronic phase, patients reported numerous symptoms. Symptom management may be improved in several ways. First and foremost, HF therapy should be optimized according to the recommendations in the guidelines.[1] However, existing literature[2-5, 8] as well as our study showed that patients continued to have symptoms despite HF treatment. Therefore, additional treatment strategies should be developed. For example, as stated in the ESC position statement on palliative care in HF,[19] palliative care should be more incorporated in the care of patients with (advanced) HF with individual needs of patients taken into account. Further, we think that patient education, HF self-management and self-care, psychoeducational intervention and symptoms recognition and response training by patients[20-25] may also reduce the symptom burden. Lastly, patients' psychological and non-psychological comorbidities, which are also partly responsible for the reported symptoms, also need adequate care and treatment.

Like others,[2] we also found a higher symptom occurrence and symptom burden in HF patients with depression than in those without depression. Depression has been associated with higher nonadherence to medical therapy, lack of social support and reduced self-care.[26] These factors may induce higher symptom occurrence and symptom burden. Indeed, there is overlap between HF-related and depression-related symptoms. However, given the adverse impact of depression on prognosis in HF, it is important to recognize depression in patients with HF. Therefore, routine screening for depression with validated questionnaires, such as the HADS, may be considered in order to diagnose depression in an early stage and offer specialized psychological treatment, if required.[1]

Since it has been demonstrated that there is a dose-dependent relation between depression and symptomatology,[2] treatment of depression is important to induce symptom relief. Depression may be treated pharmacologically with selective serotonin reuptake inhibitors,[1] although no benefit has been observed of this treatment in patients with HF.[27] Besides pharmacological treatment, non-pharmacological therapies like cognitive behavioral therapy[28] and exercise training[29] have been reported to be effective.

HRQoL in patients with and without depression

In this study, we not only assessed symptom occurrence and symptom burden but also the HRQoL. We determined the HRQoL not only with the general, non-disease-specific EQ-5D questionnaire but also with the HF-specific KCCQ. Our results, both in the acute and in the more chronic phase of HF, are in accordance with existing literature reporting a worse HRQoL in chronic HF patients with depression than in those without depression.[2, 30, 31] For example, patients with depression had a low score on the social limitation domain.

Furthermore, patients with depression had lower scores on the clinical summary score and the overall summary scores as measured with the KCCQ.

Since the maximum score of the KCCQ is 100, it should be emphasized that both in patients with and without depression the median score of almost all subdomains was below 50 at discharge. Despite the fact that patients reported a higher HRQoL after 1 year of follow-up, the HRQoL was far from optimal, especially in those with depression. These results underscore that clinicians should pay attention to improvement of HRQoL with extra attention to patients with depression. Beyond improvement in patient's well-being, a good HRQoL is associated with a better prognosis.[32]

NYHA class in patients with and without depression

Results of our study confirm previous observations that HF patients with depression have a higher NYHA class than those without depression.[10] Until now, it has never been studied what might explain this difference in NYHA classification. Do HF patients with depression really have more symptoms than there non-depressed counterparts? Or is a higher symptom burden the explanation for the higher NYHA classification in HF patients with depression? Alternatively, are both symptom occurrence and symptom burden responsible for the difference in NYHA classification between patients with and without depression? As a result of this study, we can conclude that both a higher symptom occurrence and a higher burden are associated with a higher NYHA classification in patients with depression. Because the study design, we cannot state whether there was causality between depression and higher NYHA classification. However, based on our results, it is very likely that the worse NYHA classification in patients with depression was not only caused by parameters of worse cardiac function since LVEF, NT-proBNP and renal function were comparable in patients with and without depression.

Strengths and limitations

This study is a multicenter (14 Dutch centers), prospective cohort study addressing the important, and perhaps somewhat underexposed, topic of symptoms in patients with HF. We distinguished between patients with and without depression and we had results during the acute and chronic phase of HF. Further, we used not only one questionnaire but a comprehensive set of four questionnaires in this study. This study is the first reporting HRQoL and symptom occurrence and burden (assessed with a comprehensive set of general and disease-specific questionnaires) in relation to the presence of depression in a relatively high number, as compared with previous studies,[2-5] of patients with acute HF. Despite the strengths of this study, some limitations should be mentioned. First, almost 70% of the initial study population completed the HADS questionnaire at discharge. Therefore, there may have been selection bias because 30% of the originally-included patients were not included in our analysis sample. However, we found that responders and non-responders had comparable medical characteristics at baseline. Indeed, we have no additional information about psychosocial characteristics in responders and non-responders. Further, we had a relatively low number of patients that also completed the HRQoL and symptom questionnaires

after 1 year follow-up. Nonetheless, we had the unique possibility to determine HRQoL, symptom occurrence and symptom burden in the acute and chronic phase of HF in one study population. Thirdly, we did not register whether the patients with depression received (psycho)therapy against their depression. Therefore, we did not know what anti-depressive therapy was given at baseline and during follow-up. Fourth, depression was not diagnosed by a psychiatrist or psychologist. However, a HADS score above 8 on the depression scale has found to be a good indication for depression.[14] Lastly, for assessing the symptom occurrence and symptom burden, this study did not use a more validated questionnaire like Memorial Symptom Assessment Scale[33] or Edmonton Symptom Assessment Scale.[34] However, it is important to mention that these questionnaires are not HF-specific. Moreover, the total symptom score of the validated and HF-specific KCCQ showed comparable results as our questionnaire about symptom occurrence and burden, which was developed for assessing symptoms that were shown to be important HF-related symptoms.

Conclusion

In conclusion, patients with HF reported a high symptom occurrence and a high symptom burden, which was substantially worse in patients with depression than in those without depression. Furthermore, we found lower HRQoL in patients with depression. We did not only find this at discharge but also after 1 year of follow-up. In our opinion, clinicians should give more attention to symptom management, especially in patients with depression. More research is needed to determine whether optimal HF therapy, effective treatment of comorbidities and incorporating additional supportive strategies for the management for HF such as education, self-management, symptom-recognition and palliative medicine may be helpful to reduce symptoms, symptom burden and, hence, to improve depression and HRQoL. Additionally, routine screening for depression may be useful in order to recognize depression in HF patients. If present, additional cognitive behavioral therapy and exercise therapy may be effective in patients with depression.

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Supplemental material

Supplemental Table 1. Baseline characteristics of patients who completed the HADS questionnaire at baseline and those who did not

	Completed HADS at baseline n=325	Not completed HADS at baseline n=150	p-value
Demographics			
Age, years	74 (65-81)	72 (64-79)	0.22
Male	212 (65%)	86 (57%)	0.1
Caucasian	310 (95%)	139 (93%)	0.2
Medical history			
Previous heart failure	209 (65%)	92 (62%)	0.62
Previous heart failure hospitalization within last 6 months	66 (20%)	28 (19%)	0.71
Ischemic heart failure	153 (47%)	76 (51%)	0.41
Heart failure with reduced ejection fraction	223 (85%)	85 (78%)	0.11
Hypertension	160 (49%)	82 (55%)	0.21
Diabetes mellitus	112 (35%)	60 (41%)	0.18
Atrial fibrillation	141 (43%)	57 (39%)	0.32
COPD	64 (20%)	28 (19%)	0.87
Chronic kidney dysfunction	54 (17%)	37 (25%)	0.03
CVA	51 (16%)	30 (20%)	0.22
Depression	25 (8%)	6 (4%)	0.14
Baseline measurements			
Body mass index, kg/m^2	28 (25-31)	27 (25-32)	0.86
Systolic blood pressure, mmHg	125 (110-145)	130 (110-148)	0.4
Diastolic blood pressure, mmHg	74 (64-85)	75 (66-89)	0.35
Heart rate, bpm	85 (73-100)	83 (70-100)	0.31
Kreatinin, umol/L	122 (100-158)	130 (103-170)	0.18
NT-proBNP, pg/ml	3738 (1928-8601)	5509 (2732-10026)	0.009
Left ventricular ejection fraction, %	30 (21-40)	31 (23-47)	0.15
NYHA classification			0.73
I	32 (12%)	13 (15%)	
II	125 (47%)	44 (50%)	
III	98 (37%)	27 (31%)	
IV	12 (5%)	4 (5%)	
Depression*	121 (37%)	NA	NA

Results depicted as n (%) or median (interquartile range)

*Depression according to the HADS criteria

COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; HADS, Hospital Anxiety and Depression Scale; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association

Supplemental Table 2. Symptom occurrence and symptom burden after 12 months follow-up in heart failure patients with and without depression

	Symptom occurrence			Symptom burden		
	Depression +	Depression -	p value	Depression +	Depression -	p value
1. Ankle edema when you got out of bed	13 (39%)	19 (17%)	0.005	6 (5-7)	4 (1-6)	0.001
2. Ankle edema during the day	17 (52%)	29 (25%)	0.004	6 (5-8)	5 (4-5)	<0.001
3. Troubles with falling asleep	12 (36%)	38 (33%)	0.75	7 (5-7)	6 (5-7)	0.75
4. Troubles with sleeping trough	16 (49%)	50 (44%)	0.67	7 (5-8)	6 (4-7)	0.06
5. Decreased appetite	19 (58%)	20 (18%)	<0.001	6 (5-8)	6 (3-8)	0.32
6. More fatigue than before	25 (76%)	36 (32%)	<0.001	7 (6-8)	6 (4-7)	0.04
7. Shortness of breath at rest	11 (33%)	20 (18%)	0.05	5 (4-8)	5 (4-7)	0.53
8. Dyspnoea d'effort	30 (91%)	67 (59%)	0.001	7 (5-8)	7 (5-8)	0.98
9. Orthopnoea	10 (32%)	21 (19%)	0.11	7 (5-8)	6 (4-7)	0.57
10. Cough	14 (44%)	51 (45%)	0.89	5 (4-6)	5 (4-7)	0.23
11. Dry cough	14 (44%)	43 (38%)	0.56	5 (2-7)	5 (3-7)	0.83

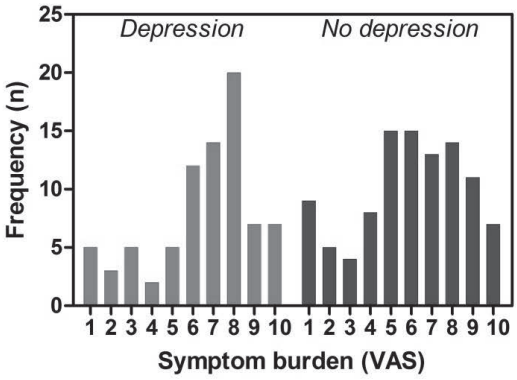
Results of symptom occurrence depicted as n (%); results of symptom burden depicted as median (IQR)

Supplemental Table 3. Health-related quality of life after 12 months follow-up in patients with and without depression

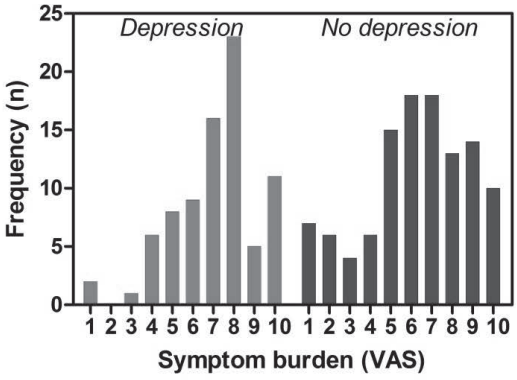
	Depression +	Depression -	p-value
EQ-5D			
EQ-5D score	0.48 (0.23-0.65)	0.86 (0.78-1.00)	<0.001
EQ-5D VAS	56 (40-60)	72 (63-80)	<0.001
KCCQ			
Physical limitation	32 (21-46)	73 (47-92)	<0.001
Symptom stability	50 (25-50)	50 (50-75)	0.002
Symptom frequency	46 (33-56)	88 (70-100)	<0.001
Symptom burden	33 (25-54)	92 (58-100)	<0.001
Total symptom score	42 (33-52)	89 (65-100)	<0.001
Self-efficacy score	75 (50-94)	100 (88-100)	<0.001
Quality of life score	42 (17-50)	83 (58-92)	<0.001
Social limitation	31 (16-50)	75 (50-92)	<0.001
Clinical summary score	40 (33-46)	80 (57-95)	<0.001
Overall summary score	36 (26-48)	78 (59-90)	<0.001

EQ-5D, EuroQuality-of-life 5 Dimensions; KCCQ, Kansas City Cardiomyopathy Questionnaire; VAS, visual analogue scale

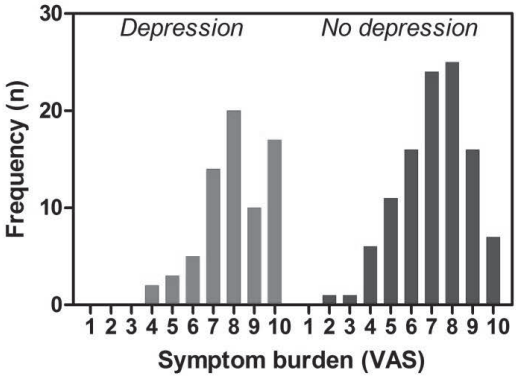
1. Ankle edema when you got out of bed

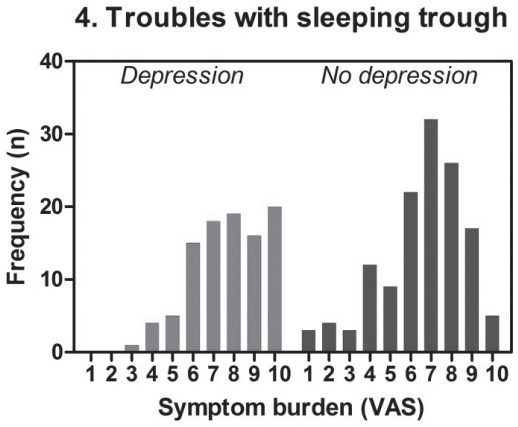


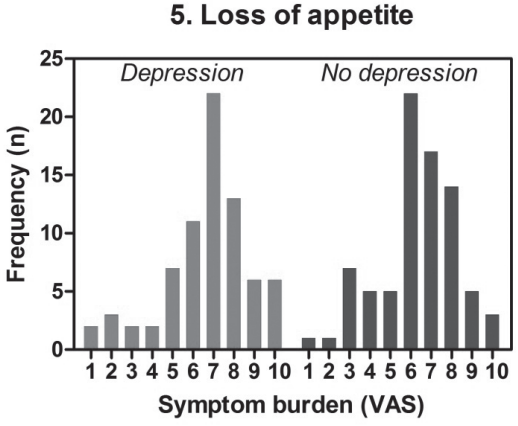
2. Ankle edema during the day

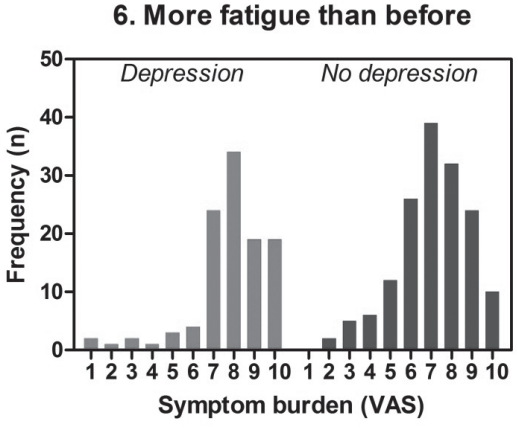


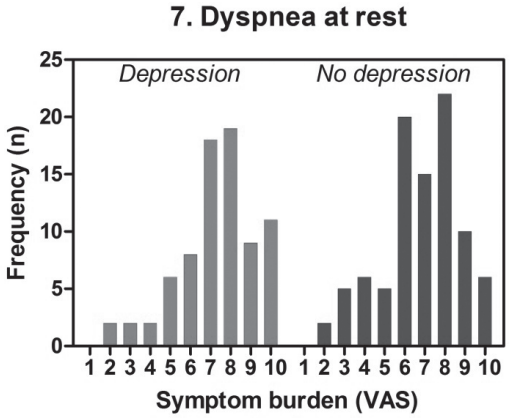
3. Troubles with falling asleep

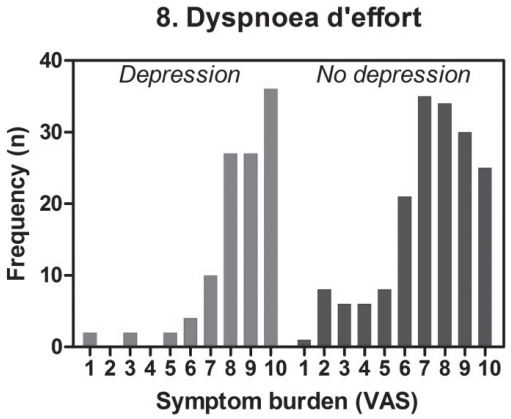


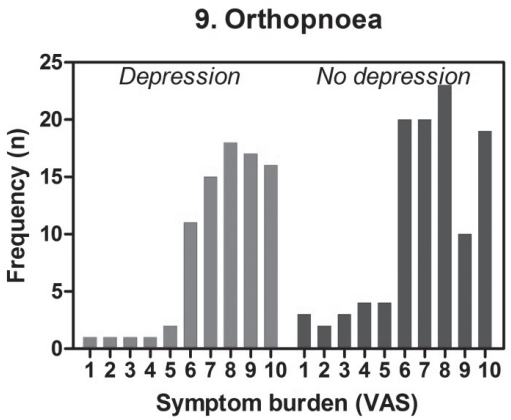

4. Troubles with sleeping trough
Depression
No depression
Frequency (n)
0
10
20
30
40
1 2 3 4 5 6 7 8 9 10 1 2 3 4 5 6 7 8 9 10
Symptom burden (VAS)

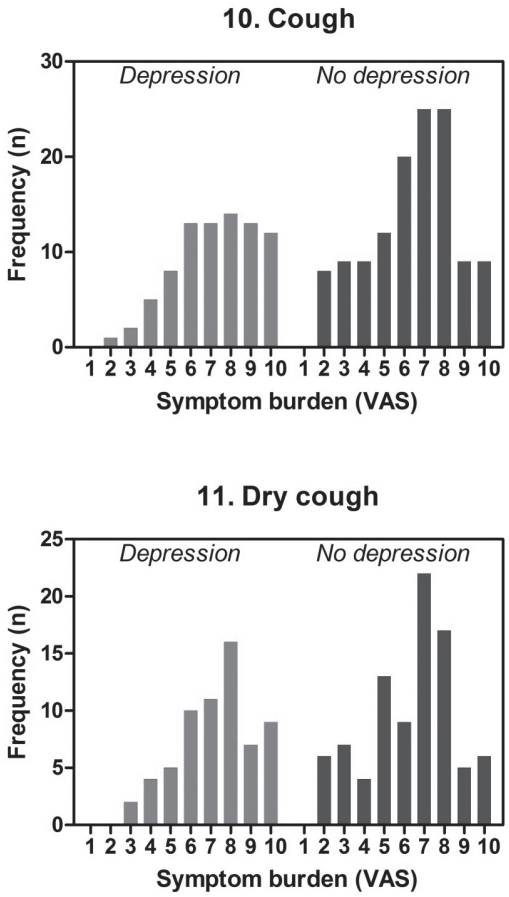

5. Loss of appetite
Depression
No depression
Frequency (n)
0
5
10
15
20
25
1 2 3 4 5 6 7 8 9 10 1 2 3 4 5 6 7 8 9 10
Symptom burden (VAS)


6. More fatigue than before
Depression
No depression
Frequency (n)
0
10
20
30
40
50
1 2 3 4 5 6 7 8 9 10 1 2 3 4 5 6 7 8 9 10
Symptom burden (VAS)


7. Dyspnea at rest
Depression
No depression
Frequency (n)
0
5
10
15
20
25
1 2 3 4 5 6 7 8 9 10 1 2 3 4 5 6 7 8 9 10
Symptom burden (VAS)


8. Dyspnoea d'effort
Depression
No depression
Frequency (n)
0
10
20
30
40
1 2 3 4 5 6 7 8 9 10 1 2 3 4 5 6 7 8 9 10
Symptom burden (VAS)


9. Orthopnoea
Depression
No depression
Frequency (n)
0
5
10
15
20
25
1 2 3 4 5 6 7 8 9 10 1 2 3 4 5 6 7 8 9 10
Symptom burden (VAS)



Supplemental Figure 1. Histograms of symptom burden at baseline for the eleven heart failure symptoms in patients with and without depression.
VAS, visual analogue scale

Symptom occurrence and symptom burden

Complaints and symptoms and the extent to which these complaints occurred.

Instruction question 1 until 11

In this example, you give the report number 7 as an answer to the question.

1	2	3	4	5	6	7	8	9	10

Not Always

The numbers correspond to the following appreciation:

1 = not
2 = almost not
3 = very little
4 = little
5 = not often, not little
6 = somewhat
7 = quite often
8 = often
9 = almost always
10 = always

1. Did you suffer from ankle edema when you got out of bed during the last month?

Yes
No

If yes, to what extent were these complaints present?

1	2	3	4	5	6	7	8	9	10

2. Did you suffer from ankle edema during the day during the last month?

Yes
No

If yes, to what extent were these complaints present?

1	2	3	4	5	6	7	8	9	10

3. Did you suffer from troubles with falling asleep during the last month?

Yes
No

If yes, to what extent were these complaints present?

1	2	3	4	5	6	7	8	9	10

4. Did you suffer from troubles with sleeping through during the last month?

Yes
No

If yes, to what extent were these complaints present?

1	2	3	4	5	6	7	8	9	10

5. Did you suffer from loss of appetite during the last month?

Yes
No

If yes, to what extent were these complaints present?

1	2	3	4	5	6	7	8	9	10

6. Did you suffer from more fatigue than before during the last month?

Yes
No

If yes, to what extent were these complaints present?

1	2	3	4	5	6	7	8	9	10

7. Did you suffer from shortness of breath at rest during the last month?

Yes
No

If yes, to what extent were these complaints present?

1	2	3	4	5	6	7	8	9	10

8 Did you suffer from shortness of breath during exercise during the last month?

Yes
No

If yes, to what extent were these complaints present?

1	2	3	4	5	6	7	8	9	10

9. Did you suffer from shortness of breath when lying flat during the last month?

Yes
No

If yes, to what extent were these complaints present?

1	2	3	4	5	6	7	8	9	10

10. Did you suffer from coughing during the last month?

Yes
No

If yes, to what extent were these complaints present?

1	2	3	4	5	6	7	8	9	10

11. Did you suffer from dry cough during the last month?

Yes
No

If yes, to what extent were these complaints present?

1	2	3	4	5	6	7	8	9	10

PART III

Heart failure at a population level

CHAPTER 11

Implications of the ACC/AHA risk score for prediction of heart failure: The Rotterdam Study.

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Abstract

Background: Despite the growing burden of heart failure (HF), there have been no recommendations for use of any of the primary prevention models in the existing guidelines. HF was also not included as an outcome in the American College of Cardiology/ American Heart Association (ACC/AHA) risk score.

Methods: Among 2743 men and 3646 women ≥55 years free of HF from the population-based Rotterdam Study cohort, 4 Cox models were fitted using the predictors of the ACC/AHA, ARIC, Health-ABC and ACC/AHA+NT-proBNP. Performance of the models for 10-year HF prediction was evaluated. Afterwards, net reclassification improvement (NRI) for adding NT-proBNP to the ACC/AHA model was assessed.

Results: During a median follow-up of 13 years, 429 men and 489 women developed HF. The ARIC model had the highest performance [c-statistic (95% confidence interval[CI]): 0.80 (0.78; 0.83) and 0.80 (0.78;0.83) in men and women, respectively]. The c-statistic for the ACC/AHA model was 0.76 (0.74;0.78) in men and 0.77 (0.75; 0.80) in women. Adding NT-proBNP to the ACC/AHA model increased the c-statistic to 0.80 (0.78 to 0.83) in men and 0.81 (0.79 to 0.84) in women. Sensitivity and specificity of the ACC/AHA model did not drastically change after addition of NT-proBNP. NRI(95%CI) was -23.8%(-19.2%;-28.4%) in men and -27.6%(-30.7%;-24.5%) in women for events and 57.9% (54.8%; 61.0%) in men and 52.8%(50.3%; 55.5%) in women for non-events.

Conclusions: Acceptable performance of the model based on risk factors included in the ACC/AHA model advocates use of this model for prediction of HF risk in primary prevention setting. Addition of NT-proBNP modestly improved the model performance but did not lead to relevant discrimination improvement in clinical risk reclassification.

Background

Heart failure (HF) remains a major public health problem among men and women worldwide.[1, 2] The growing morbidity and mortality of HF, along with poor quality of life and prognosis, high costs, and the challenges of treating clinically overt HF highlight the need for more efficient preventive strategies.[3, 4] To identify high risk individuals who would benefit most from early prevention, several HF risk prediction models have been developed.[5, 6] However, none of these models have been recommended for routine use in clinical practice.[5]

The recent American College of Cardiology (ACC)/American Heart Association (AHA) guidelines use the pooled cohort equations (PCE) to predict 10-year risk of atherosclerotic cardiovascular disease (ASCVD). Compared to the previous guidelines, the newer guidelines have expanded the focus from coronary heart disease (CHD) only to an ASCVD outcome that additionally includes stroke.[7] Due to variability between studies in ascertainment of HF, incident HF has not been included in this newly expanded outcome. The PCE is comprised of the traditional cardiovascular risk factors which were among the ten most consistently reported predictors included in HF prediction models in a recent meta-analysis.[6] Compared to the more specific HF prediction models, risk factors included in the PCE are simple to measure and available in most clinical settings.

In this study, we assessed the performance of a model fitted based on the risk factors used in the PCE (ACC/AHA model) for 10-year HF prediction among men and women from the large prospective population-based Rotterdam Study. We also compared the performance of this model for HF prediction with the performance of models based on risk factors included in the two risk scores that have been specifically developed and validated to predict HF in the general population; namely the Atherosclerosis Risk in Communities (ARIC) and the Health Aging and Body Composition (Health ABC) HF risk scores.[8, 9] Furthermore, we investigated whether addition of NT-proBNP, to the ACC/AHA risk score improved HF risk prediction.

Methods

Study sample

This project was carried out within the framework of the Rotterdam Study, a prospective population-based study among subjects 45 years and older in Rotterdam, the Netherlands. The baseline examination of the Rotterdam Study included 7983 individuals and was completed between 1989-1993 (RS-I). The cohort has been extended twice (3011 individuals, RS-II , recruited in 2000-2001 and 3932 individuals, RS-III, in 2006) to include participants who were 45 years or older or had moved to the study area. Rotterdam Study participants have been followed-up ever since and the examinations have been repeated every 3-4 years. The overall response for all three study cycles at entry was 72.0% (14,926 of 20,744). The rationale and design of the study have been previously described.[10] The Rotterdam Study has been approved by the Medical Ethics Committee

of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare, and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalog number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained information from their treating physicians.

The present study used data from the third examination of the original cohort (RS-I-3, 1997-1999, n = 4755) and the first examination of the extended cohort (RS-II-1, n=3011) had blood samples (RS-I-3, n=4063 and RS-II-1, n=2630) . We excluded participants with a history of HF at baseline (n = 258), those with incomplete data at baseline or lost to follow-up (n=46). After exclusions, 6389 participants (2743 men, 3646 women) were included in the study. (Figure 1)

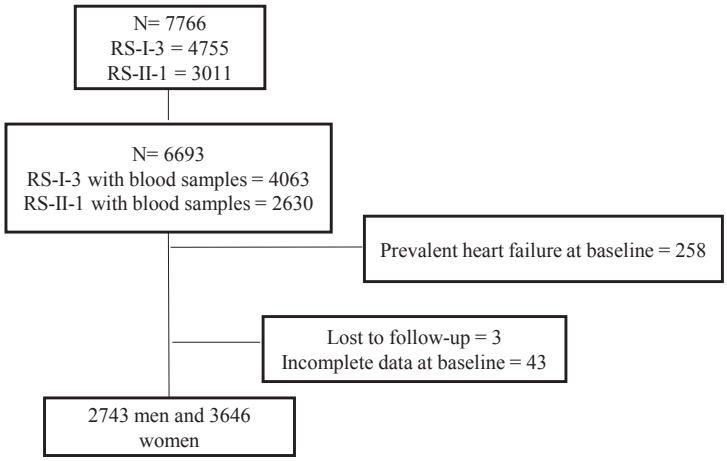

Figure 1. Flowchart of the included study participants

Predictors of HF

Body mass index (BMI) was calculated based on weight in kilograms divided by height in meters squared. Blood pressure was measured on the right arm using a random-zero sphygmomanometer at sitting position. Two measurements were performed and the average of the two was used in the analyses. Antihypertensive treatment for hypertension, use of lipid lowering medication, history of diabetes mellitus and history of CHD were based on clinical information obtained from general practitioners and letters or discharge reports from medical specialists.[11] Information on smoking behavior was acquired from questionnaires. For the ACC/AHA model, participants were classified as current smokers versus former or never smokers. For the Health ABC and ARIC models, smoking status was classified as current, former and never. Fasting serum glucose levels were determined using the glucose hexokinase method and serum total and high-density lipoprotein (HDL) cholesterol were measured using an automatic enzymatic procedure (Hitachi 911, Roche CHOD PAP). Serum

creatinine levels were measured using an enzymatic assay (Roche Diagnostics, Mannheim, Germany) which was calibrated by isotope dilution mass spectrometry. Serum NT-proBNP was measured using a commercially available electrochemiluminescence immunoassay (Elecsys proBNP, F Hoffman-La Roche Ltd) on an Elecsys 2010 analyzer.[12] Left ventricular hypertrophy (LVH) was diagnosed based on Sokolov-Lyon criteria by the Modular ECG Analysis System program with an algorithm taking into account QRS voltages with an age-dependent correction and repolarization.[13] Presence of atrial fibrillation (AF) was based on the clinical and ECG evidence from medical records.[11]

HF Assessment

Ascertainment of HF for the Rotterdam Study has been previously described.[11] Information on prevalent HF cases at entry were obtained from a database containing hospital discharge diagnoses from all hospitals in Rotterdam at entry.[11, 14] During follow-up, diagnosis of incident HF was also based on clinical information systematically collected from the general practitioner medical records and verified hospital discharge diagnoses collected from all hospitals in Rotterdam. Based on the criteria of the European Society of Cardiology (ESC), the diagnosis of definite HF was based on the presence of two signs or symptoms suggestive of HF, established by objective evidence of cardiac dysfunction, confirmed by a medical specialist.[15] HF was classified as probable if at least two typical symptoms of HF were present and at least one of the following: history of CVD (MI, valvular heart disease, hypertension), response to treatment for HF or objective evidence of cardiac dysfunction, while symptoms could not be attributed to another disease. In accordance with the ESC guidelines, only definite and probable cases were used in the Rotterdam study definition. [15]

The incident date for HF was defined as the date of the first occurrence of symptoms suggestive of HF from the medical records or the day of receipt of a first prescription for a loop diuretic or an angiotensin-converting enzyme inhibitor, whichever one preceded.[11]

Statistical Analysis

Baseline characteristics of men and women were presented as mean [standard deviation (SD)] for normally distributed data and as median [interquartile range (IQR)] for skewed data and were compared using the Student-t tests for continuous variables and χ^2 tests for categorical data. Logarithmic transformation was made on NT-proBNP to account for its skewed distribution. We used multiple imputation for missing values on covariates (All missing <5%).[16] Parameter estimates were obtained by pooling 5 imputed datasets using Rubin rules.[16]

Three different Cox proportional hazards models were developed by refitting risk factors from the PCE risk score (ACC/AHA model), the ARIC HF risk score (ARIC model) and the Health ABC HF risk score (Health ABC model). Although these models were refitted, for simplicity we call them ACC/AHA, ARIC, and Health ABC models.10-year HF risk was estimated per model. Predictors included in the ACC/AHA model were age, total and HDL

cholesterol, systolic blood pressure, antihypertensive treatment, current smoking, and history of diabetes. The ARIC model included age, heart rate, systolic blood pressure, antihypertensive treatment, history of diabetes, history of CHD, smoking status (current, former, never), BMI and NT-proBNP. The Health ABC model included age, history of CHD, LVH, systolic blood pressure, heart rate, smoking status (current, former, never), glucose and creatinine. Due to unavailability, albumin measurement was left out of the Health ABC model. In addition, a fourth model was built that additionally included NT-proBNP in the ACC/AHA model as a predictor (ACC/AHA+NT-proBNP model). All models were separately developed for men and women.

For each model, a full model including interaction terms between age and NT-proBNP and between SBP and antihypertensive medication use (if applicable) and natural splines with 2 knots for age and NT-proBNP (if applicable) was first specified, forcing on the variables of the respective risk scores. Schoenfeld's test of residuals using the Kaplan-Meier estimate of the survival function was used to check the proportionality of the regressions. Then, backward selection was performed using log likelihood ratio to compare all these nested models. A *P*-value of 0.2 was considered for inclusion of nonlinear and interaction terms in multivariable models.

To compare the models, Akaike information criterion (AIC) was used. Calibration of the models was graphically evaluated by creating model-based risk plots and was further assessed with the Greenwood-D'Agostino-Nam test.[17] The discriminative performance of the fitted models was assessed by calculating the modified c-statistic by using the technique of inverse probability of censoring weighting (IPCW) for censored data.[18]

To evaluate the implication of NT-proBNP on risk assessment, performance of the ACC/AHA and the ACC/AHA+NT-proBNP models for 10-year HF prediction were compared. We assessed the performance of the two models by calculating the time-dependent sensitivity, specificity, positive and negative predicted values for survival data. To do this, risk cut-offs introduced by the ACC/AHA guideline for ASCVD (5%, 7.5% and 20%) were used.[19] We also calculated continuous and categorical NRIs. Reclassification tables were constructed to investigate the number of individuals with and without the HF event, reclassified to a higher or lower category of 10-year risk for HF. Risk categories were defined using the same cut-offs [low-risk (<5%), borderline risk (≥5% and <7.5%), intermediate risk (≥7.5% and <20%) and high risk (≥20%)].

The original ACC/AHA model was developed for ASCVD risk calculation among asymptomatic individuals. Therefore, as a sensitivity analysis, the performance of the ACC/AHA model was also evaluated after addition of CHD history to the model. Furthermore, all analyses were once repeated in a sample with further exclusions for prevalent CHD and AF and use of lipid lowering medication based on the ACC/AHA guidelines.

All analyses were performed using R version 3.6.1 (Packages: mice, rms, survC1, timeROC, ggplot2)

Results

Mean (SD) age was 68.0 (7.78) years in men and 69.2 (8.58) years in women (Table 1). Mean BMI (kg/m^2) was slightly higher in women [26.5 (3.27) in men versus 27.3 (4.39) in women]. Glucose and creatinine levels were higher in men [6.09 (1.70) mmol/l in men and 5.87 (1.47) mmol/l in women for glucose and 89.0 (18.2) mmol/l in men and 70.8 (13.5) mmol/l in women for creatinine]. However, total and HDL cholesterol levels were higher in women. 33% of men and 35% of women used antihypertensives while 14% and 12% took lipid lowering medications, respectively. More men (13.8%) had a history of CHD than women (3.3%). Likewise, more men had diabetes (14.7% compared to 11.6% in women). Median NT-proBNP levels were higher in women [median (IQR): 8.19 (13.4) in men and 10.8 (13.2) in women]. Data on covariates were missing for less than 5% in men and women.

Table 1. Characteristics of the study population

Clinical features	Men (N = 2743)	Women (N = 3646)	P-value*
Age, years	68.0 (7.78)	69.2 (8.58)	<0.001
BMI, kg/m^2	26.5 (3.27)	27.3 (4.39)	<0.001
Systolic blood pressure, mmHg	142 (20.8)	143(21.5)	0.350
Hear rate, bpm	69.4 (11.9)	71.7 (10.9)	0.032
Total cholesterol, mmol/l	5.54 (0.95)	6.01 (0.95)	<0.001
HDL, mmol/l	1.24 (0.32)	1.50 (0.40)	<0.001
Antihypertensive use, N (%)	856 (32.7)	1220 (35.3)	<0.001
Lipid lowering medication, N (%)	364 (13.8)	420 (12.0)	<0.001
Creatinine, mmol/l†	89.0 (18.2)	70.8 (13.5)	<0.001
Glucose, mmol/l	6.09 (1.70)	5.87 (1.47)	<0.001
LVH, N (%)	176 (7.30)	119 (3.80)	0.034
NT-proBNP, pmol/l†	8.19 (13.4)	10.8 (13.2)	<0.001
Prevalent CHD, N (%)	370 (13.8)	118 (3.30)	<0.001
Prevalent diabetes, N (%)	403 (14.7)	423 (11.6)	0.009
Smoking, N (%)			<0.001
Current	652 (25.3)	614 (17.2)	-
Past	1604 (62.2)	1315 (36.8)	-
Never	322 (12.5)	1648 (46.1)	-

Data are mean (standard deviation (SD))for continuous variables, †median (interquartile range (IQR)) for skewed variables, and number (percentage) for categorical variables from the original data.

BMI; body mass index, CHD; coronary heart disease, HDL; high-density lipoprotein, LVH; left ventricular hypertrophy

* P-value for differences in characteristics between men and women.

Proportion of missing: Among men: SBP: 0.18%, heart rate: 0.55%, total cholesterol, BMI and glucose: each 0.9%, HDL: 1.7%, creatinine:1.6%, NT-proBNP: 1.6%, antihypertensive use: 2%, smoking: 2.7%, LVH: 2.9%.

Among women: SBP: 0.86%, heart rate: 1.43%, total cholesterol, glucose: 1.6 %, antihypertensive use: 1.8%, smoking: 1.9%, BMI:2.1%, creatinine:1.8%, NT-proBNP: 2%, HDL: 2.6%, LVH: 2.6%.

During a median follow-up of 13 years, 429 and 489 incident cases of HF were identified in men and women, respectively (incident rate: 14.5 per 1000 person-years in men and 11.4 per 1000 person-years in women). Supplemental Table 1 details the multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) for 10-year incident HF for the ACC/AHA, the ARIC, the Health ABC and the ACC/AHA+NT-proBNP models in men and women.

Comparing the models, the Health ABC model had the lowest AIC in men and women (5651.2 and 6656.2, respectively) with 11 degrees of freedom (See Supplemental Table 2). The overall fit of the ARIC model was 5953.2 in men 6908.0 in women with 9 degrees of freedom. The AIC of the ACC/AHA model was 6213.4 in men and 7503.2 in women. The AIC of the ACC/AHA model improved substantially (P for the log-likelihood ratio test <0.001) after adding NT-proBNP (5970.9 in men and 7179.4 in women). Calibration plots of observed and predicted risks were reasonable (See Supplemental Figure 1). The Greenwood-D 'Agostino-Nam test also indicated that all models were well-calibrated (All P >0.20).

Figure 2 shows the discriminative performance of each model in men and women. The ARIC model had the highest discriminative ability in men and women [c-statistic (95% CI): 0.80 (0.78 to 0.83) and 0.80 (0.78 to 0.83), respectively]. The c-statistic for the ACC/AHA model was 0.76 (0.74 to 0.78) in men and 0.77 (0.75 to 0.80) in women. By adding NT-proBNP to the ACC/AHA model, the c-statistic increased to 0.80 (0.78 to 0.83) in men and 0.81 (0.79 to 0.84) in women.

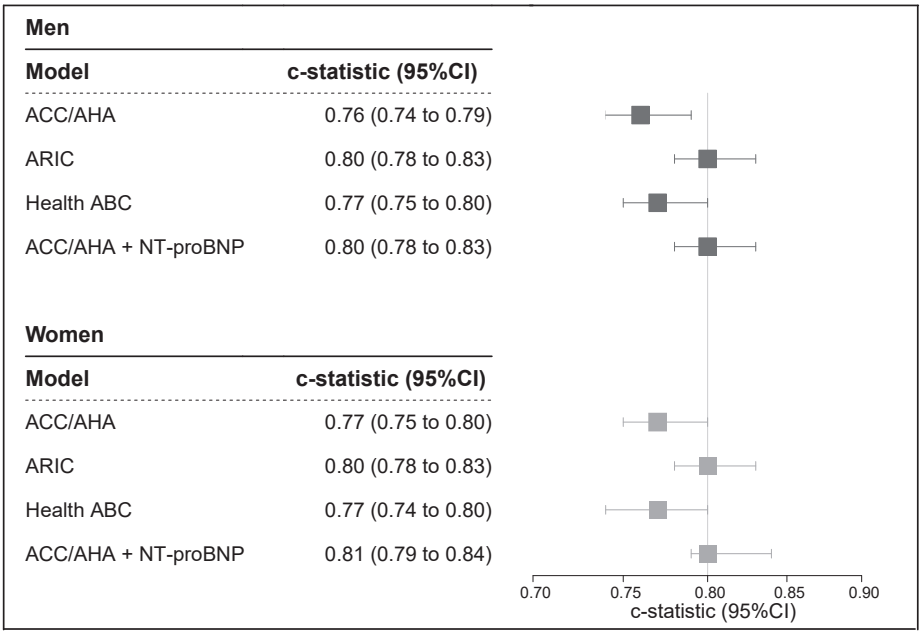

Figure 2. Discriminative performance of models for 10-year heart failure prediction

Using cut-offs introduced by the recent ACC/AHA guidelines, the ACC/AHA model categorized 0.04% of men as low risk, 1.5% as borderline, 27.6% as intermediate and 70.9% as high risk (Figure 3). Among women, the ACC/AHA model allocated 7% as low risk, 14.4% as borderline, 38.2% as intermediate and 40.4% as high risk. Continuous NRI (95% CI) after adding NT-proBNP to the ACC/AHA model was 0.075 (-0.08 to 0.16) in men and 0.12 (0.02 to 0.22) in women. As for categorical NRI, event NRI (95% CI) was -23.8% (-28.4% to -19.2%) and non-event NRI (95% CI) was 57.9% (54.8% to 61.0%) for men. Among women, event and non-event NRI (95% CI) were -27.6% (-30.7% to -24.5%) and 52.8% (50.3% to 55.5%) respectively (See Supplemental Table 3). Reclassification of individuals with and without the HF event to higher or lower risk categories is depicted in (See Supplemental Figure 2).

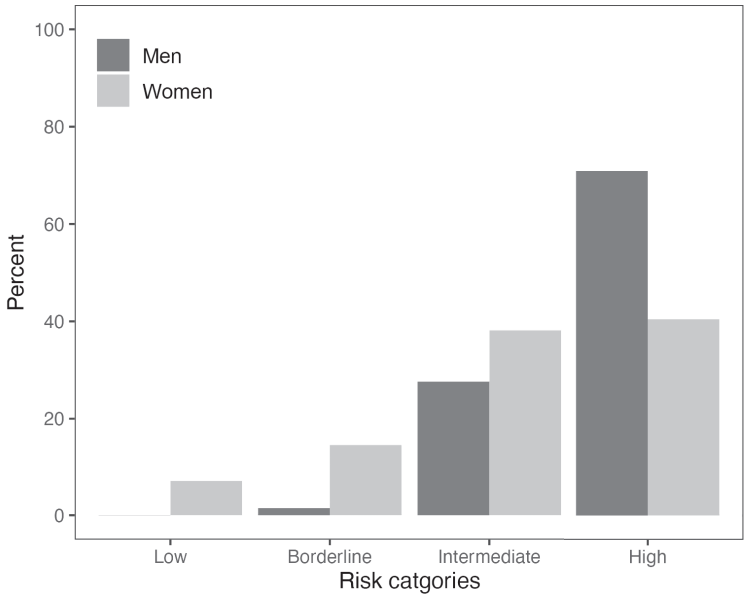

Figure 3. Observed risk categories based on the ACC-AHA model in men and women
Risk categories are: low-risk (<5%), borderline risk (≥5% and <7.5%), intermediate risk (≥7.5% and <20%) and high risk (≥20%)]

Overall the sensitivity of the ACC/AHA + NT-proBNP model was higher using different cut-offs in men and women. Specificity and predictive discrimination values were similar for both models at the 5.5 and 7.5% risk thresholds (Supplemental Table 4). As expected, the sensitivity declined and the specificity increased for both models when risk threshold increased from 5% to 7.5% and to 20%. Using a cut-off of 20%, the ACC/AHA model correctly classified 9% of men and women who developed HF during follow-up at high risk (sensitivity). Also, 99% of men and women who remained event free during follow-up were correctly classified at low risk (specificity) by the ACC/AHA model. But, for the ACC/AHA+NT-proBNP model, the sensitivity and specificity were 16% and 99% in men, and 21% and 99% in women. From men and women categorized as >20% risk by the ACC/AHA

model 88% and 57% developed HF during follow-up (positive predicted value), whereas from those categorized at low-risk group 89% of men and 92% of women remained event free during the follow-up (negative predicted value). For ACC/AHA+NT-proBNP model, the positive and negative predicted values were 84% and 90% in men, respectively. In women, the ACC/AHA+NT-proBNP model, the positive and negative predicted values were 69% and 93%, respectively. Results for the analyses using the thresholds of 5%, 7.5% and 20% 10-year HF risk are shown in Table 2.

In sensitivity analyses, prevalent CHD was added to the ACC/AHA and the ACC/AHA+NT-proBNP models. We also repeated the analyses excluding participants with AF and prevalent CHD and those using lipid lowering medication according to the ACC/AHA guidelines. The performance of the models did not change substantially (data not shown).

Table 2. Comparison of the performance of the ACC/AHA model and ACC/AHA model with addition of NT-proBNP

	Risk thresholds		
Men	**5%**	**7.5%**	**20%**
Sensitivity			
ACC/AHA	80% (78% to 82%)	50% (47% to 53%)	9% (8% to 11%)
ACC/AHA + NT-proBNP	83% (81% to 85%)	58% (55% to 61%)	16% (14% to 18%)
Specificity			
ACC/AHA	70% (69% to 71%)	90% (89% to 91%)	99% (99% to 100%)
ACC/AHA + NT-proBNP	72% (71% to 73%)	90% (89% to 91%)	99% (99% to 100)
Positive predicted value (95%CI)			
ACC/AHA	27% (25% to 28%)	40% (37% to 43%)	88% (80% to 96%)
ACC/AHA + NT-proBNP	29% (27% to 30%)	44% (41% to 46%)	84% (79% to 90)
Negative predicted value (95%CI)			
ACC/AHA	96% (96% to 97%)	93% (92% to 93%)	89% (87% to 89%)
ACC/AHA + NT-proBNP	97% (96% to 97%)	94% (93% to 95%)	90% (89% to 90%)
Women	**5%**	**7.5%**	**20%**
Sensitivity (95%CI)			
ACC/AHA	81% (79% to 83%)	52% (49% to 55%)	9% (8% to 12%)
ACC/AHA + NT-proBNP	85% (83% to 87%)	63% (60% to 66%)	21% (18% to 23%)
Specificity (95%CI)			
ACC/AHA	67% (66% to 78%)	89% (88% to 90%)	99% (99% to 100%)
ACC/AHA + NT-proBNP	69% (68% to 70%)	87% (86% to 88%)	99% (99% to 100%)
Positive predicted value (95%CI)			
ACC/AHA	19% (18% to 20%)	31% (29% to 33%)	57% (48% to 67%)
ACC/AHA + NT-proBNP	21% (20% to 22%)	33% (31% to 35%)	69% (64% to 74%)
Negative predicted value (95%CI)			
ACC/AHA	97% (97% to 98%)	95% (95% to 96%)	92% (91% to 93%)
ACC/AHA + NT-proBNP	98% (98% to 99%)	96% (95% to 96%)	93% (92% to 93%)

Discussion

A simple model based on traditional cardiovascular risk factors included in the ACC/AHA model showed a reasonable performance in predicting 10-year HF among men and women from the population-based Rotterdam Study. The performance of the model based on ACC/AHA risk factors for HF prediction was comparable to the models based on risk factors included in the ARIC and Health ABC HF models. Adding NT-proBNP to the ACC/AHA model modestly improved model performance but did not lead to relevant clinical improvement in risk reclassification.

Compared to CHD and stroke, prediction of incident HF remains a challenge.[5, 6] In spite of the large number of risk prediction models developed for incident HF, there have been no recommendations for routine clinical use of any of the models in the existing guidelines.[5] This is while, preventive interventions significantly reduce the risk of incident HF.[3] In addition to generalizability issues and methodological heterogeneity, models specifically developed to predict HF are based on various markers which have higher technical demands and might not be available in all clinical settings.[5, 8, 9, 20] HF can have ischemic or non-ischemic origins. Although CHD and hypertension are the leading causes of HF, a high proportion of this syndrome is attributed to other cardio-metabolic risk factors.[21] Moreover, biomarkers have shown limited predictive capability for HF risk stratification and have not profited clinical decision making.[22] The ACC/AHA model for ASCVD risk assessment consists of the traditional cardiovascular risk factors that are also associated with HF.[7] In our analysis, the model based on traditional cardiovascular risk factors included in the ACC/AHA model had a performance almost similar to the Health ABC model and close to the ARIC model for HF risk assessment in general population. In a meta-analysis of HF prediction models, among the 53 potential predictors considered in 19 studies between 1990 and 2016, age, sex and systolic blood pressure were the most common selected predictors.[6] To note, the predictors in the ACC/AHA model were among the 10 most used predictors in these dedicated HF prediction models. They are also commonly used in predicting HF prognosis and other cardiovascular outcomes.[23] The acceptable performance of the model based on risk factors from the ACC/AHA algorithm for HF prediction in our study advocates implementing this model for primary HF prevention. Addition of NT-proBNP to the ACC/AHA model improved model performance in both sexes. There was overlap between men and women in the discrimination of both the ACC/AHA and the ACC/AHA+NT-proBNP models. Nevertheless, the improvement in the c-statistic after addition of NT-proBNP was slightly greater among women. To note, levels of NT-proBNP/BNP have not shown to be different between men and women with acute or chronic HF.[24] Also, women have slightly lower NT-proBNP/BNP levels in clinical setting which has been attributed to higher prevalence of HF with preserved ejection fraction among women.[25] Thus, an overlap in the performance of the model by adding this biomarkers is not far from expectation.

Studies have shown mixed results regarding the contribution of NT-proBNP/BNP to improvement of CVD risk predictions in men and women.[26] NT-proBNP has displayed no or only modest impact in increasing the discriminative ability or risk classification of the CVD risk prediction models in general population.[22, 25, 27-29] On the contrary, in high-risk individuals with previous history of CVD, higher prognostic ability has been reported.[25] It should be considered that a wide variety of cardiac and non-cardiac conditions are also associated with elevated serum levels of this biomarker.[30] Moreover, high levels of NT-proBNP are associated with creatinine levels, sex, age and inversely associated with BMI independent of ventricular function.[1, 19, 31] This is probably why its discriminative ability for detection of left ventricular systolic dysfunction has been suboptimal, limiting its utility in mass screening.[32]

Using different cut-offs, addition of NT-proBNP was accompanied by slight increases in the sensitivity and specificity of the models in both sexes. Only at the 20% cut-off, the difference in the sensitivity and specificity of the two models was more evident and NT-proBNP increased the NPV and PPV of the model more evidently. Also, continuous NRI in men was smaller than women. However, using the ACC/AHA risk cut-offs, NT-proBNP mainly correctly down-classified participants without the event in both sexes and did not show large improvement in reclassifying participants with the event. In line with our study, Willeit et al. showed a strong association between NT-proBNP and the composite outcome of stroke, CHD and HF.[28] But the increase in the c-statistic of the model after adding NT-proBNP was modest. Interestingly, they also specified that NT-proBNP improved risk prediction by appropriately down classifying the clinical risk of those without the event. Moreover, they observed similar changes using cut-offs used by different guidelines. [28]

NT-proBNP/BNP is an established diagnostic and prognostic biomarker in HF patients.[31] For prediction of incident HF alone, NT-proBNP/BNP has shown to improve model performance.[8, 33, 34] However, despite the association of increasing NT-proBNP/BNP levels with substantial risk of HF, it is not a cost-effective screening tool to assess for preclinical heart failure or LV dysfunction, limiting its utility to highly selected populations.[30] In this regard, NT-proBNP testing has a clear and valuable role in the diagnosis of CHF in the emergency diagnosis of patients with dyspnea.[35] The strength of BNP is in its ability to rule out CHF in this setting. Likewise, the favorable clinical utility of adding NT-proBNP to the ACC/AHA model in risk reclassification was mainly limited to the non-events in our study. To add, BNP has shown a high NPV to rule out diastolic dysfunction or LVH.[36, 37] The ACC/AHA +NT-proBNP model also showed a high NPV for HF in our study using different risk cut-offs but the differences were more evident among those at high risk, using a cut-off of 20% which again emphasizes that NT-proBNP might be useful in prediction of HF only among high risk populations. Specifically, this utilization might be more towards ruling out HF rather than its rule-in ability.[30]

Strengths of our study are use of a large sample size and detailed long follow-up data. Our HF event adjudication was robust and well-defined. Moreover, a large set of various and precisely measured variables were available for this study. There are also limitations. The Rotterdam Study population is mainly white and 45 years of age and older, compared with the ARIC and the PCE study populations. Mean age of the study population in the ARIC study [54.1(6.0) years] was younger than our total population [69.7 (8.27)] while mean age in the health ABC study [73.6 (2.9)] was somewhat closer to our study population, but with less variability. As the strongest predictor of HF, differences in age could explain to some extent the differences in the performance of the models. Hence, we refitted the models based on the variables used in the risk scores. Our study is an attempt for internal validation of the ACC/AHA risk score for prediction of incident HF which may have led to overestimation of its performance. To assess the transferability of predictive models, they need to be externally validated to make it possible for them to be used in clinical settings.[5, 6] Also, because of unavailability of albumin, we were not able to include it in the Health ABC model. In addition, we did not have data on HF subtypes at the time of diagnosis. Inaccessibility of data on subtypes of HF is also a limitation of population based cohort studies, like the ARIC and the health ABC studies. Moreover, our results might not be generalizable to younger individuals and other ethnicities.

Conclusion

The model based on traditional risk factors included in the ACC/AHA model had an acceptable performance, comparable to more sophisticated models, for predicting 10-year HF among men and women from general population. Our results therefore advocate use of this model for HF primary prevention. Addition of NT-proBNP to the ACC/AHA model leads to modest improvement in model performance, in particular among women. However, the clinical relevance of adding this biomarker for correct risk reclassification is limited.

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Supplemental Material

Supplemental Table 1. Hazard ratios for incident HF in the ACC/AHA model, ARIC model, Health ABC model and ACC/AHA+NT-proBNP model in men and women

	Men	Women
ACC/AHA model	**HR (95%CI)**	**HR (95%CI)**
Age	1.10 (1.09 to 1.12)	1.1. (1.09 to 1.11)
Total cholesterol	0.97 (0.88 to 1.08)	0.95 (0.86 to 1.05)
HDL cholesterol	0.56 (0.40 to 0.77)	0.83 (0.66 to 1.05)
Systolic blood pressure	1.01 (1.01 to 1.02)	1.01 (1.00 to 1.01)
Antihypertensive use	2.87 (0.77 to 10.6)	4.78 (1.41 to 16.2)
Smoking(current)	1.44 (1.15 to 1.80)	1.12 (0.85 to 1.46)
Prevalent diabetes	1.31 (1.03 to 1.67)	1.15 (0.89 to 1.49)
Systolic blood pressure: Antihypertensive use	1.00 (0.99 to 1.01)	0.99 (0.99 to 1.00)
ARIC model	**HR (95%CI)**	**HR (95%CI)**
Age	1.07 (1.05 to 1.09)	1.07 (1.06 to 1.09)
Log (NT-proBNP)	1.72 (1.57 to 1.90)	2.03 (1.83 to 2.26)
Heart rate	1.01 (1.00 to 1.01)	2.33 (0.70 to 7.70)
BMI	1.09 (1.05 to 1.12)	1.00 (1.00 to 1.01)
Systolic blood pressure	1.01 (1.00 to 1.01)	1.06 (1.03 to 1.08)
Antihypertensive use	1.27 (0.35 to 4.67)	1.00 (1.00 to 1.01)
Smoking(current)	2.1 (1.39 to 3.15)	1.24 (0.94 to 1.65)
Smoking(past)	1.47 (1.01 to 2.15)	1.22 (1.00 to 1.48)
Prevalent diabetes	1.21 (0.95 to 1.54)	1.25 (0.96 to 1.62)
Prevalent CHD	1.33 (1.05 to 1.68)	1.51 (1.06 to 2.15)
Systolic blood pressure: Antihypertensive use	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.00)
Health ABC model	**HR (95%CI)**	**HR (95%CI)**
Age	1.10 (1.08 to 1.11)	1.11 (1.09 to 1.12)
Systolic blood pressure	1.01 (1.01 to 1.01)	1.01 (1.00 to 1.01)
Smoking(current)	2.14 (1.42 to 3.22)	1.33 (1.00 to 1.76)
Smoking(past)	1.64 (1.13 to 2.39)	1.38 (1.14 to 1.67)
Prevalent CHD	2.09 (1.68 to 2.60)	2.45 (1.73 to 3.47)
Heart rate	1.00 (1.00 to 1.01)	1.00 (0.99 to 1.01)
LVH	2.10 (1.58 to 2.78)	2.21 (1.58 to 3.10)
Creatinine	1.00 (1.00 to 1.01)	1.00 (1.00 to 1.01)
Glucose	1.09 (1.04 to 1.14)	1.10 (1.04 to 1.15)

	Men	Women
ACC/AHA+NT-proBNP model	**HR (95%CI)**	**HR (95%CI)**
Age	1.07 (1.05 to 1.08)	1.07 (1.06 to 1.08)
Log (NT-proBNP)	1.73 (1.58 to 1.90)	2.02 (1.82 to 2.25)
Total cholesterol	1.03 (0.93 to 1.14)	1.01 (0.92 to 1.11)
HDL cholesterol	0.52 (0.37 to 0.71)	0.78 (0.62 to 0.98)
Systolic blood pressure	1.01 (1.00 to 1.01)	1.00 (1.00 to 1.01)
Antihypertensive use	1.97 (0.56 to 6.98)	3.20 (0.98 to 10.5)
Smoking(current)	1.34 (1.07 to 1.67)	1.07 (0.82 to 1.39)
Prevalent diabetes	1.35 (1.06 to 1.72)	1.35 (1.04 to 1.75)
Systolic blood pressure: Antihypertensive use	1.07 (1.05 to 1.08)	0.99 (0.99 to 1.00)

BMI; body mass index, CHD; coronary heart disease, Diabetes; diabetes mellitus, HDL; high-density lipoprotein, LVH; left ventricular hypertrophy, HR; hazard ratio, CI; confidence interval

Supplemental Table 2. Overall goodness-of-fit for the ACC/AHA model, ARIC model, Health ABC model and ACC+NT-proBNP model in men and women

	Men	Women	
Models	**AIC**		**degrees of freedom**
ACC/AHA	6213.38	7503.19	8
ARIC	5953.16	6908.03	11
Health ABC	5651.17	6656.15	9
ACC/AHA + NT-proBNP	5970.96	7179.38	9

AIC: Akaike information criterion

Supplemental Table 3. Risk reclassification for the ACC/AHA model after adding NT-proBNP stratified by event status

	Percent event,%*		Event NRI (95% CI),%†	Percent non-event,%*		Non-event NRI (95% CI),%†
	Up	**Down**		**Up**	**Down**	
Men	1.40	25.18	-23.8 (-19.2 to -28.4)	0.22	57.08	57.9 (54.8 to 61.0)
Women	5.52	33.13	-27.6 (-30.7 to -24.5)	2.25	55.08	52.8 (50.3 to 55.5)

† NRI (95% CI) for reclassification of events and non-events after adding NT-proBNP to the ACC/AHA model. Event NRI was calculates as: (number of events reclassified up minus number of events reclassified down) / total number of events . Non-event NRI was calculates as: (number of non-events reclassified up minus number of non-events reclassified down) / total number of non-events

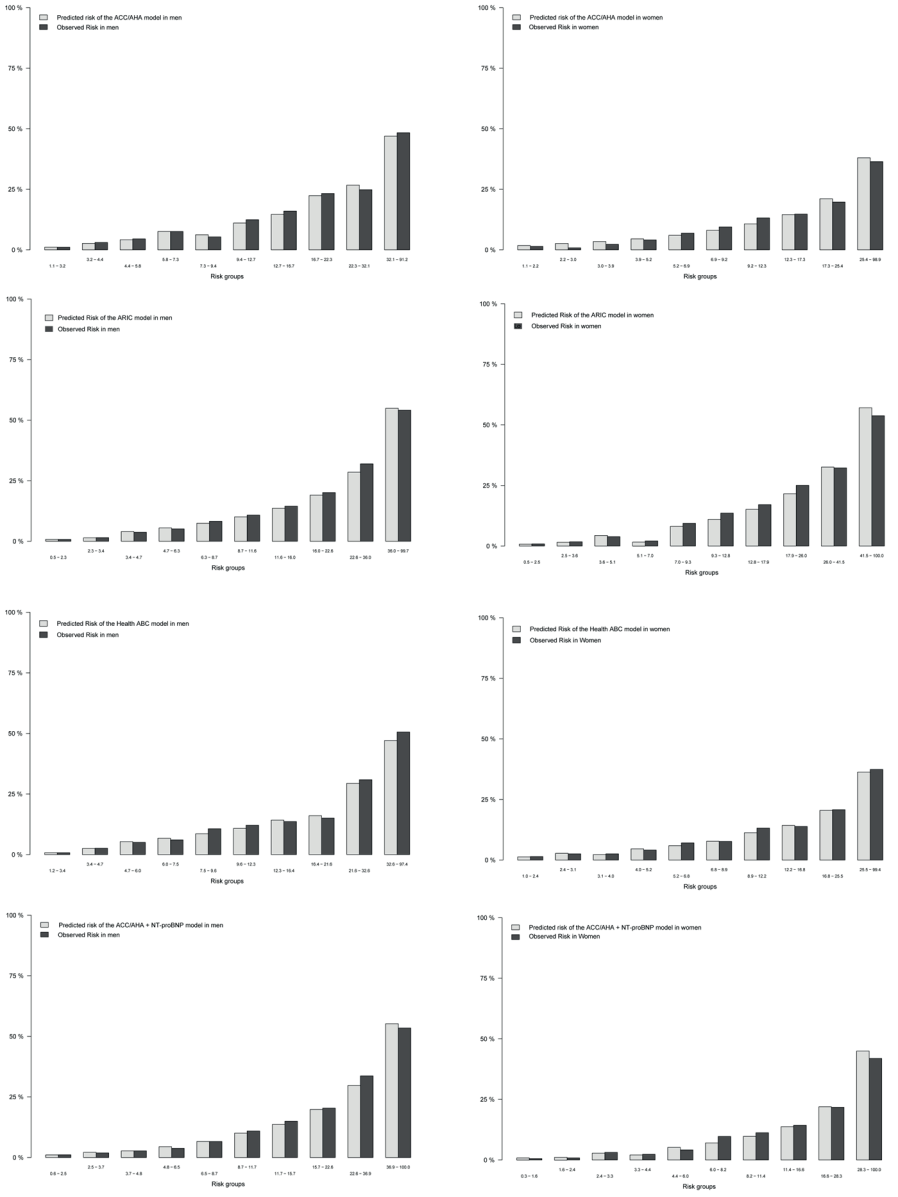
* Percentages of persons with or without an event who moved to a higher (up) or lower risk (down) category after extension of the ACC/AHA model with NT-proBNP.

Supplemental Table 4. Fine and Gray's subdistribution hazard ratios for incident HF and mortality in the ACC/AHA model, ARIC model, Health ABC model and ACC/AHA+NT-proBNP model in men and women

	Heart failure		Mortality	
	Men	**Women**	**Men**	**Women**
ACC/AHA model	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
Age	1.06 (1.04 to 1.07)	1.05 (1.04 to 1.06)	1.09 (1.08 to 1.10)	1.10 (1.10 to 1.11)
Total cholesterol	0.99 (0.89 to 1.10)	0.99 (0.89 to 1.08)	0.95 (0.69 to 1.02)	1.00 (0.93 to 1.07)
HDL cholesterol	0.59 (0.44 to 0.80)	0.91 (0.72 to 1.13)	0.97 (0.80 to 1.19)	0.83 (0.71 to 0.97)
Systolic blood pressure	1.01 (1.00 to 1.03)	1.02 (1.00 to 1.03)	1.01 (1.00 to 1.02)	1.00 (0.99 to 1.01)
Antihypertensive use	2.34 (0.64 to 8.59)	4.54 (1.36 to 15.2)	1.89 (0.75 to 4.80)	1.10 (0.44 to 2.71)
Smoking(current)	1.14 (1.10 to 1.42)	0.95 (0.73 to 1.25)	1.56 (1.36 to 1.79)	1.79 (1.55 to 2.07)
Prevalent diabetes	1.19 (0.94 to 1.53)	1.02 (0.78 to 1.33)	1.18 (0.99 to 1.40)	1.22 (1.01 to 1.46)
Systolic blood pressure: Antihypertensive use	1.00 (0.99 to 1.01)	0.99 (0.99 to 1.00)	1.00 (0.99 to 1.00)	1.00 (1.00 to 1.01)
ARIC model	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
Age	1.03 (1.02 to 1.05)	1.03 (1.02 to 1.05)	1.08 (1.07 to 1.09)	1.09 (1.08 to 1.10)
Log (NT-proBNP)	1.49 (1.34 to 1.66)	1.63 (1.45 to 1.83)	1.09 (1.02 to 1.17)	1.10 (1.02 to 1.18)
Heart rate	1.00 (1.00 to 1.01)	1.00 (0.99 to 1.01)	1.01 (1.00 to 1.01)	1.01 (1.00 to 1.01)
BMI	1.09 (1.06 to 1.13)	1.06 (1.04 to 1.08)	0.97 (0.95 to 0.99)	0.98 (0.96 to 0.99)
Systolic blood pressure	1.01 (0.99 to 1.02)	1.01 (1.00 to 1.02)	1.01 (1.00 to 1.02)	1.00 (1.00 to 1.01)
Antihypertensive use	1.08 (0.29 to 4.10)	2.51 (0.75 to 8.38)	1.89 (1.74 to 4.82)	1.34 (0.57 to 3.14)
Smoking(current)	1.74 (1.17 to 2.58)	1.07 (0.79 to 1.43)	1.58 (1.25 to 1.99)	1.77 (1.51 to 2.07)
Smoking(past)	1.55 (1.08 to 2.22)	1.26 (1.03 to 1.54)	1.07 (0.86 to 1.32)	1.00 (0.88 to 1.14)
Prevalent diabetes	1.07 (0.83 to 1.38)	1.00 (0.76 to 1.32)	1.20 (1.01 to 1.43)	1.34 (0.12 to 1.60)
Prevalent CHD	1.41 (1.10 to 1.80)	1.40 (0.93 to 2.10)	0.95 (0.79 to 1.16)	1.79 (0.52 to 1.20)
Systolic blood pressure: Antihypertensive use	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.00)
Health ABC model	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
Age	1.05 (1.04 to 1.06)	1.10 (1.51 to 1.07)	1.09 (1.08 to 1.10)	1.10 (1.10 to 1.11)
Systolic blood pressure	1.01 (1.01 to 1.02)	1.01 (1.00 to 1.01)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
Smoking(current)	1.73 (1.17 to 2.57)	1.12 (0.84 to 1.49)	1.66 (0.32 to 2.09)	1.82 (1.55 to 2.13)
Smoking(past)	1.65 (1.43 to 2.38)	1.38 (1.14 to 1.68)	1.07 (0.86 to 1.32)	1.01 (0.88 to 1.15)
Prevalent CHD	1.99 (1.59 to 2.51)	2.18 (1.49 to 3.18)	1.00 (0.84 to 1.20)	0.91 (0.61 to 1.35)
Heart rate	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.00)	1.01 (1.00 to 1.01)	1.01 (1.00 to 1.01)
LVH	2.08 (1.53 to 2.82)	1.88 (1.31 to 2.71)	0.80 (0.61 to 1.04)	0.87 (0.63 to 1.20)
Creatinine	1.00 (1.00 to 1.01)	1.00 (0.99 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.01)

	Heart failure		Mortality	
	Men	**Women**	**Men**	**Women**
Glucose	1.06 (1.01 to 1.11)	1.07 (1.02 to 1.13)	1.04 (1.00 to 1.08)	1.02 (0.98 to 1.06)
ACC/AHA+NT-proBNP model	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
Age	1.03 (1.01 to 1.04)	1.03 (1.02 to 1.04)	1.10 (1.08 to 1.10)	1.10 (1.08 to 1.11)
Log (NT-proBNP)	1.49 (1.35 to 1.65)	1.63 (1.45 to 1.82)	1.09 (1.02 to 1.17)	1.10 (1.02 to 1.18)
Total cholesterol	1.04 (0.94 to 1.15)	1.04 (0.95 to 1.14)	0.96 (0.90 to 0.03)	1.01 (0.94 to 1.08)
HDL cholesterol	0.57 (0.42 to 0.77)	0.86 (0.69 to 1.08)	0.97 (0.79 to 1.18)	0.82 (0.71 to 0.96)
Systolic blood pressure	1.01 (1.00 to 1.02)	1.01 (1.00 to 1.03)	1.01 (1.00 to 1.01)	1.00 (0.99 to 1.01)
Antihypertensive use	1.90 (0.52 to 6.93)	3.45 (1.10 to 11.2)	1.72 (0.68 to 4.37)	1.08 (0.44 to 2.65)
Smoking(current)	1.04 (1.83 to 1.31)	0.89 (0.68 to 1.17)	1.53 (1.33 to 1.76)	1.78 (1.54 to 2.06)
Prevalent diabetes	1.21 (0.94 to 1.55)	1.10 (0.84 to 1.44)	1.16 (0.97 to 1.39)	1.23 (1.02 to 1.49)
Systolic blood pressure: Antihypertensive use	1.00 (0.99 to 1.01)	0.99 (0.99 to 1.00)	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.01)

BMI; body mass index, CHD; coronary heart disease, Diabetes; diabetes mellitus, HDL; high-density lipoprotein, LVH; left ventricular hypertrophy, HR; hazard ratio, CI; confidence interval



Supplemental Figure 1. Calibration plots for the observed and predicted risk based on the ACC/AHA model, ARIC model, Health ABC model and ACC+NT-proBNP model in men and women

Supplemental Figure 2. Risk reclassification for the ACC/AHA model after adding NT-proBNP stratified by event status

A. Men

Event

ACC/AHA model \ ACC/AHA + NT-proBNP model	Low	Borderline	Intermediate	High	Total
Low	0	0	0	0	0
Borderline	1	0	0	0	1
Intermediate	4	10	22	6	42
High	0	6	87	293	386
Total	5	16	109	299	429

NRI (95% CI)* : -23.8 (-28.4 to -19.2)

Non-event

ACC/AHA model \ ACC/AHA + NT-proBNP model	Low	Borderline	Intermediate	High	Total
Low	1	0	0	0	1
Borderline	34	3	2	0	39
Intermediate	286	230	197	3	716
High	32	95	667	764	1558
Total	353	328	866	767	2314

NRI (95% CI)* : 57.9 (54.8 to 61.0)

B. Women

Event

ACC/AHA model \ ACC/AHA + NT-proBNP model	Low	Borderline	Intermediate	High	Total
Low	1	1	0	1	3
Borderline	10	6	4	0	20
Intermediate	19	19	75	21	134
High	1	9	104	218	332
Total	31	35	183	240	489

NRI (95% CI)* : -27.6 (-30.7 to -24.5)

Non-event

ACC/AHA model \ ACC/AHA + NT-proBNP model	Low	Borderline	Intermediate	High	Total
Low	238	12	3	0	253
Borderline	407	72	25	1	505
Intermediate	431	348	449	30	1258
High	10	42	501	588	1141
Total	1086	474	978	619	3157

NRI (95% CI)* : 52.8 (50.3 to 55.5)

† Persons with or without an event (Event and non-event, respectively) who moved to a higher or lower risk category after extension of the ACC/AHA model with NT-proBNP. Favorable direction of reclassification is depicted in gray (downward for non-events and upward for events) and unfavorable movement (downward for events and upward for non-events) is depicted in black.

*Event NRI was calculates as: (number of events reclassified up minus number of events reclassified down) / total number of events . Non-event NRI was calculates as: (number of non-events reclassified up minus number of non-events reclassified down) / total number of non-events

Risk categories are: low-risk (<5%), borderline risk (5% to 7.49%), intermediate risk (7.5% to 19.9%), and high risk (≥20%)]

CHAPTER 12

Risk factors for longitudinal changes in left ventricular diastolic function among women and men.

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Abstract

Objective To evaluate changes in left ventricular diastolic function (LVDF) parameters and their associated risk factors over a period of 11 years among community-dwelling women and men.

Methods Echocardiography was performed three times among 870 women and 630 men (age 67±3 years) from the prospective population-based Rotterdam Study during a period of 11 years follow-up. Changes in six continuous LVDF parameters were correlated with cardiovascular risk factors using a linear-mixed effect model (LMM).

Results In women, smoking was associated with deleterious longitudinal changes in DT (7.73; 2.56, 12.9) and high-density lipoprotein cholesterol was associated with improvement of septal e' (0.37; 0.13, 0.62) and E/e' ratio (-0.46; -0.84,-0.08) trajectories. Among men, diabetes was associated with deleterious longitudinal changes in A wave (3.83; 0.06,7.60), septal e' (-0.40; -0.70,-0.09) and E/e' ratio (0.60; 0.14,1.06) and body mass index was associated with deleterious longitudinal changes in A wave (1.25; 0.84,1.66), E/A ratio (-0.007; -0.01,-0.003), DT (0.86; 0.017, 1.71), and E/e' ratio (0.12; 0.06, 0.19).

Conclusions Smoking among women and metabolic factors (DM and BMI) among men showed larger deleterious associations with longitudinal changes in LVDF parameters. The favorable association of HDL was mainly observed among women. This study, for the first time, evaluates risk factors associated with changes over time in continuous LVDF parameters among women and men and generates new hypothesis for further medical research.

Introduction

Left ventricular diastolic dysfunction is highly prevalent and worsen with advancing age(1-3). Persistence or progression of diastolic dysfunction is a risk factor for heart failure(HF) among the elderly(2). Recent data suggest that diastolic dysfunction is present in the majority, around 70%, of patients with heart failure with preserved ejection fraction (HFpEF)(4). Although plenty of evidence-based treatments for heart failure with reduced ejection fraction (HFrEF) exist, there is no treatment with proven benefits for HFpEF(5).

Impairment of left ventricular diastolic function(LVDF) occurs gradually and has been shown to be, at least partly, reversible(1,6), Therefore, early detection of subclinical impairment in LVDF and identification and treatment of its associated risk factors to prevent or slow the progression to overt HF is important. To date, several risk factors associated with LVDF have been identified(7,8). However, longitudinal studies evaluating changes in continuous LVDF parameters over time in general population of subjects without clinically diagnosed HF are scant and have been mostly performed among middle-aged individuals. As occurrence of various HF phenotypes differs between women and men(5), it has been suggested that gender differences in susceptibility to risk factors might partly explain these dissimilarities(6). However, recent studies have failed to address gender differences in the setting of changes in LVDF and its associated risk factors(4-7). Notably, while women tend to have a better LVDF until 60 years of age, gender disparities are reversed after the menopause(5). To further clarify sex differences in the pathophysiology of diastolic dysfunction, studying changes in continuous LVDF parameters among women and men and their correlates, especially at older ages, is warranted.

We, therefore, aimed to evaluate longitudinal changes in continuous LVDF parameters during 11 years of follow-up among women and men from a large prospective population-based cohort (9). Participants were all free from clinically diagnosed HF at the time of echocardiographic examinations and during follow-up. In addition, we investigated the risk factors associated with the changes in LVDF parameters among women and men.

Methods

Study Population

The Rotterdam Study(RS) is a prospective population-based cohort that included participants aged 55 years and older in the district of Ommoord, Rotterdam, The Netherlands(9). The study started in 1990 with 7,983 participants (RS-I) and was extended twice; in 2000 (RS-II, n=3,014) and in 2006 (RS-III, n=3,932). The follow-up examinations take place every 3-4 years. The RS was approved by the Medical Ethics Committee according to the Population Study Act Rotterdam Study. All participants provided written informed consent.

The present study used data for six LVDF echocardiographic parameters from the fourth, fifth, and sixth examinations of the first cohort (RS-I) and the second, third, and fourth examinations of the second cohort (RS-II). Out of the six LVDF parameters under study, three repeated echocardiographic measurements were available for four indexes among 1,869 participants. We excluded 369 individuals due to poor echocardiographic images, atrial fibrillation, artificial pacemaker, moderate-severe valve compromise, and clinically diagnosed HF at the time of echocardiographic examinations and during the follow-up. Therefore, we included a total of 1,500 participants (630 men and 870 women) (Figure 1). For two LVDF parameters, two repeated measurements were available in a total of 1,528 (646 men and 882 women) subjects from the fifth and sixth examinations of the first cohort (RS-I) and the third and fourth examinations of the second cohort (RS-II) (Supplemental Figure 1).

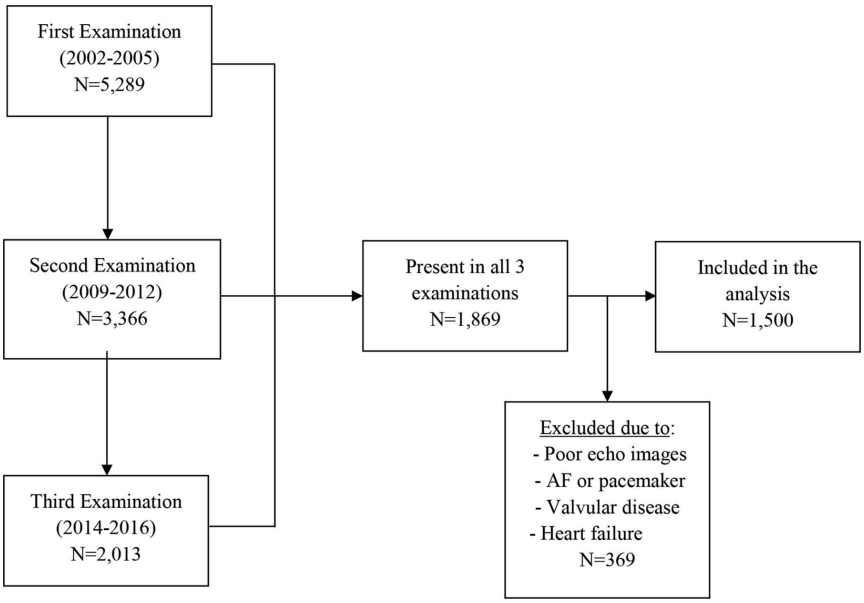


Figure 1. Flowchart for the participants included in the analysis of longitudinal changes in LVDF parameters measured 3 times over 11 years of follow-up. AF, atrial fibrillation; LVDF, left ventricular diastolic function.

Left ventricular diastolic function parameters

We studied six continuous LVDF parameters. The apical 4-chamber view was used to measure the early trans-mitral ventricular diastolic filling velocity(E wave) and late diastolic filling velocity(A wave) during three cardiac cycles. Tissue Doppler imaging (TDI) was used to measure the early diastolic longitudinal filling velocity of the septal mitral annulus (septal e') during three cardiac cycles. The means of the E wave, A wave and septal e' over the three cardiac cycles were used to calculate E/A and E/e' ratios. Mitral valve deceleration time (DT) was measured as the time between the peak E-top wave and the upper deceleration slope extrapolated to the zero baseline using a Continuous Wave Doppler(10,11). Additional information on echocardiographic measurements, is provided in the online-supplemental material.

Assessment of cardiovascular risk factors

Detailed information regarding the evaluation of cardiovascular risk factors is given in the online-supplemental material.

Statistical Analysis

In the descriptive analysis, continuous variables with normal distribution were reported as mean (standard deviations) and categorical variables as numbers (percentages). We compared the mean and percentage values for women and men using t-test and z-proportion tests respectively. Longitudinal changes in LVDF parameters over time were plotted, treating age as a time-varying covariate. For each of the six parameters, a longitudinal data analysis using a linear mixed effect model was performed. The outcome of interest in each model was the two or three repeated measurements for each index as a continuous variable. Systolic and diastolic blood pressure(SBP, DBP), heart rate (HR), total and high-density lipoprotein (HDL) cholesterol, blood pressure and lipid lowering medications (LLM), diabetes mellitus (DM), current smoking, previous coronary heart disease (CHD), left ventricular mass indexed by body surface area (LVM), left ventricular ejection fraction (LVEF), physical activity, left atrial diameter (LAD) and cohort were included in all models. Age was used as a time-varying covariate. All analyses were performed in total population and in women and men separately. We checked for possible interaction between sex and different covariates in the total population. We additionally checked for the interaction terms between age, as a time-varying, and all covariates. We also compared the characteristics of the included participants with those who did not return for the follow-up echocardiography examinations. For more details regarding the analyses consult the online supplemental material. The analyses were performed with R v.3.2.5 (R Foundation for Statistical Computing, Vienna, Austria), and STATA (version 14.0, Stata Corp, College Station, TX). A 2-sided P value of <0.05 was considered statistically significant. Additionally, we considered a more conservative Bonferroni corrected p value of <0.0083 (= 0.05/6, considering six LVDF parameters).

Results

Table 1 details the baseline characteristics of 870 women and 630 men for the analyses of E wave, A wave, E/A ratio, and DT, in whom 3 repeated measurements were available during 11.1 years of follow-up. Women had higher HR, total and HDL cholesterol, left atrial diameter (LAD) and ejection fraction. Men had larger DBP, LVM, left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD) and CHD prevalence. For septal e' and E/e' ratio, two repeated measurements were available among 882 women and 646 men during 4.2 years of follow-up (Supplemental Table 1).

Table 1. Baseline clinical and echocardiographic characteristics of the participants.

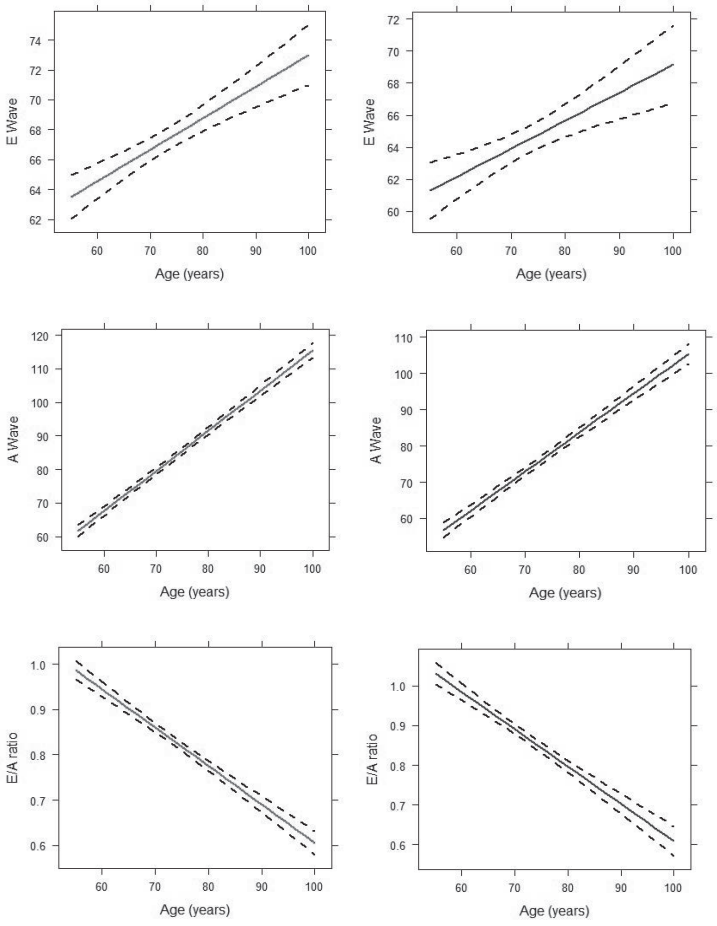
	Women (n=870)	Men (n=630)	p-value*
Clinical Features			
Age, years	67.30 (4.95)	67.29 (4.91)	0.980
BMI, kg/m²	27.42 (4.07)	27.08 (2.94)	0.069
SBP, mmHg	144.40 (18.32)	143.92 (19.20)	0.626
DBP, mmHg	79.84 (10.11)	82.01 (9.90)	<0.001
Blood Pressure Lowering Medication, n (%)	261 (30.0)	208 (33.0)	0.2130
Hypertension, n (%)	609 (70.0)	446 (70.8)	0.7378
Heart Rate, beats/min	69.36 (9.70)	65.79 (10.55)	<0.001
Total Cholesterol, mmol/L	5.96 (0.94)	5.45 (0.93)	<0.001
HDL-cholesterol, mmol/L	1.60 (0.40)	1.31 (0.31)	<0.001
Lipid Lowering Medication, n (%)	174 (20.0)	130 (20.63)	0.765
Current Smoker, n (%)	106 (12.2)	58 (9.2)	0.069
Prevalent CHD, n (%)	16 (1.84)	61 (9.68)	<0.001
Prevalent DM, n (%)	84 (9.66)	62 (9.84)	0.908
Echocardiography Features			
LVM index, g/m²	70.66 (15.47)	78.17 (18.19)	<0.001
Left Atrium Diameter/BSA, mm/m²	21.41 (2.69)	20.76 (2.45)	<0.001
LVEDD, mm	49.39 (4.96)	53.36 (4.86)	<0.001
LVESD, mm	30.12 (7.87)	33.66 (8.01)	<0.001
Relative Wall Thickness, cm	0.29 (0.06)	0.29 (0.05)	1
Ejection Fraction, %	65.87 (6.75)	63.69 (7.92)	<0.001
E wave cm/sec	67.38 (13.02)	64.48 (12.97)	<0.001
A wave cm/sec	83.33 (17.82)	76.61 (17.68)	<0.001
E/A ratio	0.83 (0.18)	0.86 (0.20)	<0.001
Deceleration time	204.4 (35.54)	209.19 (39.78)	<0.001
e`septal	6.87 (1.79)	7.29 (1.78)	<0.001
E/e`septal ratio	10.43 (2.62)	9.54 (2.51)	<0.001

* p-value for comparison of different characteristics between women and men. Values are mean (± standard deviation) or numbers (percentages). BMI: Body mass index, BSA: Body surface area, CHD: coronary heart disease, DBP: diastolic blood pressure, DM: Type 2 diabetes mellitus, LVEDD: Left ventricle end diastolic dimension, LVESD: Left ventricle end systolic dimension, LVM: Left ventricular mass, SBP: systolic blood pressure,

Longitudinal changes in LVDF among women and men

Based on the plots for each statistical model, the shapes of the longitudinal changes in all six LVDF parameters over time were similar in women and men (Figure 2). There was not interaction between age (as a time-varying covariate) and sex. The plots revealed a progressive deleterious mono-directional change in the longitudinal trajectories of all six LVDF parameters over time; i.e. a gradual rise in E wave, A wave, DT and E/e´ ratio values and a gradual decline in E/A ratio and septal e'. Despite similar trends in LVDF changes in

both sexes, there were statistically significant differences in the mean values, with overall poorer indexes in women. Supplemental Table 2 presents detailed information on cross-sectional values for LVDF parameters per age and gender category.



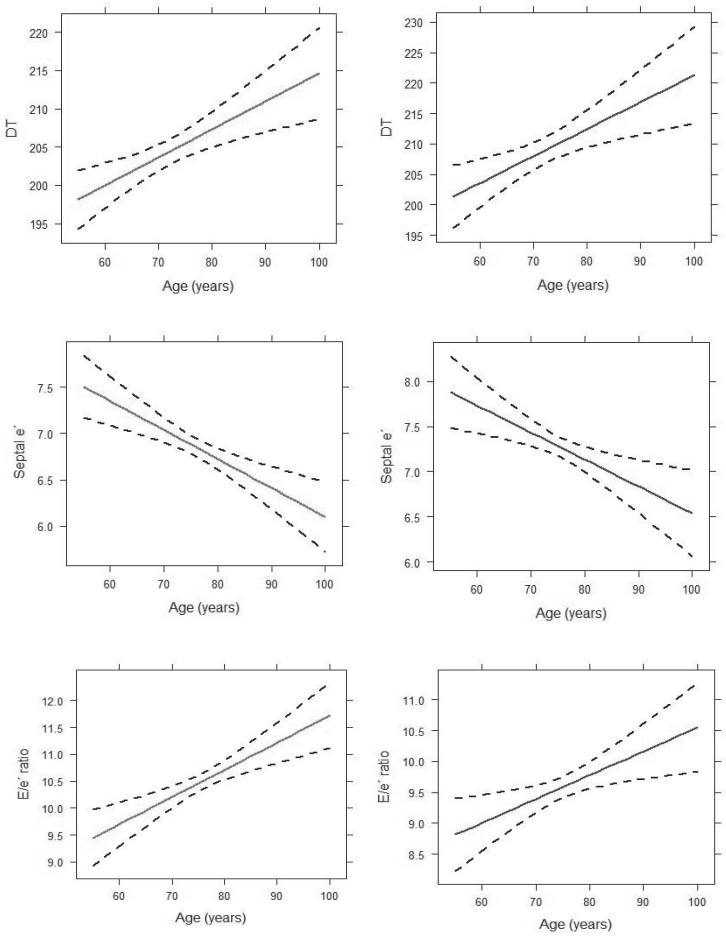


Figure 2. Plots for changes in LVDF parameters over time among women and men (left charts: women, right charts: men). LVDF, left ventricular diastolic function.

Risk factors associated with longitudinal changes in LVDF

Since E wave, A wave, DT and E/e´ ratio values progressively, and deleteriously, raised over time, a positive Beta coefficient for a risk factor means that the risk factor was associated with increment in the trajectory of these LVDF parameters over time. On the contrary, a negative Beta coefficient means that the risk factor was associated with decrement in the trajectory of these LVDF parameters over time. Therefore, a positive risk factor coefficient is associated with an unfavorable progression and a negative risk factor coefficient into a favorable progression on LVDF parameters over time. E/A ratio and septal e' values progressively, and deleteriously, diminish over time. Therefore, a

negative Beta coefficient for a risk factor means that the risk factors was associated with decrement and a positive coefficient means that the risk factor was associated with increment in the trajectory of these LVDF parameters over time. Therefore, a positive coefficient translates into a favorable progression and a negative coefficient into an unfavorable progression on LVDF parameters over time.

Table 2 and table 3 show all beta coefficients and confidence intervals of different risk factors with longitudinal changes in LVDF indexes over time among women and men. Supplemental Tables 3 and 4 show the summary of the risk factors significantly associated with longitudinal changes in LVDF parameters among women and men. Figure 3 shows the core findings of our study, summarizing the main differences among women and men in risk factors associated with changes in LVDF trajectories.

Table 2. Association of risk factors with longitudinal changes in left ventricular diastolic function parameters among women.

	E Wave	A Wave	E/A ratio	DT	Septal e'	E/e' ratio
Age*	4.43 (2.32, 6.53) †	1.22 (1.14, 1.30) †	- 0.43 (-0.47, -0.38) †	0.44 (0.20, 0.68) †	-0.02 (-0.005, -0.04) ‡	0.015 (-0.05, 0.019)
BMI	0.24 (0.04, 0.44) ‡	0.51 (0.25, 0.76) †	-0.0008 (-0.003, 0.002)	0.015 (-0.45, 0.48)	0.02 (-0.002, 0.05)	-0.015 (-0.06, 0.03)
SBP	0.11 (0.06, 0.17) †	0.18 (0.11, 0.24) †	-0.0002 (-0.0008, 0.0005)	-0.15 (-0.27, -0.03)‡	-0.006 (-0.01, 0.0009)	0.011 (-0.0005, 0.02)
DBP	-0.20 (-0.29, -0.11) †	-0.10 (-0.22, 0.01)	-0.002 † (-0.003, -0.0006)	0.10 (-0.11, 0.31)	-0.001 (-0.01, 0.01)	-0.007 (-0.03, 0.01)
BP lowering Medication	-1.63 (-3.40, 0.15)	-0.12 (-2.39, 2.16)	-0.01 (-0.03,0.01)	1.77 (-2.38, 5.91)	-0.22 (-0.44, 0.007)	0.27 (-0.074, 0.61)
Heart Rate	-0.02 (-0.10, 0.06)	0.37 (0.26, 0.47) †	-0.003 † (-0.004, -0.002)	-0.18 (-0.37, 0.005)	-0.01 (-0.02, 0.0006)	0.014 (-0.003, 0.03)
Total Cholesterol	0.009 (-0.80, 0.83)	-0.14 (-1.17, 0.89)	-0.0004 (-0.01, 0.01)	-0.62 (-2.51, 1.27)	-0.07 (-0.18, 0.032)	0.06 (-0.10, 0.23)
HDL-Cholesterol	1.19 (-0.73, 3.10)	-1.12 (-3.51, 1.27)	0.016 (-0.008, 0.04)	-3.70 (-8.07, 0.67)	0.37 (0.13, 0.62) †	-0.46 (-0.84, -0.08)‡
Lipid Lowering Medication	0.58 (-1.35, 2.50)	2.03 (-0.44, 4.49)	-0.001 (-0.03, 0.01)	-1.51 (-5.96, 2.95)	-0.28 (-0.54, -0.03)‡	0.55 (0.15, 0.96) †
Current Smoking	-1.46 (-3.66, 0.74)	-0.43 (-3.20, 2.35)	-0.02 (-0.05, 0.01)	7.73 (2.56, 12.9) †	-0.18 (-0.51, 0.14)	-0.14 (-0.66, 0.37)

	E Wave	A Wave	E/A ratio	DT	Septal e'	E/e' ratio
Left Ventricular Mass	-0.06 (-0.11, -0.01)‡	0.02 (-0.05, 0.08)	-0.0006 (-0.001, -0.0000003)	0.014 (-0.10, 0.13)	-0.02 (-0.03, -0.01) †	0.02 † (0.008, 0.03)
Prevalent CHD	-3.88 (-11.5, 3.69)	7.07 (-0.36, 14.51)	-0.06 (-0.14, 0.02)	-3.38 (-17.9, 11.22)	-0.56 (-1.07, -0.05)‡	0.84 (0.007, 1.68) ‡
Prevalent DM	1.38 (-1.20, 3.98)	1.72 (-1.50, 4.94)	-0.008 (-0.04, 0.02)	3.15 (-2.74, 9.03)	-0.03 (-0.31, 0.25)	-0.26 (-0.70, 0.18)
Ejection Fraction	0.07 (-0.04, 0.18)	0.06 (-0.09, 0.21)	0.001 (-0.0003, 0.003)	0.10 (-0.17, 0.38)	0.0007 (-0.013, 0.015)	0.011 (-0.011, 0.03)
Physical Activity	0.01 (-0.005, 0.03)	0.01 (-0.01, 0.04)	0.00005 (-0.0001, 0.0003)	-0.02 (-0.06, 0.02)	-0.002 (-0.004, 0.0005)	0.003 (-0.0005, 0.006)
Left Atrium Dimension	0.05 (-0.12, 0.21)	0.06 (-0.15, 0.28)	0.0004 (-0.001, 0.003)	-0.22 (-0.60, 0.17)	-0.0003 (-0.022, 0.021)	0.033 (-0.002, 0.07)

*Age in this analysis is used as a time-varying covariate.

†P< 0.01; ‡P<0.05. BMI: Body mass index, BP: blood pressure, CHD: Coronary heart disease, DBP: Diastolic blood pressure, DM: Diabetes Mellitus, HDL: High density lipoprotein, SBP: Systolic blood pressure.

Values are betas (95% confidence intervals).

Table 3. Association of risk factors with longitudinal changes in left ventricular diastolic function parameters among men.

	E Wave	A Wave	E/A ratio	DT	Septal e'	E/e' ratio
Age*	5.38 (2.60, 8.16) †	23.5 (20.4, 26.6) †	-0.010 (-0.012, -0.009) †	0.55 (0.23, 0.87) †	-0.006 (-0.02, 0.03)	0.015 (-0.05, 0.019)
BMI	0.22 (-0.10, 0.54)	1.25 (0.84, 1.66) †	-0.007 (-0.01, -0.003) †	0.86 (0.017, 1.71) ‡	-0.03 (-0.07, 0.006)	0.12 (0.06, 0.19) †
SBP	0.14 (0.08, 0.19) †	0.12 (0.05, 0.19) †	0.0001 (-0.0007, 0.0009)	-0.09 (-0.25, 0.05)	-0.002 (-0.01, 0.006)	0.028 (0.01, 0.04) †
DBP	-0.21 (-0.32, -0,10) †	-0.10 (-0.24, 0.03)	-0.002 (-0.003, -0.0004)‡	0.18 (-0.11, 0.46)	-0.005 (-0.02, 0.01)	-0.016 (-0.04, 0.008)
BP Lowering Medication	-0.78 (-2.79, 1.23)	1.90 (-0.66, 4.47)	-0.02 (-0.05, 0.005)	2.24 (-3.05, 7.53)	-0.09 (-0.33, 0.16)	0.11 (-0.27, 0.48)
Heart Rate	-0.10 (-0.18, 0.01)	0.21 (0.10, 0.32) †	-0.003 (-0.004, -0.002) †	-0.29 (-0.52, -0.06) ‡	0.003 (-0.007, 0.01)	-0.013 (-0.029, 0.003)

	E Wave	A Wave	E/A ratio	DT	Septal e'	E/e' ratio
Total Cholesterol	-0.55 (-1.55, 0.45)	-0.45 (-1.75, 0.84)	0.013 (-0.0005, 0.03)	1.42 (-1.23, 4.06)	-0.12 (-0.25, 0.02)	0.022 (-0.18, 0.22)
HDL-Cholesterol	-0.28 (-3.07, 2.52)	1.79 (-1.85, 5.43)	-0.005 (-0.05, 0.03)	3.03 (-4.41, 10.47)	0.17 (-0.17, 0.51)	-0.04 (-0.56, 0.48)
Lipid Lowering Medication	0.23 (-2.11, 2.58)	-2.19 (-5.20, 0.83)	0.02 (-0.02, 0.05)	2.01 (-4.35, 8.38)	-0.15 (-0.45, 0.15)	-0.038 (-0.49, 0.41)
Current Smoking	1.32 (-1.53, 4.16)	2.48 (-1.04, 6.0)	-0.007 (-0.05, 0.03)	2.72 (-4.79, 10.2)	0.04 (-0.39, 0.47)	-0.08 (-0.73, 0.57)
Left Ventricular Mass	-0.08 (-0,14, -0.03) †	-0.028 (-0.09, 0.04)	-0.0005 (-0.001, 0.0002)	0.006 (-0.13, 0.14)	-0.017 (-0.02, -0.01) †	0.017 (0.007, 0.03) †
Prevalent CHD	1.54 (-1.83, 4.91)	3.1 (-1.40, 7.54)	0.02 (-0.03, 0.06)	-1.59 (-10.96, 7.78)	-0.35 (-0.71, 0.023)	0.81 (0.26, 1.37) †
Prevalent DM	1.75 (-1.28, 4.77)	3.83 (0.06, 7.60) ‡	0.005 (-0.04, 0.05)	-1.09 (-8.94, 6.76)	-0.40 (-0.70, -0.09) ‡	0.60 (0.14, 1.06) ‡
Ejection Fraction	0.11 (-0.007, 0.22)	0.04 (-0.11, 0.18)	0.002 (0.0002, 0.003) ‡	0.28 (-0.023, 0.59)	0.004 (-0.01, 0.018)	0.011 (-0.012, 0.033)
Physical Activity	-0.005 (-0.03, 0.01)	-0.003 (-0.03, 0.02)	-0.00006 (-0.0004, 0.0002)	-0.02 (-0.07, 0.03)	0.002 (-0.0001, 0.005)	-0.003 (-0.007, 0.001)
Left Atrium Dimension	0.11 (-.0.09, 0.30)	-0.21 (-0.46, 0.04)	0.003 (0.0003, 0.006) ‡	-0.24 (-0.75, 0.27)	-0.002 (-0.02, 0.02)	-0.003 (-0.03, 0.02)

*Age in this analysis is used as a time-varying covariate.

†P< 0.01; ‡P<0.05. BMI: Body mass index, BP: blood pressure, CHD: Coronary heart disease, DBP: Diastolic blood pressure, DM: Diabetes Mellitus, HDL: High density lipoprotein, SBP: Systolic blood pressure.

Values are betas (95% confidence intervals).

E wave: Among both women and men, age and SBP were associated with rise in E wave while DBP and LVM were associated with decline in E wave over time. Although BMI was associated with rise in E wave in both sexes, this association was only significant in women(Tables 2-3 & Supplemental Tables 3-4).

A wave: Age, SBP, BMI and HR were associated with rise in A wave over time in both genders, and DM only in men (Tables 2-3 & Supplemental Tables 3-4).

E/A ratio: Risk factors associated with decline in E/A ratio were age, DBP and HR in both genders. Only in men, BMI was significantly associated with decline in E/A ratio and LVEF and LAD with rise in E/A ratio(Tables 2-3 & Supplemental Tables 3-4).

Deceleration Time: Among women, current smoking was the strongest risk factor significantly associated with rise in DT over time. Age was associated with rise in DT in both genders. SBP in women and HR in men were significantly associated with decline in DT. BMI was associated with rise in DT only in men (Tables 2-3 & Supplemental Tables 3-4).

Septal e': LVM was associated with decline in septal e' in both genders. Additionally, LLM and prevalent of CHD among women and DM among men were associated with decline in septal e'. Among women, age and HDL Cholesterol were also associated with rise in septal e' (Tables 2-3 & Supplemental Tables 3-4).

E/e' Ratio: LVM was associated with rise in E/e' ratio in both genders. Additionally, LLM was associated with rise and HDL cholesterol with decline in E/e' ratio among women. Among men, prevalent CHD, BMI and DM were associated with rise in E/e' ratio(Tables 2-3 & Supplemental Tables 3-4). P values for sex interaction in the associations of BMI and DM with E/e' ratio were significant.

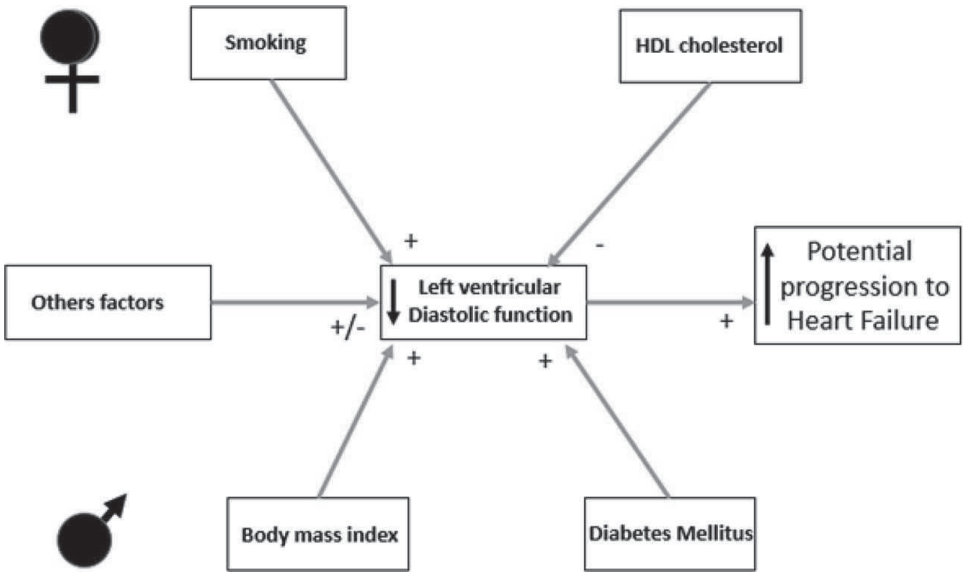


Figure 3. The core findings of our study, showing the main risk factors associated with longitudinal changes in LVDF parameters among women and men. LVDF, left ventricular diastolic function.

Discussion

In the large prospective population-based Rotterdam Study, women had poorer diastolic function than men. However, the tendency of age-related changes in LVDF parameters over time was similar in both genders. Current smoking among women and metabolic factors such as BMI and DM among men were found to be associated with deleterious progression of longitudinal changes in LVDF parameters over time. HDL cholesterol showed a favorable association with LVDF trajectories mainly in women.

Although few studies have shown the intrinsic effect of age and several cardiovascular risk factors on worsening of LVDF parameters(3,7), a comprehensive longitudinal assessment of continuous LVDF parameters by gender over time is scant(6). Patterns of longitudinal changes in the LVDF indexes over time in our study indicated a progressive impaired relaxation as well as increasing filling pressures with advancing age in both genders. In line with our findings, Kuznetsova et al(7) also found an rise in the E/e' ratio and decline in septal e' and E/A ratio over time. The LVDF parameters we reported are also comparable to those reported by Caballero et al(12) in populations older than 60 years, implying a worsening of diastolic function with ageing.

We found that the post-menopausal women in our study had a worse diastolic function compared to men, providing more evidence regarding the larger burden of diastolic dysfunction among women after menopause(5,12). In younger men, a larger decline in most of the LVDF indexes over time was observed. Women have a better diastolic function until 60 years of age after which they experience a steeper decline and worse diastolic function compared to men(5). Ageing per se seems to produce more eccentric remodeling and 3-fold larger apoptosis in men compared with women that might explain a steeper decline in diastolic reserve and the higher prevalence of diastolic dysfunction and HFpEF in women compared to men(13,14).

Longitudinal analyses of risk factors associated with changes in continuous LVDF parameters over time from a gender-specific perspective are scarce. Kuznetsova et al(7), based on the risk factors identified in cross-sectional studies, evaluated the longitudinal determinants of LVDF parameters and showed advancing age, higher insulin levels, DBP, and HR to worsen LVDF indexes over time. A recent longitudinal analyses of Framingham(15), based on categorical LVDF parameters during 5.6 years follow-up, showed that age, female sex, changes in SBP and DBP, BMI, serum triglycerides and DM were associated with worsening diastolic function in total population. Our current study expands these findings by examining the risk factors associated with changes in various continuous LVDF parameters over 11 years of follow-up from a gender-specific perspective. The main advantage of analyzing the continuous LVDF parameters is a greater power to detect associations and a lower misclassification bias than analysis based on categorical classification(16).

Association of Risk Factors on Longitudinal Changes in LVDF parameters among Women and Men

Blood Pressure: SBP and DBP showed significant associations with longitudinal changes in E wave, A wave, and E/A ratio among women and men. The opposite direction of the effect for SBP and DBP suggested the effect of pulse pressure(PP). Accordingly, when we substituted SBP and DBP with PP in our analyses, PP was significantly associated with changes in these parameters among women and men. In several epidemiological studies, PP has shown a superior predictive value compared to SBP or DBP alone (17,18). Higher PP is associated with elevated stress of the left ventricle which can result in ventricular hypertrophy and failure, critical determinants of left ventricular diastolic dysfunction(18).

Metabolic Factors: Previous cross-sectional studies have independently associated diastolic dysfunction with BMI and DM(19). In our study, DM was found to be strongly associated with worsening of LVDF parameters in men. Expanded myocardial fibrosis as well as accelerated apoptosis are among the pathophysiologic features of diabetic cardiomyopathy(20). While several previous studies have shown larger deterioration of LVDF among diabetics(8), data regarding sex differences in the association of DM on LVDF are scarce and conflicting. Diabetes was found to be an independent contributor to LVM among women in the Framingham Heart Study(21) but among both women and men from the Cardiovascular Health Study(22) and the Strong Heart Study(23).

In our study, a larger association of BMI with worsening of LVDF over time was found among men than in women. The only prior, cross-sectional, study that evaluated sex differences of obesity on LVDF, reported no association between BMI and LVDF indexes in women >65 years but did describe an association between septal e' and abdominal adiposity among younger women Among men, BMI and abdominal obesity were associated with a higher likelihood of diastolic dysfunction(24). The obesity-related mechanisms might be different for women and men. While for younger women the effect of obesity might act through its influence on SBP, the effect seems to be predominantly direct for men >65 years(24).

Smoking and Lipid Profile: Current smoking was only associated with rise in DT among women in our study. Smoking commonly precedes the development of HFpEF(25). While smoking confers a greater CHD risk in women compared to men(26), sex differences in the setting of HF have not been reported(27). Smoking has been suggested to significantly affect LVDF independently of its role as a risk factor for coronary atherosclerosis and through other independent pathways(28).

We found a favorable association of HDL-cholesterol with diastolic function over time among women. Moreover, use of lipid lowering medication, as a proxy for chronic dyslipidemia, was associated with worse LVDF over time. Previous cross-sectional studies have associated hyperlipidemia with coronary endothelial dysfunction and with myocardial damage independent of ischemia, leading to diastolic dysfunction(29). Low levels of HDL cholesterol and elevated levels of total cholesterol are known risk factors

for CHD and increasing LVM, both important factors leading to diastolic dysfunction. While increasing HDL levels have a more favorable effect in women compared to men, such gender differences in the association of HDL with LVDF require further study.

Study Strengths and Limitations

Our study was based on a large group of women and men from a population-based cohort with repeated echocardiographic examinations over 11 years of follow-up. The longitudinal design allowed the use of linear mixed effect models to analyze progressive long-term alterations in continuous LVDF parameters. Availability of the well-defined set of covariates and detailed characterization of the cohort allowed to examine LVDF parameters and their correlates from a gender-specific perspective. Nevertheless, limitations of our study also merit consideration. The gold standard for diastolic function measurement is the pressure-volume relationship which is an invasive approach. However, Doppler measurements of mitral inflow and TDI allows for a valid non-invasive measurement of diastolic function(10,30). Echocardiography has proven to be a useful tool for assessing diastolic function, in order to minimize inherent limitations operator-dependent, a standardized protocol was used by 4 trained echocardiographers with good inter and intra-reader agreement(11). Our population included individuals of European ancestry. Therefore, the generalizability of our findings to other ethnicities should be performed with caution. As inherited to all longitudinal cohort studies, survival bias cannot be entirely ruled out.

Conclusions

In our large population-based study, women were found to have poorer diastolic function than men. However, age-related changes in continuous LVDF parameters were comparable in both genders. Our findings highlight the correlates of asymptomatic diastolic dysfunction among women and men. The differential association of risk factors with LVDF among women and men could provide further hypothesis regarding transition from a healthy heart to the development of HFpEF(5).

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Supplemental Material

Supplemental Methods

Echocardiography:

For each participant, one echocardiogram was obtained at each examination. In the first examination, the first 40% of the echocardiograms were performed with a commercially available ultrasonography system (AU3 Partner, Esaote Biomedica, with a 3.5/2.5 MHz transducer) and the followings with Acuson Cypress, with a 3V2c transducer. For the subsequent second and third examinations, a standardized protocol was used which also included two-dimensional resting transthoracic echocardiography performed by experienced echocardiographers with an identical standardized protocol for all participants and a commercially available ultrasonography system (Vivid I, GE Healthcare, Little Chalfont, UK), with a 2.5 MHz transducer. All examinations were performed by the same echocardiographers using the same protocol. As described previously, inter-reader and intra-reader agreements were good(1). All images were digitally stored and assessed offline by the echocardiographers.

The protocol included 2-dimensional scanning in the parasternal long and short axis views, the apical and subcostal views. In addition, 2-dimension guided M-mode measurements of left ventricle were obtained by scanning in the parasternal long axis view.

Left atrial diameter (LAD), left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), interventricular septum thickness (IVST), left ventricular posterior wall thickness (LVPWT) and left ventricular ejection fraction were the left-sided measurements. Relative wall thickness was calculated according to the formula (2 * LVPWT)/(LVEDD) (2). Left ventricular mass (LVmass) in grams was calculated according to the formula by Devereux and colleagues as 0.8 * (1.04 * ((LVEDD + IVST + LVPWT)3 - LVEDD3)) + 0.6(3), and was indexed with Body Surface Area (BSA) (2). Left ventricular fractional shortening (FS) was calculated using the formula: FS = (LVEDD-LVESD)/LVEDD * 100%(4).

Assessment of Cardiovascular Risk Factors:

Medical history, current health status, smoking and use of medications were assessed by a trained interviewer at the home visit using a computerized questionnaire. Body mass index (BMI) was calculated as weight in kilograms divided by height in squared meters. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice in sitting position at the right upper arm. We used the average of two consecutive measurements. Hypertension was defined as SBP >140 mm Hg, DBP >90 mm Hg, or use of blood pressure-lowering medication with an indication for hypertension. Heart rate (HR) was measured with an oximeter in the second finger of the right hand and the average of two consecutive measurements was used. Total and high density lipoprotein (HDL) cholesterol and glucose levels were measured with the use of standardized laboratory techniques. Diabetes mellitus (DM) was defined as fasting glucose >6.9 mmol/L, nonfasting glucose >11.0 mmol/L, use of blood glucose-lowering medication, or a previous diagnosis of DM. A history of coronary heart disease (CHD) was defined as a myocardial infarction

or coronary revascularization procedure (5, 6). Physical activity was evaluated using LASA questionnaire (LAPAQ) and accelerometer (Actiwatch) (7).

Statistical Analysis:
For the analysis of the diastolic dysfunction indices, using each of the parameters as continuous variables, distribution of the outcome variable was graphically assessed for normality (histograms, box plots, and QQ plots). To select the correct function for the variable age (as a time-varying covariate), several different initial models including linear and non-linear functions together with interaction terms for age with other covariates were built. Outlier values were removed. The following covariates were included in the fixed part of the linear mixed models: Age (as time-varying covariate), systolic and diastolic blood pressure (SBP, DBP), heart rate (HR), total and high-density lipoprotein (HDL) cholesterol, blood pressure and lipid lowering medications, diabetes mellitus (DM), current smoking, previous coronary heart disease (CHD), left ventricular mass indexed by body surface area (LVM), left ventricular ejection fraction (LVEF), physical activity, left atrial diameter (LAD) and cohort. In the random part of the linear mixed model, age was the only variable (as a time-varying covariate) included. First, we evaluated a full model, including interactions terms, comparing model with random intercept vs model with both intercept and slope random. Second, we evaluated the linear and non-linear terms in the random part of the model and selected the model with lower AIC. Third, we evaluated the fixed part of the model, comparing full model with interactions terms vs model without interactions terms and selected the model with lower AIC. Finally, we evaluated the linear and non-linear terms in the fixed part of the model and selected the model with lower AIC. Non-linear terms evaluated were polynomials, and natural splines quadratic and cubic. Convergence problems of some models were solved increasing the mathematical iterations, using optimizer (bobyqua optimizer) and centralized continuous variables if it was needed.

A residual analysis was made to all final models. Several covariates were missing in <5% of the participants and were imputed using fully conditional specification (Markov chain Monte Carlo method) with a maximum iteration number of five.

Supplemental Results

Non-returning participants:
From the 3,420 participants who were present at examination 1 but not at the follow-up examinations, 1,867 had died before the next follow-up visit. Of the 3,422 surviving participants, 1,553 did not return for the follow-up examinations. Survivors who did not return were older; more often women, hypertensive, current smoker, and diabetic; and had higher mean values for BMI, SBP, and HR. Among the echocardiographic parameters, the non-returning participants had larger LVM and left atrial (LA) diameter, larger chamber dimensions, higher relative wall thickness (RWT), smaller FS, higher A wave and DT, and lower E/A ratio. (Supplemental Table 5)

Supplemental Table 1. Baseline clinical and echocardiographic characteristics of the participants for the analysis of two left ventricular diastolic function parameters.

	WOMEN (n=882)	MEN (n=646)	p-value*
Clinical Features			
Age, years	73.63 (4.98)	73.64 (4.95)	0.990
BMI, kg/m²	27.27 (4.22)	27.02 (3.06)	0.201
SBP, mmHg	150.82 (20.86)	152.35 (20.13)	0.151
DBP, mmHg	85.50 (11.00)	85.81(10.98)	0.594
Blood pressure Lowering Medication, n (%)	414 (46.94)	338 (52.32)	0.038
Hypertension, n (%)	764 (86.6)	583 (90.3)	0.027
Heart Rate, beats/min	68.15 (9.46)	65.21 (10.64)	<0.001
Total Cholesterol, mmol/L	5.73 (1.04)	5.06 (1.04)	<0.001
HDL-cholesterol, mmol/L	1.64 (0.42)	1.34 (0.34)	<0.001
Lipid Lowering Medication, n (%)	232 (26.3)	236 (36.5)	<0.001
Current Smoker, n (%)	83 (9.4)	43 (6.7)	0.048
Prevalent CHD, n (%)	35 (3.97)	99 (15.3)	<0.001
Prevalent DM, n (%)	137 (15.5)	108 (16.7)	0.531
Echocardiography Features			
LVM index, g/m²	66.96 (14.80)	74.47(19.38)	<0.001
Left Atrium Diameter/BSA†, mm/m²	22.79 (2.93)	22.18 (2.83)	<0.001
LVEDD, mm	49.36 (4.29)	53.23 (5.07)	<0.001
LVESD, mm	28.31 (3.50)	31.35 (4.97)	<0.001
Relative Wall Thickness, cm	0.27 (0.05)	0.27 (0.05)	1.0
Fractional Shortening, %	43.14 (5.99)	41.92 (7.80)	<0.001

* p-value for comparison of different characteristics between men and women.
Values are mean (± standard deviation) or numbers (percentages).
BMI: Body mass index, BSA: Body surface area, CHD: coronary heart disease, DM: Type 2 diabetes mellitus, DBP: Diastolic blood pressure, LVEDD: Left ventricle end diastolic dimension, LVESD: Left ventricle end systolic dimension, LVM: Left ventricular mass, SBP: Systolic blood pressure.

Supplemental Table 2. Left ventricular diastolic function parameters stratified by age and gender.

	55 – 64 years old			65 – 74 years old			>= 75 years old		
	Women	**Men**	**p-value***	**Women**	**Men**	**p-value***	**Women**	**Men**	**p-value***
E wave, cm/s	N:276 68 (13.08)	N:194 65.94 (12.41)	0.0867	N: 1253 67.37 (13.0)	N: 934 64.03 (12.8)	<0.001	N: 946 67.14 (13.19)	N: 693 64.6 (13.69)	<0.001
A wave, cm/s	N: 291 73.07 (13.27)	N: 201 68.83 (13.19)	<0.001	N: 1332 80.79 (17.04)	N: 960 73.53 (16.42)	<0.001	N:1013 89.86 (17.9)	N:711 82.2 (18.51)	<0.001
E/A ratio	N:274 0.947 (0.195)	N: 183 0.97 (0.20)	0.22	N: 1259 0.854 (0.175)	N: 875 0.88 (0.19)	0.0013	N:954 0.77 (0.17)	N: 658 0.80 (0.19)	<0.001
Deceleration Time, msec	N: 289 199 (33.25)	N: 207 201.86 (37.8)	0.365	N:1325 204.01 (33.83)	N:973 207.5 (38.48)	0.021	N: 1018 207.23 (39.24)	N: 714 213.67 (42.33)	0.0012
Septal e', cm/s	N/A†	N/A†	N/A†	N: 863 7.22 (1.78)	N:651 7.52 (1.67)	<0.001	N:981 6.5 (1.73)	N:713 6.99 (1.87)	<0.001
E/e' ratio	N/A†	N/A†	N/A†	N:799 10.06 (2.5)	N: 610 9.28 (2.41)	<0.001	N: 884 10.86 (2.73)	N:638 9.89 (2.64)	<0.001

Values are mean (± standard deviation).

* p-value for comparison of different values of left ventricular diastolic function parameters for women and men in each age group.

† N/A indicates that e' and E/e' ratio were not available at the indicated examination.

Supplemental Table 3. Association of risk factors with longitudinal changes in left ventricular diastolic function parameters among women.

WOMEN	E wave MIXED	A wave MIXED	E/A MIXED	DT MIXED	e`septal MIXED	E/e` MIXED
Agetime	†	†	†	†	‡	
BMI	‡	†				
SBP	†	†		‡		
DBP	†		†			
BP lowering medication						
Heart rate		†	†			
Total Cholesterol						
HDL Cholesterol					†	‡
Lipid low medication					‡	†
Current SMK				†		
LVM	‡				†	†
Prevalent CHD					‡	‡
Prevalent DM						
Ejection fraction						
Physical activity						
LAD						

*Age in this analysis is used as a time-varying covariate. †P< 0.0083 (significant at Bonferroni corrected P value); ‡P<0.05.

BMI: Body mass index, BP: blood pressure, CHD: Coronary heart disease, DBP: Diastolic blood pressure, DM: Diabetes Mellitus, HDL: High density lipoprotein, SBP: Systolic blood pressure.

Values are betas (95% confidence intervals). All presented betas (95% confidence intervals) are based on fully adjusted models

Sex-specific differences are highlighted in gray in the table.

Supplemental Table 4. Association of risk factors with longitudinal changes in left ventricular diastolic function parameters among men.

MEN	E wave MIXED	A wave MIXED	E/A MIXED	DT MIXED	e`septal MIXED	E/e` MIXED
Agetime	†	†	†	†		
BMI		†	†	‡		†
SBP	†	†				†
DBP	†		‡			
BP lowering medication						
Heart rate	‡	†	†	‡		
Total Cholesterol						
HDL Cholesterol						
Lipid low medication						
Current SMK						
LVM	†				†	†
Prevalent CHD						†
Prevalent DM		‡			‡	‡
Ejection fraction			‡			
Physical activity						
LAD			‡			

*Age in this analysis is used as a time-varying covariate. †P< 0.0083 (significant at Bonferroni corrected P value); ‡P<0.05.

BMI: Body mass index, BP: blood pressure, CHD: Coronary heart disease, DBP: Diastolic blood pressure,

DM: Diabetes Mellitus, HDL: High density lipoprotein, SBP: Systolic blood pressure.

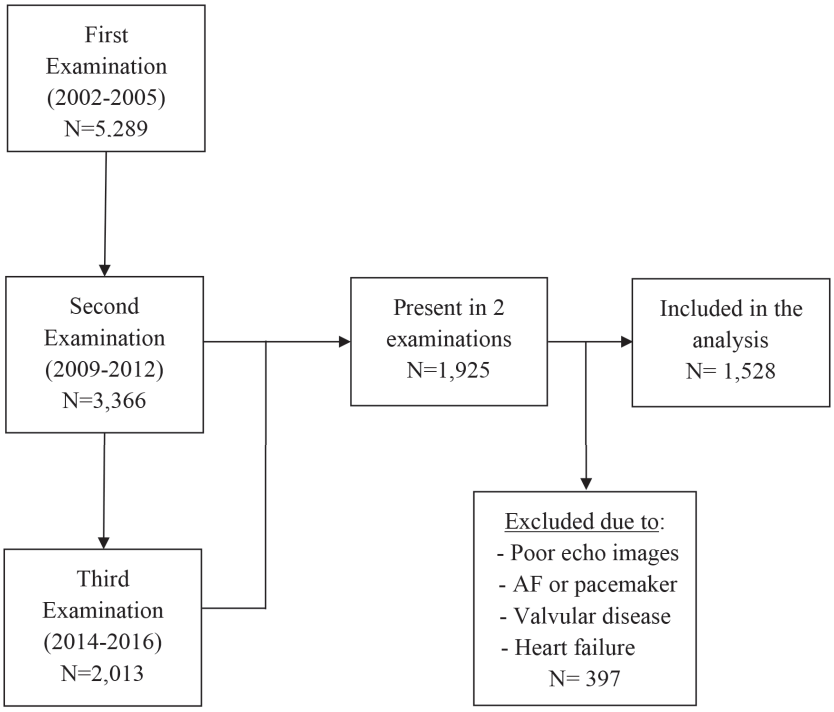
Values are betas (95% confidence intervals). All presented betas (95% confidence intervals) are based on fully adjusted models

Sex-specific differences are highlighted in gray in the table.

Supplemental Table 5. Clinical and echocardiographic characteristics at the first examination for the individuals that participated only at the first examination and did not return for the two follow-up examinations.

	Participants (n=1,619)	Non-Returning Individuals (n=1,553)	p-value*
Clinical Features			
Age, years	67.45 (5.03)	71.47 (6.33)	<0.001
Female Sex, n (%)	931 (57.5)	1016 (65.4)	<0.001
BMI, kg/m²	27.37 (3.72)	27.88 (4.17)	<0.001
SBP, mmHg	144.70 (18.90)	150.16 (20.54)	<0.001
DBP, mmHg	80.85 (10.08)	80.18 (10.32)	0.065
Blood Pressure Lowering Medication, n (%)	531 (33.1)	708 (46.2)	<0.001
Hypertension, n (%)	1055 (65.9)	1140 (74.7)	<0.001
Heart Rate, beats/min	67.85 (10.27)	69.34 (10.93)	<0.001
Total Cholesterol, mmol/L	5.73 (0.98)	5.71 (0.96)	0.562
HDL-cholesterol, mmol/L	1.47 (0.39)	1.49 (0.40)	0.154
Lipid Lowering Medication, n (%)	343 (21.4)	355 (23.2)	0.568
Current Smoker, n (%)	166 (10.5)	207 (13.6)	0.363
Prevalent CHD, n (%)	91 (5.6)	106 (6.8)	0.728
Prevalent DM, n (%)	160 (9.9)	201 (12.9)	0.376
Echocardiography Features†			
LVM index, g/m²	72.29 (17.33)	74.35 (18.19)	0.013
Left Atrium Diameter/BSA‡, mm/m²	21.13 (2.61)	21.56 (2.99)	<0.001
LVEDD, mm	51.08 (5.03)	50.91 (5.28)	0.353
LVESD, mm	30.71 (4.76)	31.11 (5.30)	0.025
Relative Wall Thickness, cm	0.29 (0.05)	0.30 (0.06)	<0.001
Fractional Shortening, %	38.52 (14.54)	36.50 (16.26)	<0.001
E wave, cm/s	65.53 (14.56)	64.97 (15.74)	0.305
A wave, cm/s	73.26 (15.58)	77.32 (16.73)	<0.001
Deceleration Time, msec	207.86 (40.43)	214.15 (46.86)	<0.001
E/A ratio	0.93 (0.23)	0.88 (0.36)	<0.001

*p-value for comparison of different characteristics between participants and non-returning individuals.
† In the first evaluation measurements of Echo TDI were not available.
Values are mean (± standard deviation) or numbers (percentages).
BMI: Body mass index, BSA: Body surface area, CHD: coronary heart disease, DM: Type 2 diabetes mellitus, DBP: Diastolic blood pressure, LVEDD: Left ventricle end diastolic dimension, LVESD: Left ventricle end systolic dimension, LVM: Left ventricular mass, SBP: Systolic blood pressure.



Supplemental Figure 1. Flow chart for the participants included in the analysis of two left ventricular diastolic function parameters measured two times.

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PART IV

Epilogue

IV

CHAPTER 13

Summary and general discussion

13

This thesis describes different outcome measures in patients with heart failure (HF), including short- and long-term prognosis, mortality over time, left ventricular remodeling and patient-reported outcomes. We studied the impact of changes in HF therapy on prognosis and left ventricular remodeling, and investigated determinants of health-related quality of life (HRQoL) in different types of patients with acute HF, and studied incident HF prediction models and sex-related differences in developing diastolic dysfunction. This thesis has been divided in three parts:

I. Impact of improved heart failure therapy on left ventricular remodeling and prognosis
II. Patient-reported outcomes in acute heart failure
III. Heart failure at a population level

This chapter summarizes our findings, translates these findings into clinical practice and offers suggestions for further research.

Part I: Impact of improved heart failure therapy on left ventricular remodeling and prognosis

Because HF therapy was developed since the 1980s, one may – with time - expect improved survival of patients admitted with acute HF. We investigated this hypothesis with the use of a database including 1810 patients admitted with acute HF at the (Intensive) Coronary Care Unit of the Erasmus Medical Center. Patients were prospectively included in the period from 1985 through 2008. The primary endpoint was the composite of all-cause mortality, heart transplantation or implantation of a left ventricular assist device (LVAD).

As shown in **Chapter 2**, the included patients with acute HF have a poor prognosis with 35% and 76% of the them reaching the primary endpoint after 1 and 10 years follow-up, respectively. Patients with ischemic origin of HF had the worst prognosis. Also, male sex, diabetes mellitus, older age and poor left ventricular ejection fraction (LVEF) were associated with worse prognosis. However, in the period, from 1985 until 1999, there was no significant improvement of the prognosis of the patients admitted. We found that the prognosis improved modestly in the period 2000-2008, as compared with the earliest time period. However, this improvement was only observed in patients with a reduced LVEF and not in patients with a preserved ejection fraction. Moreover, the improved prognosis only concerned the long-term prognosis (i.e. 10 years) and not the short-term prognosis. The reason why the short-term prognosis did not improve is most likely due the a lack of improvement in the therapy of *acute* HF. In contrast, improved therapy for *chronic* HF (such as angiotensin-converting enzyme [ACE] inhibitor, beta-blocker, mineralocorticoid receptor antagonist [MRA] and intracardiac defibrillator [ICD]) was most likely the main determinant of the improved long-term outcome. This conclusion is supported by the fact that (1) prognostic improvement was only found after long-term follow-up; (2) the development of new therapeutic options is in line with the prognostic improvement; (3) the new HF therapy was found to be effective in patient with reduced ejection fraction which is exactly the subset of patients with HF in whom the improved prognosis was observed.

The next chapters discuss the prognosis and prognostic improvement in subcategories of patients with acute HF. **Chapter 3** describes the difference in prognosis between women and men with acute HF. Over half of the included patients were men (64%). Women were found to have a better prognosis than men, both after 1 year of follow-up (primary outcome 30% vs. 38%) and after 10 years of follow-up (72% vs. 79%). This difference was most pronounced in patients with poor LVEF. Furthermore, we demonstrated an improvement in prognosis of patients admitted in the period 2000-2008, as compared to those admitted from 1985 through 1999. This improvement was comparable among women and men. This led to our conclusion that women and men have benefited equally from the improvement in HF therapies over time.

Differences in prognosis of acute HF patients with and without diabetes mellitus were studied in **Chapter 4**. The distribution of patients with and without diabetes was 21% vs. 79%, respectively. We found that patients with diabetes had better 30-day (9% vs. 16%), comparable 1-year (32% vs. 36%) and worse 10-year (87% vs. 76%) outcome than men and women without diabetes. Worse 30-day outcome in patients with diabetes has been previously reported[1, 2] but no clear explanation has been reported for this finding. One possible explanation may be that our patients without diabetes more frequently had cardiogenic shock, a condition associated with worse prognosis[3]. The prognostic disadvantage of HF patients with diabetes in the long term could possibly not only be explained by HF-related factors but also with long-term complications of diabetes. Importantly, the improvement of long-term prognosis over time was found to be comparable between patients with and without diabetes. It is likely that the prognostic improvement of patients with diabetes may be related to both the improvement of HF therapy as well as the ameliorated diabetes treatment.

Chapter 5 examines the relation between renal function, anemia and prognosis in patients with acute HF. In this study, 61% of the patients had an impaired renal function, including 18% with a severely impaired renal function (eGFR <30 ml/min). Impaired renal function was found to be a strong predictor of both poor short- and long-term outcome. Prognosis became worse when the renal function was more severely impaired. In contrast to patients with preserved renal function, the long-term prognosis of patients with impaired renal function did not improve over time. This may be explained by the fact that patients with renal dysfunction were less frequently treated with the new developed medication (like ACE inhibitors and MRAs) since these therapeutic modalities interact with renal function, and cannot be employed beneficially in this population. Another possible explanation is the poor prognosis of the renal insufficiency itself. Furthermore, anemia was associated with worse short-term prognosis in both patients with and without renal dysfunction. For long-term prognosis, anemia was only a prognosticator in patients with impaired renal function and not in those with preserved renal function. The mechanism of this difference is unclear.

A relatively new concept in cardiovascular research to measure prognosis, namely relative conditional survival, was discussed in **Chapter 6**. Relative survival compares the survival of the patient at issue to the survival of the sex- and age-matched general population. Using conditional survival enables to determine the prognosis after surviving a certain period. We found that the relative conditional survival of patients with acute HF was significantly worse than that of the general population. This remained the case after stratifying for several factors. This finding is especially important for young patients with HF since their prognosis will be severely diminished. A striking finding in this study was the fact that the prognosis improved when patients survived the first year after the hospitalization. Clinicians may use relative conditional survival to inform patients more clearly about their prognosis.

Chapter 7 describes a retrospective study that included 111 patients admitted with de novo, acute HF with reduced LVEF in the period from 2008 until 2016. In total, 62% had HF based on non-ischemic causes. This study investigated left ventricular remodeling and subsequent prognosis. Left ventricular remodeling was assessed by left ventricular end-diastolic and end-systolic diameter and the presence and degree of mitral valve regurgitation. Significantly higher rates of LVEF recovery were found in patients with non-ischemic origin of HF (almost 40%) compared to those with HF of ischemic origin (10%). Left ventricular remodeling (for the vast majority occurring in patients with non-ischemic HF) was already present after 6 months in a significant number of patients. Importantly, LV function improved further during the next 2 years of follow-up, and improvement of LVEF was found to be associated with an improved prognosis. Thus, both the etiology of HF (i.e. non-ischemic origin) and the achievement of optimal HF therapy with medication are the major determinants of improvement of left ventricular function.

Chapter 8 is a qualitative review discussing a cut-off value of 35% for the LVEF as qualifying ejection fraction for implantation of an ICD for primary prevention. Based on so-called landmark trials in both patients with HF with ischemic and non-ischemic origin, we advocate that an LVEF <30% (and symptomatic HF) should be the new criterion for ICD-implantation for primary prevention. Several arguments support this position of which the most important are: (1) most patients included in the trials had an LVEF <30%; (2) the original trials are relatively old, and since then HF therapy has significantly improved with better prognosis and lower rates of sudden cardiac death as result; (3) cost-effectiveness of ICD therapy decreases due to better HF therapy; (4) while the current preventive effect of the ICDs in this era is attenuated, the short- and long-term risk associated with ICD remains a concern.

Part II: Patient-reported outcomes in acute heart failure

Studies on patient-reported outcomes included in this thesis are based on data of the TRIUMPH study. TRIUMPH was a prospective, observational, multicenter trial including 496 patients admitted with acute HF in the period September 2009 until December 2013.[4] TRIUMPH examined the clinical value of repeated measurements of several biomarkers.

A secondary aim was to investigate the HRQoL in patients admitted with acute HF. HRQoL was measured with two questionnaires: the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the EuroQuality-of-life 5 Dimensions (EQ-5D). The Hospital Anxiety and Depression Scale (HADS) was used to examine symptoms of anxiety and depression. Lastly, a questionnaire on symptom occurrence and symptom burden regarding HF-related symptoms was used. Patients were asked to complete these questionnaires at discharge and after 9-12 months of follow-up. In total, 70% of the included patients completed the questionnaires at baseline. After 1 year of follow-up, about 60% of the patients who were alive at that time completed the questionnaires.

Four non-cardiac comorbidities that frequently accompany HF including chronic kidney disease, diabetes mellitus, chronic obstructive pulmonary disease (COPD) and cerebrovascular accident (CVA) were studied in relation to the patient-reported outcomes. **Chapter 9** investigated whether the determinants of HRQoL were different between HF patients with and without those comorbidities (61% vs. 39%). At hospital discharge, patients with comorbidities had worse HRQoL (as measured with the KCCQ) and more depressive symptoms than those without comorbidities. Also, after 1 year of follow-up, the HRQoL was worse in patients with comorbidities. Female sex, previous HF, increasing body mass index, higher NT-proBNP, higher systolic blood pressure and presence of anxiety and depression were negatively associated with HRQoL in HF patients with these comorbidities. Among patients without comorbidities, we did not found other determinants of HRQoL besides anxiety and depression. In such patients, HF itself may be the major determinant of impaired HRQoL.

Chapter 10 showed that HF patients with depression (37% of the included patients; depression according to the HADS) had higher symptom occurrence and higher symptom burden than patients without depression. Patients with depression had a significant lower HRQoL. These findings were not only present at baseline but also after 1 year of follow-up. Results of this study emphasize that depression is often present in patients with HF and indicate the need for recognition and adequate treatment of depression in patients with HF.

Part III: Heart failure at a population level

The third part of this thesis included studies based on data of the Rotterdam Study. The Rotterdam Study is a prospective, population-based, cohort study among men and women living in Rotterdam (district Ommoord). The study started in 1990 and includes people of 40 years of age and older. The Rotterdam Study investigates the major determinants of most chronic diseases including HF and other cardiovascular disorders.[5]

In **Chapter 11**, we evaluated different models to predict 10-year incident HF. The included population consists of 2743 men and 3646 women aged 55 years and older of which 429 (16%) men and 489 (13%) women developed HF during a median follow-up time of 13 years. The ACC/AHA model was found to be a reasonable prediction model in both men

and women. The performance of this model was comparable with two other prediction models (ARIC model[6] and Health ABC model[7]). The advantage of the ACC/AHA model is its simplicity as it considers determinants that are easily available (age, total cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive use, smoking status and diabetes). The addition of NT-proBNP to the ACC/AHA model resulted in only a modest improvement of the model performance but not in a significant shift in risk classification. Therefore, the outcome of the ACC/AHA model could be used for primary prevention purposes of HF in both men and women.

Longitudinal changes in left ventricular diastolic function and their risk factors among men and women included in the Rotterdam Study are studied in **Chapter 12**. During 11 years of follow-up, echocardiographic measurements were made in 630 men and 870 women without know HF. At baseline, women were found to have more severe left ventricular diastolic dysfunction than men. During a follow-up period of 11 years, the age-related change in parameters of diastolic dysfunction were comparable in both sexes. However, risk factors for changes in diastolic dysfunction differed between men and women. Whereas smoking and lower HDL cholesterol levels were the main risk factors for worse left ventricular diastolic function over time among women, deleterious change in diastolic function was predominantly determined by the presence of diabetes and higher body mass index in men. Since impaired left ventricular diastolic function has been associated with development of HF,[8] recognition and treatment of such risk factors are important in order to prevent development of HF.

Clinical implications

Based on this thesis, several lessons for clinical practice may be learned. First, since acute HF has such a poor prognosis, it is paramount to prevent it. To prevent de novo HF, risk factors for development of HF should be recognized at an early stage and should be adequately treated in the general population. In our thesis, for example diabetes, hypertension, hypercholesterolemia and smoking were found to be crucial risk factors for HF amenable to proper treatment. New developments in prevention and therapy of these risk factors, for example sodium-glucose cotransporter-2 inhibitors for diabetes, should be helpful in this regard.[9] The other category of acute HF is decompensated (or acute on) chronic HF that might be prevented by adequate monitoring and optimal treatment of chronic HF. The initial therapy of patients with this syndrome should comprise medical treatment with ACE-inhibitors, beta-blockers, MRAs and diuretics and, if this is insufficient, with more advanced therapy like angiotensin receptor neprilysin inhibitor (ARNI), cardiac resynchronization therapy and ivabradine.[10] It may also be considered to give ARNIs in an earlier stage in order to replace ACE-inhibitors.[11] These therapeutic modalities may not only prevent HF deterioration but they may even induce left ventricular remodeling. Moreover, close monitoring (e.g. with telemonitoring) of HF patients may be a promising tool in the prevention of decompensation of chronic HF when this would result in earlier and successful interventions. Furthermore, non-drug therapy, as discussed below, is important to prevent acute HF.

Secondly, since we showed that left ventricular remodeling occurred in a significant part of patients with de novo HF under optimal medical therapy, decisions for interventions such as heart transplantation or LVAD implantation and ICD implantation should not be made too early and quickly. Both interventions have their own important and potentially lethal complications.[12, 13] Moreover, especially for countries in which heart transplantation of LVAD implantation is not or hardly feasible, the possibility of left ventricular remodeling with medical treatment has relevant implications.

Third, it should be considered to implant ICDs for primary prevention only if the LVEF <30%. Nowadays, LVEF<35% is the cut-off level for implantation of an ICD but, as mentioned before, this recommendation is based on relatively old studies and, even more important, these studies included predominantly patients with LVEF <30%. As HF treatment has been substantially improved since then, ICD shocks have become less common. However, the risk for ICD-related complications like inappropriate shocks and device infection is still there. Therefore, the indication for ICD for primary prevention should be considered carefully. Another issue that is increasingly raised is that patients become older and develop other serious conditions while an ICD is in situ. This confronts you with the difficult question of when to turn off the ICD.

Fourth, cardiologists may consider to consult their HF patients about conditional survival instead of short- and long-term survival rates. Conventionally, cardiovascular research reports prognosis as cumulative survival rates. However, this is difficult to translate to patients' personal situation in an understandable way. It could be more understandable for individual patients to understand their prognosis when using conditional survival instead. Relative survival provides additional prognostic information about their prognosis compared to the general population with the same sex and age. This could also be informative for patients with HF.

Five, not only prognosis, but also HRQoL deserves more attention in patients with HF. To this end, optimal HF treatment should be pursued to improve not only prognosis but also quality of life. However, more action may be needed in order to improve HRQoL. Adequate treatment of comorbidities in HF patients is important. Furthermore, it is essential to recognize depression and to install proper treatment. Indeed, there is overlap between HF symptoms and depressive symptoms. Therefore, a depression screening tool should be employed more frequently. Lastly, it is important to refer patients for cardiac rehabilitation. In addition to improvement of HRQoL, cardiac rehabilitation has been shown to be effective in preventing more symptoms and clinical events.[14] Indeed, cardiac rehabilitation already has a strong recommendation in HF guidelines,[10] but clinical practice shows that the number of referrals could be increased.[15]

Sixth, clinicians should pay more attention to symptom management. There are different ways to achieve this. Education of patients, training of patients in symptom recognition and psychoeducational intervention may all be appropriate . Furthermore, following on the ESC position paper about palliative care in HF,[16] incorporation of palliative care in patients with HF should receive more attention.

Lastly, it remains important to realize the difference between men and women, both in research and in clinical practice. For example, this thesis shows relevant sex differences in prognosis, etiology of HF, risk factors in developing diastolic dysfunction and distribution in preserved versus reduced ejection fraction.

Future challenges

No improvement of short-term prognosis was observed in patients with acute HF. Therefore, new therapies to improve treatment and prognosis of acute HF at clinical presentation are clearly and urgently needed. Unfortunately, results of several studies in this respect have been disappointing.[17] One of the reasons might be the heterogeneity of acute HF. Indeed, it is sound clinical practice and specifically recommended to manage triggers for acute decompensation like acute coronary syndromes, arrhythmias and hypertensive emergencies as soon as possible to prevent further deterioration.[10] However, there is no suitable therapy to amend the syndrome acute HF itself. Further studies on personalized acute HF therapy are strongly needed.

So far, it is also not clear what the optimal therapy should be in patients in whom LVEF has recovered following treatment with HF therapy. There is evidence suggesting negative influence of stopping HF medication.[18] In general, patients with recovered LVEF should continue to use ACE-inhibitors and beta-blockers. Other HF medication may be discontinued. However, scientific evidence for such action is currently lacking.

Despite the fact that HF is a heterogeneous syndrome, current guidelines provide recommendations for patients over the entire spectrum of HF and not further specified to different HF phenotypes. Especially the pathogenesis of dilated cardiomyopathy is very heterogeneous. Therefore, addition therapy specifically-targeted to the underlying etiology or pathological mechanism to the current HF treatment may be of added value to improve patients' prognosis. Different studies investigating this topic have been performed or are currently under investigation,[19] but only a few targeted therapeutics are incorporated in the guidelines until now.

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CHAPTER 14

Nederlandse samenvatting

14

Dit proefschrift behandelt verschillende uitkomstmaten bij patiënten met hartfalen (HF), waaronder korte- en lange-termijn mortaliteit, trends in mortaliteit, linker ventrikel *remodeling* en patiënt-gerapporteerde uitkomsten (bijv. kwaliteit van leven, symptomen). Het proefschrift had als doel om (1) te onderzoeken wat de invloed is van veranderingen in de HF-behandeling op prognose en linker ventrikel *remodeling*, (2) te bestuderen wat de determinanten zijn van gezondheidsgerelateerde kwaliteit van leven in verschillende groepen van patiënten met HF, en (3) predictiemodellen voor het ontwikkelen van HF te onderzoeken alsook het bestuderen van geslacht-gerelateerde verschillen in het ontwikkelen van diastolische dysfunctie. Dit proefschrift is opgedeeld in drie onderdelen:

I. De invloed van verbetering in hartfalen behandeling op linker ventrikel *remodeling* en prognose
II. Patiënt-gerapporteerde uitkomsten in acuut hartfalen
III. Hartfalen op populatieniveau

Deel I: De invloed van verbetering in hartfalen behandeling op linker ventrikel remodeling en prognose

Aangezien er sinds de jaren '80 nieuwe HF-therapie is ontwikkeld, werd onderzocht of dit zich vertaalde naar een betere prognose in patiënten met acuut HF. Hiervoor is een gegevensbestand gebruikt van 1810 patiënten opgenomen vanwege acuut HF op de (Intensive) Coronary Care Unit van het Erasmus Medisch Centrum. De patiënten werden prospectief geïncludeerd in de periode 1985 tot en met 2008.

De gegevens gepresenteerd in **Hoofdstuk 2** laten zien dat patiënten met acuut HF een slechte prognose hebben waarbij 35% van de patiënten de combinatie van mortaliteit, harttransplantatie en implantatie van een linker ventrikel assist device (LVAD) bereikte na 1 jaar follow-up en 76% na 10 jaar follow-up. Patiënten met een ischemische oorzaak van het HF hadden de slechtste prognose. Verder waren mannelijk geslacht, diabetes mellitus, oudere leeftijd en slechte linker ventrikel ejectiefractie (LVEF) geassocieerd met een slechte uitkomst. Er werd geen significante verbetering in prognose gezien gedurende 1985 tot en met 1999. Ten opzichte van deze periode verbeterde de prognose wel in de periode 2000 tot en met 2008. Deze prognostische verbetering werd alleen gezien bij patiënten met een slechte LVEF en niet bij patiënten met een behouden LVEF. Bovendien werd de prognostische verbetering alleen gezien op de lange-termijn en niet op de korte-termijn. Het ontbreken van verbetering in de behandeling van *acuut* HF is waarschijnlijk de oorzaak dat de prognose op korte termijn niet verbeterde. Anderzijds is de belangrijkste oorzaak van de verbetering in prognose op lange termijn de verbetering in de behandeling van *chronisch* HF (met onder andere angiotensin-converting enzym [ACE] remmer, bètablokker, mineralocorticoïde receptor antagonist [MRA] en intracardiale defibrillator [ICD]). Deze veronderstelling wordt ondersteund door het feit dat (1) de verbeterde prognose alleen op de lange termijn werd gezien; (2) de ontwikkeling van nieuwe therapeutische opties synchroon liep met de prognostische verbetering; (3) de nieuw ontwikkelde therapie alleen bewezen effectief was bij patiënten met verminderde LVEF.

De hoofdstukken hierna behandelen de prognose en de verbetering hiervan in subgroepen van patiënten met acuut HF. **Hoofdstuk 3** beschrijft de verschillen in prognose tussen mannen en vrouwen met acuut HF. Van de geïncludeerde patiënten was de grote meerderheid man (64%). In deze studie hadden vrouwen een betere prognose dan mannen, zowel na 1 jaar follow-up (30% vs. 38%) als na 10 jaar follow-up (72% vs. 79%). Dit verschil was het meest uitgesproken bij patiënten met een slechte LVEF. Verder werd ook hier een verbetering gezien in klinische uitkomst bij patiënten opgenomen in de periode 2000-2008 vergeleken met patiënten opgenomen tussen 1985 en 1999. Deze betere uitkomst was vergelijkbaar tussen mannen en vrouwen. De conclusie is dan ook dat mannen en vrouwen evenveel baat hebben gehad van de verbetering in de behandeling van HF.

De verschillen in prognose van acuut HF-patiënten met of zonder diabetes mellitus zijn onderzocht in **hoofdstuk 4.** De verhouding tussen patiënten met en zonder diabetes was respectievelijk 21% vs. 79%. Wij zagen dat patiënten met diabetes een betere 30-dagen (9% vs. 16%), vergelijkbare 1-jaars (32% vs. 36%) en slechtere 10-jaars (87% vs. 76%) uitkomst hadden dan patiënten zonder diabetes. Een slechtere 30-dagen prognose is al eerder beschreven in de literatuur. De auteurs van dit artikel hadden hiervoor geen duidelijke verklaring en wij hebben die ook niet kunnen vaststellen. Een van de verklaringen zou kunnen zijn dat in onze studie de patiënten zonder diabetes vaker een cardiogene shock hadden hetgeen geassocieerd is met een slechtere prognose. Het prognostisch nadeel van patiënten met diabetes zal naast HF-gerelateerde factoren ook te verklaren zijn door lange-termijn complicaties door diabetes mellitus. De verbetering van de lange-termijn prognose was vergelijkbaar tussen de patiënten met en zonder diabetes. De prognostische verbetering van patiënten met diabetes is mogelijk niet alleen te verklaren door verbetering in de HF-behandeling, maar ook door een betere behandeling van de diabetes zelf.

In **Hoofdstuk 5** werd de relatie tussen nierfunctie, anemie en prognose in patiënten met acuut HF onderzocht. In de onderzochte populatie had 61% een verminderde nierfunctie, 18% had een ernstig gestoorde nierfunctie (eGFR <30). Daarnaast had ongeveer de helft van de patiënten een anemie. Een verminderde nierfunctie bleek een sterke voorspeller van slechte korte- en lange-termijn prognose. Hoe slechter de nierfunctie, hoe slechter de prognose. De lange-termijn prognose verbeterde niet over de tijd in patiënten met een verminderde nierfunctie, dit in tegenstelling tot patiënten met een behouden nierfunctie. Een verklaring hiervoor kan zijn dat patiënten met een verminderde nierfunctie minder vaak werden behandeld met de nieuw ontwikkelde medicijnen (zoals ACE-remmers en MRAs) aangezien die een negatieve invloed hebben op de nierfunctie. Om deze reden hadden deze patiënten niet het prognostische voordeel van deze medicijnen. Een andere mogelijke verklaring is de slechte prognose van de nierinsufficiëntie zelf. Daarnaast werd aangetoond dat ook de anemie zelf geassocieerd was met een slechtere korte-termijn prognose, onafhankelijk van de nierfunctie. Echter, voor de lange-termijn prognose was anemie alleen een voorspeller van slechte prognose bij patiënten met nierfalen en niet bij patiënten met een behouden nierfunctie. Het is onduidelijk wat dit verschil kan verklaren.

Een relatief nieuw concept in de cardiovasculaire wereld om prognose te bepalen, de zogenaamde *relative conditional survival*, werd behandeld in **Hoofdstuk 6.** *Relative survival* vergelijkt de overleving van de geïncludeerde patiënt met de prognose van een persoon uit de algemene bevolking met hetzelfde geslacht en dezelfde leeftijd. Bij het gebruik van *conditional survival* kan de prognose bepaald worden wat vanaf het moment dat de patiënt een bepaalde periode heeft overleefd. In deze studie bleek de *relative conditional survival* van patiënten met acuut HF slechter dan die van de algemene bevolking. Dit was ook zo na stratificatie op verschillende factoren. Deze bevinding is in de praktijk vooral van belang voor jonge patiënten. Een belangrijke bevinding was dat de prognose sterk verbeterde na overleving van het eerste jaar na de ziekenhuisopname. Clinici zouden *relative conditional survival* kunnen gebruiken om op een eenvoudiger manier de prognose met hun patiënt te bespreken.

Het onderzoek in **Hoofdstuk 7** is gebaseerd op een retrospectieve studie van 111 patiënten die in de periode van 2008 tot en met 2016 opgenomen waren vanwege *de novo,* acuut HF met een slechte LVEF. In totaal had 62% van deze patiënten niet-ischemisch hartfalen. We onderzochten specifiek de ontwikkeling van de linker ventrikel *remodeling*. Linker ventrikel *remodeling* werd vastgesteld door middel van linker ventrikel eind-diastolische en eind-systolische diameter en de ernst van mitralisklep insufficiëntie. Wij zagen dat herstel van LVEF veel vaker voorkwam (ongeveer 40%) bij patiënten met niet-ischemisch HF dan bij patiënten met ischemisch HF (10%). Linker ventrikel *remodeling* (voor de meerderheid in patiënten met niet-ischemisch HF) was in een belangrijk deel van de patiënten al aanwezig na 6 maanden follow-up en zette verder door gedurende de volgende 2 jaar follow-up. Er werd een belangrijke relatie gevonden tussen linker ventrikel *remodeling* en een betere prognose. Naast de etiologie van HF is optimale HF-behandeling met medicatie en devices van invloed op het optreden van de linker ventrikel *remodeling*.

Hoofdstuk 8 is gebaseerd op een review waarbij LVEF <35% als criterium voor een ICD-implantatie ter primaire preventie ter discussie wordt gesteld. Gebaseerd op de *landmark trials* bij patiënten met ischemisch en niet-ischemisch HF wordt daarin bepleit dat LVEF <30% (en symptomatisch HF) het (nieuwe) criterium zou moeten zijn voor een ICD-implantatie ter primaire preventie. Hiervoor zijn diverse valide redenen: (1) de meeste patiënten geïncludeerd in de studies hadden een LVEF <30%; (2) de oorspronkelijke studies zijn gedateerd, en sindsdien is de HF behandeling sterk verbeterd met een betere prognose en kleine kans op plotse hartdood als resultaat; (3) de kosteneffectiviteit van een ICD-implantatie neemt af door betere HF behandeling; (4) daarnaast blijft het risico op complicaties van de ICD bestaan.

Deel II: Patiënt-gerapporteerde uitkomsten in acuut hartfalen

De studies in dit proefschrift over patiënt-gerapporteerde uitkomsten zijn tot stand gekomen met data van de zogenaamde TRIUMPH studie. TRIUMPH was een prospectieve, observationele, multicenter studie van 496 patiënten opgenomen met acuut HF in de periode tussen september 2009 en december 2013. TRIUMPH onderzocht de klinische waarde van het herhaald meten van verschillende biomarkers. Onderzoek van de gezondheidsgerelateerde kwaliteit van leven was een tweede doel van deze studie. De gezondheidsgerelateerde kwaliteit van leven werd gemeten middels twee vragenlijsten: de Kansas City Cardiomyopathy Questionnaire (KCCQ) en EuroQuality-of-life 5 Dimensions (EQ-5D). Symptomen van angst en depressie werden gescoord met behulp van de Hospital Anxiety and Depression Scale (HADS). Tot slot was er een vragenlijst over het voorkomen van HF gerelateerde symptomen en de hierdoor ervaren symptoombelasting. Patiënten werden gevraagd om deze vragenlijst in te vullen bij het ontslag uit het ziekenhuis en na 9-12 maanden follow-up. In totaal vulden 70% van de geïncludeerde patiënten de vragenlijst in bij ontslag. Na 1 jaar follow-up vulde 60% van de toen nog levende patiënten de vragenlijst in.

Chronische nierinsufficiëntie, diabetes mellitus, chronische obstructieve longziekte (COPD) en cerebrovasculair accident (CVA) zijn vier niet-cardiale comorbiditeiten die vaak voorkomen in patiënten met HF. Het onderzoek beschreven in **Hoofdstuk 9** ging na wat de determinanten van gezondheidsgerelateerde kwaliteit van leven verschillend waren bij HF-patiënten met of zonder een van deze comorbiditeiten. De uitkomst van het onderzoek was dat HF-patiënten met comorbiditeit (61% van de geïncludeerde patiënten) bij ziekenhuisontslag slechtere gezondheidsgerelateerde kwaliteit van leven (gemeten met de KCCQ) en meer symptomen van depressie hadden dan patiënten zonder comorbiditeit. Ook na 1 jaar follow-up was de gezondheidsgerelateerde kwaliteit van leven slechter bij patiënten met comorbiditeit. Vrouwelijk geslacht, HF in de voorgeschiedenis, verhoogde BMI, hogere NT-proBNP concentratie, hogere systolische bloeddruk en de aanwezigheid van angst en depressie hadden een negatieve invloed op de gezondheidsgerelateerde kwaliteit van leven in HF-patiënten met comorbiditeit. Bij patiënten zonder comorbiditeit werden, behoudens angst en depressie, geen andere determinanten gevonden voor slechtere gezondheidsgerelateerde kwaliteit van leven. Bij hen is het HF zelf vermoedelijk de belangrijkste determinant van slechtere gezondheidsgerelateerde kwaliteit van leven.

De resultaten van het onderzoek beschreven in **Hoofdstuk 10** toonden aan dat HF-patiënten met depressie (37% van de geïncludeerde patiënten; depressie gedefinieerd volgens de HADS) meer symptomen en een hogere symptoomlast hadden dan patiënten zonder depressie. Daarnaast bleek dat patiënten met depressie een significant lagere gezondheidsgerelateerde kwaliteit van leven hadden dan patiënten zonder depressieve klachten. Deze bevindingen waren niet alleen aanwezig op baseline, maar ook na 1 jaar follow-up. De resultaten van deze studie benadrukken de noodzaak om depressie in HF-patiënten te herkennen en een adequaat behandelingsplan hiervoor op te stellen.

Deel III: Hartfalen op populatieniveau

In het derde deel van dit proefschrift werd gebruik gemaakt van gegevens van de zogenaamde Rotterdam Study. De Rotterdam Study is een prospectief cohortonderzoek bij een populatie in de Rotterdamse wijk Ommoord, die een redelijke afspiegeling vormt van de gemiddelde Nederlandse bevolking van oudere leeftijd. De studie startte in 1990 en betreft personen van 40 jaar en ouder. De Rotterdam Study onderzoekt de determinanten van verschillende ziekten, inclusief HF en andere cardiovasculaire ziekten.

In **Hoofdstuk 11** werd onderzocht wat de validiteit is van verschillende bestaande predictiemodellen om het ontwikkelen van HF in de komende 10 jaar te voorspellen. De onderzochte populatie bestond uit 2743 mannen en 3646 vrouwen van 55 jaar en ouder waarvan 429 (16%) mannen en 489 (13%) vrouwen HF ontwikkelden gedurende een mediane follow-up van 13 jaar. Het bleek dat het ACC/AHA model als een redelijk voorspelmodel kon worden aangemerkt bij zowel mannen als vrouwen. De nauwkeurigheid was vergelijkbaar met twee andere voorspelmodellen (ARIC model en Health ABC model), maar het voordeel van het ACC/AHA model is de eenvoud. Het bestaat uit relatief makkelijk te verkrijgen en te bepalen parameters en determinanten, zoals leeftijd, totaal cholesterol, HDL cholesterol, systolische bloeddruk, gebruik van antihypertensiva, rookverleden en diabetes. De toevoeging van de biomarker NT-proBNP aan het ACC/AHA model leidde tot een beperkte verbetering in de nauwkeurigheid van het model maar niet in een wijziging in de risicoclassificatie. Het gebruik van het ACC/AHA model, in combinatie met de toepassing van de geijkte leefstijlaanpassingen en andere therapeutische modaliteiten (medicatie), zonder twijfel kan een rol spelen bij de primaire preventie van HF bij zowel mannen als vrouwen.

Longitudinale veranderingen in de diastolische functie van de linker ventrikel met hun risicofactoren in zowel mannen en vrouwen zijn beschreven in **Hoofdstuk 12.** Echocardiografische metingen werden gedurende een periode van 11 jaar drie keer verricht in een populatie die bestond uit 630 mannen en 870 vrouwen zonder bekend HF. Vrouwen bleken ernstiger diastolische dysfunctie te hebben dan mannen. Niettemin was de leeftijdsgerelateerde verandering in parameters van de diastolische dysfunctie vergelijkbaar bij mannen en vrouwen gedurende een follow-up van 11 jaar. De risicofactoren hiervoor waren wel verschillend tussen beide geslachten. Terwijl bij vrouwen roken en een lager HDL cholesterol als de belangrijkste risicofactoren voor slechtere linker ventrikel diastolische functie over de tijd naar voren kwamen, werd achteruitgang van de diastolische functie onder mannen met name bepaald door de aanwezigheid van diabetes en een hoger BMI. Aangezien afname van diastolische functie geassocieerd is met de toekomstige ontwikkeling van HF, is de herkenning en behandeling van deze risicofactoren van belang om de ontwikkeling van HF te voorkomen.

Klinische consequenties

Gebaseerd op dit proefschrift kunnen verschillende lessen voor de klinische praktijk getrokken worden. Ten eerste, vanwege de slechte prognose van acuut HF, is het van groot belang dit ziektebeeld te voorkomen. Om *de novo* HF te voorkomen moeten de risicofactoren voor het ontwikkelen van HF vroeg herkend en adequaat behandeld worden. Uit dit proefschrift blijkt dat bijvoorbeeld diabetes, hypertensie en hypercholesterolemie belangrijke behandelbare risicofactoren voor HF zijn. Ook ten aanzien van de behandeling van deze risicofactoren zijn er nieuwe ontwikkelingen, zoals bijvoorbeeld SGLT2-remmers voor mensen met diabetes. De andere groep patiënten met acuut HF zijn patiënten met *acute-on-chronic* HF. Deze complicatie kan voorkomen worden door goede behandeling van chronisch HF. De eerste stap in de medicamenteuze behandeling bestaat uit ACE-remmers, bètablokkers, MRAs en diuretica. Als dit onvoldoende is moet gestart worden met meer geavanceerde therapie zoals angiotensin receptor neprilysin inhibitors(ARNI), cardiale resynchronisatie therapie en ivabradine. Nieuwe richtlijn suggereren dat ARNIs in een eerder stadium gegeven kunnen worden, namelijk in plaats van een ACE-remmer. Deze therapie kan niet alleen de achteruitgang van HF voorkomen, maar het kan zelfs linker ventrikel *remodeling* induceren. Dit is vooral bij patiënten met niet-ischemische oorzaak voor het HF van toepassing. Verder is nauwkeurige monitoring (bijv. met telemonitoring) van HF-patiënten veelbelovend bij het voorkomen van *acute-on-chronic* HF mits dit ook tot vroege en succesvolle interventie leidt. Tot slot zijn leefstijlaanpassingen (zoals vocht- en zoutbeperking) en niet-medicamenteuze interventies, welke verderop zullen worden besproken, zeker ook van belang in het voorkomen van acuut HF.

Ten tweede, aangezien *remodeling* van de linker ventrikel optreedt bij een aanzienlijk deel van de patiënten met *de novo* HF ingesteld op optimale therapie, ligt het gevaar op de loer om te vroeg te beslissen om over te gaan tot ICD-implantatie, harttransplantatie of LVAD-implantatie. Beide interventies kennen hun eigen, soms zelfs dodelijke, complicaties. Verder is, zeker in landen waar harttransplantatie of LVAD-implantatie niet of nauwelijks een optie is, het feit dat linker ventrikel *remodeling* mogelijk is met medicamenteuze therapie een belangrijke boodschap.

Ten derde moet overwogen worden om ICDs ter primaire preventie alleen te implanteren als de LVEF <30% is. Tot op heden is het implantatie criterium een LVEF <35%, maar deze aanbeveling is, zoals eerder besproken, gebaseerd op oude studies die vooral patiënten met LVEF <30% includeerden. ICD-shocks komen minder vaak voor sinds de behandeling van HF is verbeterd. Het risico op ICD-gerelateerde complicaties zoals onterechte shocks en device infectie blijft vanzelfsprekend echter aanwezig. Hierom dient de indicatie voor ICD-implantatie ter primaire preventie zorgvuldig overwogen te worden.

Ten vierde moeten cardiologen overwegen om *conditional survival* te gebruiken als ze het hebben over de prognose van de individuele patiënt. Traditioneel wordt prognose gerapporteerd in de vorm van cumulatieve survival. Het is echter lastig om dit op een begrijpelijke wijze aan de individuele patiënt uit te leggen. Bij het gebruik van *conditional survival* is de patiënt beter in staat te begrijpen wat zijn of haar verwachte prognose is.

Relative survival geeft patiënten extra informatie over hun prognose aangezien dit wordt afgezet tegen de prognose van de algemene bevolking van hetzelfde geslacht en met dezelfde leeftijd.

Ten vijfde moet er niet alleen aandacht zijn voor de prognose bij HF-patiënten, maar ook gezondheidsgerelateerde kwaliteit van leven. Hiervoor is het belangrijk om optimale HF-behandeling na te streven. Goede behandeling van comorbiditeit is een belangrijke factor in het verbeteren van gezondheidsgerelateerde kwaliteit van leven. Verder is het belangrijk om depressie te herkennen en dit ziektebeeld vervolgens ook adequaat te behandelen. Het is juist dat er overlap is in HF-symptomen en depressieve klachten. Daarom kan overwogen worden om een depressie screeningsinstrument te gebruiken bij patiënten met HF. Tot slot is het van belang om patiënten te verwijzen naar hartrevalidatie. Dit is, naast het verbeteren van gezondheidsgerelateerde kwaliteit van leven, ook effectief voor andere uitkomstent. Hartrevalidatie heeft al een sterke aanbeveling heeft in de richtlijnen, maar de klinische praktijk wijst uit dat het aantal verwijzingen verder zou moeten toenemen.

Ten zesde zouden clinici en patiënten meer aandacht moeten hebben voor het omgaan met symptomen, zeker ten aanzien van de verergering van klachten die duiden op een dreigend acuut HF. Dit kan op verschillende manieren. Educatie van patiënten, trainen van symptoomherkenning bij patiënten en psycho-educatie zijn aan de orde. Verder zou, in navolging van het ESC position paper over palliatieve zorg in HF, palliatieve zorg vaker moeten worden toegepast in patiënten met HF.

Tot slot blijft het belangrijk om te realiseren dat er verschillen zijn tussen mannen en vrouwen, zowel gevonden in het beschreven onderzoek als in de klinische praktijk. Wij vonden bijvoorbeeld verschillen in prognose, etiologie van HF, risicofactoren in het ontwikkelen van diastolische dysfunctie en verdeling in van goede versus slechte LVEF. Dergelijke verschillen hebben praktische betekenis.

Toekomstige uitdagingen

De korte-termijn prognose van patiënten met acuut HF is niet of nauwelijks verbeterd in de afgelopen jaren. Om deze reden is het belangrijk om nieuwe behandelingen voor het acuut HF te ontwikkelen. Tot op heden zijn de resultaten van de verschillende studies echter teleurstellend. Een van de redenen hiervoor kan zijn dat acuut HF een heterogeen ziektebeeld is. Het is juist dat in de richtlijnen wordt aanbevolen om triggers voor acute decompensatie zoals acuut coronair syndroom, ritmestoornissen en hypertensieve emergency zo snel mogelijk te behandelen om verder verslechtering te voorkomen. Maar niettemin er is nog geen behandeling voor het HF zelf op het acute moment. Verder onderzoek naar gepersonaliseerde behandeling van acuut HF is nodig.

Tot op heden is het onduidelijk wat de beste behandeling is van patiënten met een herstelde LVEF. Onderzoek suggereert dat het stoppen van HF-medicatie negatieve gevolgen heeft. Over het algemeen gebruiken patiënten met een herstelde LVEF levenslang ACE-remmers en bètablokkers, overige HF medicatie wordt meestal beëindigd. Duidelijk wetenschappelijk bewijs voor deze handelwijze ontbreekt echter.

Ondanks dat HF een heterogeen ziektebeeld is, geven richtlijnen aanbevelingen die gelden voor het hele spectrum van HF patiënten en niet verder zijn toegespitst op de verschillende fenotypes. Gedilateerde cardiomyopathie is met name een erg heterogeen ziektebeeld. De prognose zou mogelijk kunnen verbeteren als, naast de huidige HF behandeling, doelgerichte therapie gericht op de etiologie of pathofysiologisch mechanisme gegeven zou worden. Verschillende studies naar doelgerichte therapie zijn al gedaan of worden nog verricht, maar er zijn maar enkele therapieën die ook daadwerkelijk zijn opgenomen in de richtlijnen.

CHAPTER 15

Dankwoord

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Dr. M. Kavousi, beste Maryam, via Jaap ben ik betrokken geraakt met de Rotterdam Study. Het begon allemaal met het coderen van hartfalen events, maar via jou heb ik ook kansen gekregen om mee te mogen werken aan artikelen. Wie weet zit er nog een vervolg in.

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Iemand die zeker niet mag ontbreken in mijn dankwoord is dr. R.T. van Domburg. Ron, ik kan me het moment van onze kennismaking nog herinneren. Al vanaf het eerste moment wist je me te enthousiasmeren om mijn masteronderzoek bij jou te doen. Je nuchtere en pragmatische kijk op bepaalde zaken was soms een verademing. Jij wist ingewikkelde statistische problemen te vereenvoudigen zodat het voor iedereen te begrijpen was. Ik zou je tekortdoen als ik niet zou vermelden dat jij degene was die ervoor heeft gezorgd dat ik dit promotietraject ben begonnen. Al tijdens mijn masteronderzoek vroeg jij of ik een PhD-traject wilde starten. Uiteindelijk is dit proefschrift eruit voortgekomen. Nogmaals dank!

Als je mensen bij naam gaat noemen, schuilt altijd het gevaar dat je anderen vergeet. Geloof me, dat is niet met opzet. Ik wil alle coauteurs bedanken voor hun bijdrage aan mijn manuscripten. Daarnaast wil ik alle collega's bedanken die op wat voor wijze hun bijdrage hebben geleverd. Dank aan alle promovendi en studenten uit 'het hok' (Ee-218 en later Ee-1640) voor de gezellige momenten die we hebben gehad. In dit kader denk ik ook aan de promovendi van de KLEP-groep. Als 'adoptiekindje' van de KLEP-groep heb ik de wetenschappelijke discussies en ontspannen momenten zeer gewaardeerd.

Na 3 jaar onderzoek ben ik gestart in de kliniek. Dank aan alle arts-assistenten, opleiders en specialisten in het Albert Schweitzer Ziekenhuis en het Erasmus MC voor de fijne en leerzame tijd die ik heb gehad. Ondertussen ben ik al enige tijd werkzaam in het Ikazia Ziekenhuis, het zit er al weer bijna op. Het is een genoegen om deel te mogen zijn van jullie team! Vanaf dag 1 voelde ik me op m'n plek en nu zit mijn tijd bij jullie er al weer op. Ik hoop dat de 'Ikazia sfeer' altijd behouden zal blijven.

Dank aan Henk-Jan en Stefan dat jullie mijn paranimfen willen zijn. Hoewel het een puur ceremoniële functie lijkt te zijn (en dat is het eigenlijk ook), vind ik het fijn om jullie aan mijn zijde te hebben tijdens mijn verdediging. Henk-Jan, onze vrouwen zijn er 'schuldig' aan dat we elkaar kennen (waarvoor dank). Al jaren zijn we goede vrienden en ik hoop dat dit nog lange tijd zo zal blijven. Stefan, mijn stabiel en rustig broertje. Je had vast niet verwacht om ooit paranimf te zijn.

Ik ben ervan overtuigd dat je op je werk alleen kan functioneren als er in de privésfeer mensen achter je staan. Ik wil dan ook alle familie en vrienden bedanken die op wat voor wijze met me hebben meegeleefd en hebben geholpen. Vaak heb ik uit moeten leggen wat voor onderzoek ik deed en wat promotieonderzoek inhoudt. Bij de meesten is dat tot op vandaag volgens mij nog steeds niet duidelijk, maar dat geeft niet. Ik hoop dat het na mijn 'lekenpraatje' tijdens mijn verdediging duidelijk geworden is.

In het bijzonder wil ik mijn (schoon)ouders nog noemen. Pa en ma, bedankt voor de steun die jullie me hebben gegeven. We zijn een familie van weinig woorden, maar ik weet dat jullie achter me staan. Enorm veel dank aan mijn schoonouders voor hun nimmer aflatende interesse tijdens het hele promotraject.

Lieve Afke, het zit erop! Jij was me vaak kwijt toen ik weer avond aan avond achter de laptop moest, met name de laatste jaren toen ik het moest combineren met mijn klinische werkzaamheden. Jij stimuleerde me altijd om door te gaan, ook al was mijn motivatie soms wat minder. Je was en bent er altijd voor me. Ik hoop er vanaf nu ook weer meer voor jou te zijn.

Lieve Thomas en Sarah, jullie enthousiasme als ik thuiskom, stimuleert me iedere dag weer om snel naar huis te komen. Ik hoop vanaf nu meer tijd te hebben voor datgene waar jullie zo van genieten: samen spelen, boekjes lezen en andere leuke dingen doen. Jullie maken mij een trotse papa!

CHAPTER 16

List of publications

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Unpublished

1. **van den Berge JC**, Constantinescu AA, van Domburg RT, Deckers JW, Akkerhuis KM. Trends in long-term mortality in women compared to men with acute heart failure between 1985 and 2008. *Submitted*
2. **van den Berge JC,** van Vark LC, Postmus D, Utens EMWJ, Hillege HL, Boersma E, Lesman-Leegte I, Akkerhuis KM. Symptoms and depression in acute heart failure patients. *Submitted*
3. **van den Berge JC,** van Vark LC, Postmus D, Utens EMWJ, Hillege HL, Boersma E, Lesman-Leegte I, Akkerhuis KM. Determinants of quality of life in acute heart failure patients with and without comorbidities. *European Journal of Cardiovascular Nursing: accepted for publication*
4. Deckers JW, Arshi B, **van den Berge JC,** Constantinescu AA. Preventive ICD-therapy in Contemporary Clinical Practice; More stringent selection criteria long overdue. *ESC Heart Failure: accepted for publication*

Published

1. **van den Berge JC**, Vroegindewey MM, Veenis JF, Brugts JJ, Caliskan K, Manintveld OC, Akkerhuis KM, Boersma E, Deckers JW and Constantinescu AA. Left ventricular remodelling and prognosis after discharge in new-onset acute heart failure with reduced ejection fraction. *ESC Heart Failure*. 2021.
2. Baart SJ, **van den Berge JC,** Akkerhuis KM, Deckers JW, van Domburg RT, Boersma E and Kardys I. Relative conditional survival analysis provides additional insights into the prognosis of heart failure patients. *European Journal of Preventive Cardiology*. 2021.
3. Arshi B, **van den Berge JC,** van Dijk B, Deckers JW, Ikram MA and Kavousi M. Implications of the ACC/AHA risk score for prediction of heart failure: the Rotterdam Study. *BMC Med*. 2021;19:43.
4. Brankovic M, Akkerhuis KM, Hoorn EJ, van Boven N, **van den Berge JC,** Constantinescu A, Brugts J, van Ramshorst J, Germans T, Hillege H, Boersma E, Umans V and Kardys I. Renal tubular damage and worsening renal function in chronic heart failure: Clinical determinants and relation to prognosis (Bio-SHiFT study). *Clin Cardiol*. 2020;43:630-638.
5. Veenis JF, Boiten HJ, **van den Berge JC,** Caliskan K, Maat A, Valkema R, Constantinescu AA, Manintveld OC, Zijlstra F, van Domburg RT and Schinkel AFL. Prediction of long-term (> 10 year) cardiovascular outcomes in heart transplant recipients: Value of stress technetium-99m tetrofosmin myocardial perfusion imaging. *J Nucl Cardiol*. 2019;26:845-852.
6. Rueda-Ochoa OL, Smiderle-Gelain MA, Rizopoulos D, Dhana K, **van den Berge JK,** Echeverria LE, Ikram MA, Deckers JW, Franco OH and Kavousi M. Risk factors for longitudinal changes in left ventricular diastolic function among women and men. *Heart*. 2019;105:1414-1422.
7. **van den Berge JC,** Constantinescu AA, van Domburg RT, Brankovic M, Deckers JW and Akkerhuis KM. Renal function and anemia in relation to short- and long-term prognosis of patients with acute heart failure in the period 1985-2008: A clinical cohort study. *PLoS One*. 2018;13:e0201714.
8. **van den Berge JC,** Constantinescu AA, Boiten HJ, van Domburg RT, Deckers JW and Akkerhuis KM. Short- and Long-term Prognosis of Patients With Acute Heart Failure With and Without Diabetes: Changes Over the Last Three Decades. *Diabetes Care*. 2018;41:143-149.
9. Boiten HJ, **van den Berge JC,** Valkema R, van Domburg RT, Zijlstra F and Schinkel AFL. Ischemia burden on stress SPECT MPI predicts long-term outcomes after revascularization in stable coronary artery disease. *J Nucl Cardiol*. 2018;25:958-966.

10. Ariotti S, van Leeuwen M, Brugaletta S, Leonardi S, Akkerhuis KM, Rimoldi SF, Janssens GN, Ortega-Paz L, Gianni U, **van den Berge JC,** Karagiannis A, Windecker S, Valgimigli M and Investigators H-T. Effects of Ticagrelor, Prasugrel, or Clopidogrel at Steady State on Endothelial Function. *J Am Coll Cardiol*. 2018;71:1289-1291.

11. Ariotti S, Ortega-Paz L, van Leeuwen M, Brugaletta S, Leonardi S, Akkerhuis KM, Rimoldi SF, Janssens G, Gianni U, **van den Berge JC,** Karagiannis A, Windecker S, Valgimigli M and Investigators H-T. Effects of Ticagrelor, Prasugrel, or Clopidogrel on Endothelial Function and Other Vascular Biomarkers: A Randomized Crossover Study. *JACC Cardiovasc Interv*. 2018;11:1576-1586.

12. Ariotti S, van Leeuwen M, Brugaletta S, Leonardi S, Akkerhuis KM, Rexhaj E, Janssens G, Ortega-Paz L, Rizzotti D, **van den Berge JC,** Heg D, Francolini G, Windecker S, Valgimigli M and Investigators H-T. Rationale and design of the Hunting for the off-target propertIes of Ticagrelor on Endothelial function and other Circulating biomarkers in Humans (HI-TECH) trial. *Am Heart J*. 2017;189:128-136.

13. **van den Berge JC,** Dulfer K, Utens E, Hartman EMJ, Daemen J, van Geuns RJ and van Domburg RT. Predictors of subjective health status 10 years post-PCI. *Int J Cardiol Heart Vasc*. 2016;11:19-23.

14. **van den Berge JC,** Akkerhuis MK, Constantinescu AA, Kors JA, van Domburg RT and Deckers JW. Temporal trends in long-term mortality of patients with acute heart failure: Data from 1985-2008. *Int J Cardiol*. 2016;224:456-460.

15. **van den Berge JC,** Utens EM, Dulfer K, Hartman EM, van Geuns RJ, Daemen J and van Domburg RT. Can anxiety and depression, separately or in combination predict subjective health status 10 years post-PCI? *Int J Cardiol*. 2015;186:57-9.

16. Hartman EM, Dulfer K, Utens EM, **van den Berge JC,** Daemen J and van Domburg RT. Gender differences in quality of life after PCI attenuate after a 10 year follow-up. *Int J Cardiol*. 2014;176:1179-80.

CHAPTER 17

PhD portfolio

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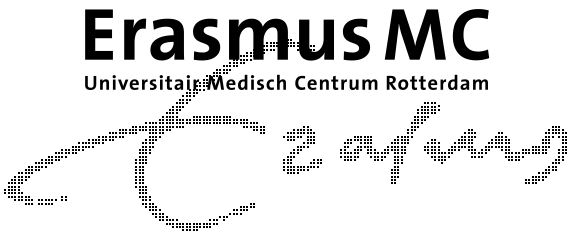

PhD Portfolio Summary

Summary of PhD training and teaching activities

Name PhD student: J.C. van den Berge
Erasmus MC Department: Cardiology
Research School: COEUR

PhD period: 2015-2021
Promotor(s): Prof. dr. J.W. Deckers
Supervisor: dr. K.M. Akkerhuis

1. PhD training

	Year	Workload (Hours/ECTS)
General academic skills		
• BROK course	2016	1.5
• Systematic Literature Retrieval	2017	0.9
Research skills		
• Biostatistical Methods I: Basic Principles	2016	2
• Survival Analysis	2016	1.4
• Regression Analysis	2017	1.4
In-depth courses (e.g. Research school, Medical Training)		
• COEUR PhD Course 'Heart Failure Research'	2016	1.5
• COEUR PhD Course 'Cardiovascular Imaging and Diagnostics'	2017	1.5
• COEUR PhD Course 'Congenital Heart Disease' Part I	2017	0.5
• COEUR PhD Course 'Intensive Care' Part I	2017	0.5
• COEUR PhD Course 'Sex and Gender in Cardiovascular Research	2018	0.5
• COEUR PhD Course 'Pathophysiology of Ischemic Heart Disease'	2018	1

International conferences

• NVVC voorjaarscongres in Noordwijkerhout with oral abstract presentation	2016	1.1
• ESC Heart Failure congress in Florence with oral abstract presentation	2016	1.7
• ESC Congress in Rome with poster presentation	2016	1.8
• NVVC voorjaarscongres in Arnhem with oral abstract presentation	2016	1.1
• NVVC voorjaarscongres in Noordwijkerhout with oral abstract presentation	2017	1.1
• NVVC voorjaarscongres in Arnhem	2017	0.6
• NVVC voorjaarscongres in Noordwijkerhout with oral abstract presentation	2018	1.1
• ESC Heart Failure congress in Vienna with poster presentations	2018	2.1

Other

• COEUR Research Seminar 'Current insights in inherited cardiomyopathies'	2015	0.2
• COEUR Symposium 'Translational Research'	2016	0.2
• COEUR Symposium 'Omics in Cardiovascular Medicine Research'	2017	0.4
• COEUR Symposium 'Enhancing precision medicine through protein biomarker profiling'	2017	0.2
• Fundamental Critical Care Support Course	2019	1.5
• Advanced Life Support Course	2019	1.5
• CVOI cursus "Anamnese en lichamelijk onderzoek"	2021	0.5

2. Teaching activities

	Year	Workload (Hours/ECTS)
Lecturing		
• Journal Club	2017	0.3
• Journal Club	2018	0.3
• Presentation ESC Guideline	2019	0.3
Supervising practicals and excursions		
• 2nd year medical students: performing a systematic review	2016	0.6
• 2nd year medical students: performing a systematic review	2017	0.6
• 2nd year medical students: performing a systematic review	2018	0.6

CHAPTER 18

About the author

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About the author

Jan Cornelis (Jan-Kees) van den Berge was born in Goes, the Netherlands, on the 19th of June 1991. After graduating secondary school (Calvijn College, Goes) in 2009, he started medical school at the Erasmus University Rotterdam. He obtained his medical degree in 2015. He subsequently started his PhD-project at the department of Cardiology of the Erasmus Medical Center (supervisors: prof. dr. Jaap W. Deckers and dr. K. Martijn Akkerhuis). The results of this research are presented in this thesis. In October 2018, he became a resident at the department of Internal Medicine and Cardiology of the Albert Schweitzer Hospital in Dordrecht (supervisors: dr. Peter J. H. Smak Gregoor and Ewout-Jan van den Bos). Afterwards, he started as resident at the department of Cardiology of the Erasmus Medical Center in Rotterdam in August 2019. In December 2019, he was accepted as resident in training to cardiologist (supervisors: dr. Tjebbe W. Galema and dr. Eric A. Dubois). Now, he is working at the department of Internal Medicine of the Ikazia Hospital in Rotterdam (supervisors: dr. Felix E. de Jongh and drs. M. Wabbijn).
Besides, he is married to Afke Bout. They have two children, named Thomas and Sarah.