BNP and NT-proBNP in cardiovascular disease

Linssen, Gerardus Christiaan Maria

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CIP-GEGEVENS KONINKLIJKE BIBLIOTHEEK, DEN HAAG

Linssen, G.C.M.
BNP and NT-proBNP in cardiovascular disease.

Proefschrift Groningen – Met literatuuropgave en samenvatting in het Nederlands.

Part of the research described in this thesis was supported by a grant of the Dutch Heart Foundation (2000Z003).
Part of the research was supported by a grant of the Dutch Kidney Foundation (E.013).

ISBN 978-94-6191-084-4

Lay out: Ontwerpbureau Demeneer, Enschede.
Cover illustration: “Lovely Heart” by Anne Linssen.
Printed by: Ipskamp Drukkers, Enschede, the Netherlands.

rijksuniversiteit groningen

BNP and NT-proBNP in cardiovascular disease

Proefschrift

ter verkrijging van het doctoraat in de
Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. E. Sterken,
in het openbaar te verdedigen op
maandag 28 november 2011
om 16.15 uur

door

Gerardus Christiaan Maria Linssen
geboren op 17 augustus 1961
te Maasbracht

Promotores:	Prof. dr. D.J. van Veldhuisen
	Prof. dr. J.L. Hillege
	Prof. dr. A.A. Voors
	Prof. dr. T. Jaarsma
Beoordelingscommissie:	Prof. dr. M.P. van den Berg
	Prof. dr. W.H. van Gilst
	Prof. dr. A.W. Hoes

Paranimfen: Dr. Ivonne G.A.T. Lesman-Leegte
Drs. Susanne M. van der Sluijs

Financial support by the following sponsors for the publication of this thesis is gratefully acknowledged:

Rijksuniversiteit Groningen, UMCG, Raad van Bestuur van de Ziekenhuisgroep Twente (ZGT Almelo en Hengelo), Maatschap Almelose Cardiologen, Stichting Hartcentrum Twente, Withering Stichting Nederland (WSN), Amgen, Bayer, Boehringer Ingelheim, MSD, Novartis Pharma, Roche Diagnostics, Servier, Sorin Groep

Contents

Chapter 1

Introduction and aims of the thesis

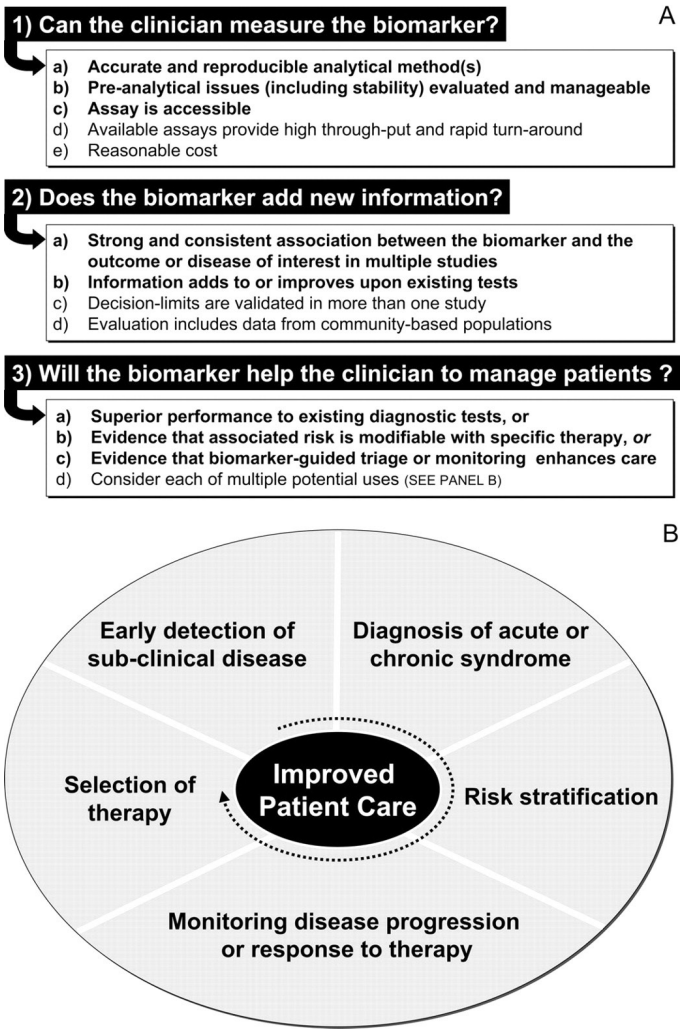
Introduction

In the last decades, the field of management of cardiovascular diseases (CVD) has moved forward impressively, offering large numbers of patients and subjects at risk for acute and chronic diseases of the heart and vessels a better survival, decreased morbidity and an improved quality of life.

In recent years the role of biomarkers, which are specific analytical tests on enzymes, hormones, and other biological substances mostly derived from the blood or urine, has become increasingly important and has expanded exponentially.[1,2] Biomarkers may optimally serve as simple, non-invasive tools to select alternative strategies to personalize risk stratification, advanced diagnostic testing and medical therapies. As such, a "perfect" biomarker has the ability to define the presence of cardiovascular disease, to select those individuals who are at high risk for future adverse events and benefit from an intervention. Morrow and de Lemos have proposed three basic criteria for (new) candidate biomarkers to be addressed: firstly, can the clinician measure it, secondly, does it add new information, and thirdly, does it help the clinician better manage patients, see *Figure 1 (Panel A).*[3] The desired attributes of a cardiovascular biomarker to improved patient care depend on how it is intended to be used. Common clinical applications are presented in *Figure 1 (Panel B).* In clinical cardiology, serum biomarkers are established tools in the evaluation and management of patients with (suspected) acute and chronic ischemic heart diseases. The use and interpretation of cardiac markers including troponins are fundamental for the diagnosis of myocardial infarction. Both central laboratory and point-of-care testing strategies can be applied. Faster medical decision making may be achieved by point-of-care assays in the prehospital setting, in ambulances and in remote locations like cruise ships.

In the field of heart failure (HF), accounting for a growing number of affected and hospitalized patients in the Western world, major diagnostic and therapeutic advances have led to earlier identification and improved clinical outcome. However, the prognosis of a substantial number of HF patients is still adverse. Selection of earlier and more effective therapies may improve outcome in those patients. The clinical application of established biomarkers in HF holds promise to meet those needs. In recent years, biomarker evaluation, particularly testing of circulating B-type natriuretic peptides has become an integral part of acute and chronic HF management, after thousands of papers published, a decade of clinical experience and incorporation in international guidelines.[4-8]

Figure 1. Evaluation of biomarkers in cardiovascular medicine



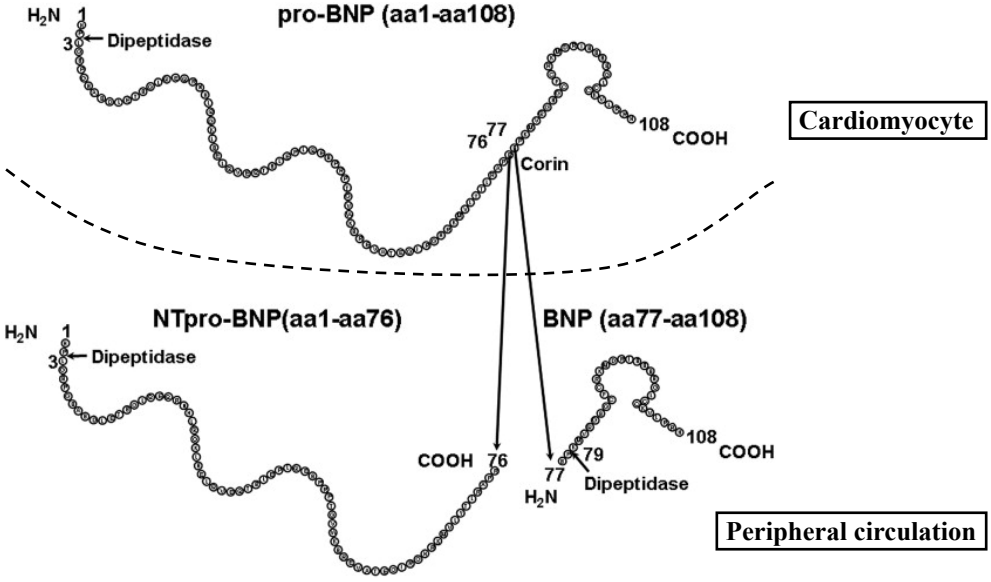
Panel A: criteria for assessment of novel cardiovascular biomarkers for clinical use.

Statements in bold fonts are the highest priority.

Panel B: Clinical application of cardiovascular biomarkers.

Reprinted with permission from Morrow et al.[3]

Figure 2. ProBNP processing



ProBNP is a 108-amino acid (aa) precursor protein which is cleaved by the endoprotease corin to form the bioactive 32 aa BNP peptide (referred to as BNP_{1-32} or as $proBNP_{77-108}$) and the inert 76 aa N-terminal-proBNP peptide ($proBNP_{1-76}$). Each fragment undergoes further N-terminal dipeptidase digestion, as might proBNP itself. BNP = B-type natriuretic peptide.

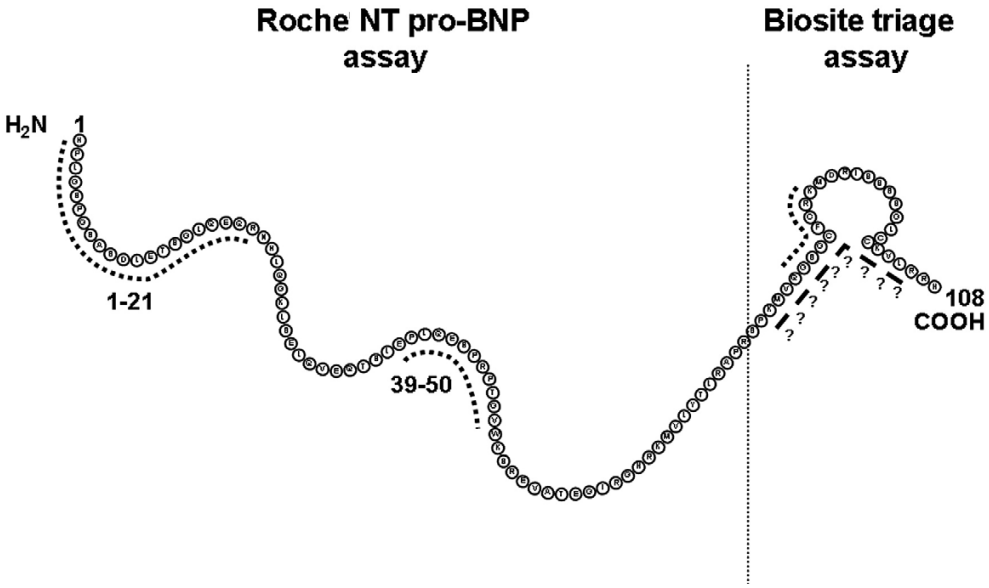
Reprinted with permission from Lam et al.[11]

Biology of B-type natriuretic peptides

The biological active B-type natriuretic peptide (BNP, amino acids 77-108) and its corresponding inactive fragment amino-terminal proBNP (NT-proBNP, amino acids 1-76) are secreted predominantly from the myocardium into the circulation, as a response to cardiomyocyte stretch, see *Figure 2*.[9-11]

The genetic expression and myocardial secretion is also modulated by many other factors including neurohumoral activation and hypoxia/myocardial ischemia. The main source of (NT-pro)BNP is the left ventricle (LV), although significant secretion from the atria and right ventricle may occur in advanced HF, severe valvular heart disease or pulmonary embolism and hypertension.[5,12,13] The proteolytic cleavage of the prohormone proBNP (amino acids 1-108), largely within the cardiomyocytes, produces equimolar amounts of BNP and NT-proBNP which can be detected in the peripheral circulation and measured by commercially available immunoassays.[11] In *Figure 3*, two common and widely used immunoassays of BNP and NT-proBNP, respectively, are depicted. Both assays are also used in the setting of the observational studies which are described in this thesis.

Figure 3. Commercial BNP or NT-proBNP assays



Commercial BNP or NT-proBNP assays utilize dual antibody systems which recognize 2 separate segments of BNP1-32 or of NT-proBNP1-76, respectively. (Left) The Roche NT-proBNP assay combines a capture antibody targeting proBNP aa 1-21 with a detection antibody recognizing proBNP aa 39-50. (Right) The Biosite Triage assay combines the monoclonal Scios 106.3 antibody, which binds somewhere in the proBNP aa 82-90 region, with the Biosite polyclonal antibody, which binds somewhere in the proBNP aa 79-108 region. Other abbreviations as in Figure 2.

Reprinted with permission from Lam et al.[11]

Interestingly, among patients with HF, those analytical assays appear to measure also significant amounts of circulating proBNP and fragments of BNP, which have no or markedly reduced biological activity.[11,14,15] The physiologic effects of BNP include renal excretion of sodium and water, vasodilatation by relaxation of vascular smooth muscle cells, improved diastolic relaxation, inhibition of the renin-angiotensin system, and prevention of myocardial fibrosis.[10] BNP has a shorter half-life due to both renal clearance and active enzymatic and receptor-clearance. Circulating levels of the more stable NT-proBNP are therefore 5-10 fold higher than BNP.[16] Plasma levels of BNP and NT-proBNP are relatively higher in older subjects, females, in anemic patients and in case of impaired renal function.[17-26] Levels are inversely related to obesity.[27,28] Both analytical and particularly biological variation of plasma levels are significant, in total up to 25-50%, and therefore, need to be taken into account when interpreting serial test results, e.g. in the tailored management of HF patients.[5] In *Table 1*, characteristics of BNP and NT-proBNP are summarized.

Table 1. Characteristics of BNP and NT-proBNP

	BNP	NT-proBNP
Amino acids	32	76
Molecular weight (kD)	3.47	8.46
Half-life (min)	22	60-120
Clearance	NEP, NPC-R, renal	Renal and extra-renal
Biologically active	Yes	No
Point-of-care	Yes	Yes
Analytical range (pg/mL)	5-5000	5-35,000
Reference values (pg/mL)	< 20-30	< 125 (≤ 75 years) < 450 (> 75 years)

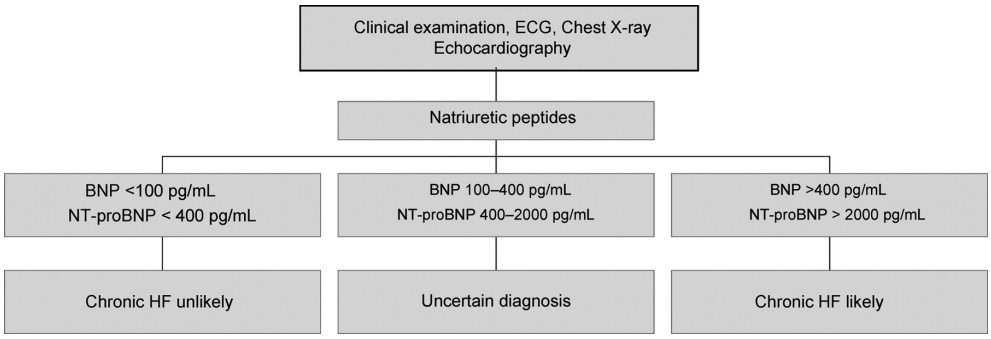
BNP = brain natriuretic peptide; eGFR = estimated glomerular filtration rate (in mL/min/1.73 m^2); NT-proBNP = amino-terminal pro-hormone BNP; kD = kiloDalton; NEP = neutral endopeptidase; NPC-R = natriuretic peptide clearance receptor.

SI conversion factors: To convert BNP to picomoles per liter, divide by 3.47; NT-proBNP to picomoles per liter, divide by 8.46.

Clinical applications of BNP and NT-proBNP in heart failure

Numerous clinical studies revealed that levels of both peptides correlate well with severity of heart failure, and positively with LV geometry, pressure, volume loading and dysfunction (particularly systolic and to a lesser degree in cases with diastolic impairment). The use of BNP and NT-proBNP is incorporated in current guidelines on the diagnosis and treatment of acute and chronic HF.[6-8] In *Figure 4*, an algorithm for the diagnosis of HF or LV dysfunction is shown.

Figure 4. Diagnosis of heart failure



Flow chart according to the European guidelines for the diagnosis of heart failure (HF) with natriuretic peptides in untreated patients with symptoms suggestive of HF.

SI conversion factors: To convert BNP to picomoles per liter, divide by 3.47; NT-proBNP to picomoles per liter, divide by 8.46.

Reprinted with permission from Dickstein et al.[6]

The degree of elevation of plasma levels of (NT-pro)BNP is associated with worse outcome in both acute and chronic HF and augments risk stratification.[4,5] Observational HF studies demonstrated that serial monitoring of (NT-pro)BNP provides independent prognostic information incremental to single baseline values.[29-35] Plasma levels in HF can not only be used to monitor and predict the response to medical therapy, (acutely) unloading the heart, but also reflects, semi-quantitatively, the response to biventricular pacing in patients with advanced HF, which correlated with changes in LV volumes and ejection fraction.[36,37] In view of the compelling evidence for widespread use of the powerful biomarkers BNP and NT-proBNP in the broad spectrum of HF, the concept of BNP/NT-proBNP guided therapy seems attractive to improve clinical outcome. However, several randomized clinical trials have showed heterogeneous results which may be explained by different patient profiles, target levels of BNP/NT-proBNP, titration protocols and outcome measures.[38] Especially in patients younger than 75 years a significant survival benefit of BNP/NT-proBNP guided medical therapy was observed.[39] One of the proposed mechanisms of benefit in the younger age group is the higher rate of achieved target dose of ACE inhibitors and betablockers in the hormone-guided group. The older age group (≥75 years), derived less survival benefit from BNP/NT-proBNP guided therapy, which may partly be related to more comorbid diseases, impairing the ability to tolerate target doses of HF medication. Nevertheless, knowledge of a patient's BNP or NT-proBNP level when clinically stable remains to be very useful for monitoring, as a substantial increase (>25%) during follow-up indicates an important clinical change and high risk of decompensation, while also taken indices of clinical status and renal function into account.[4,5,40]

Although, a large amount of data on both BNP and NT-proBNP are reported in the literature, there remain several important epidemiological and clinical issues to be clarified. For example, the added value of measurement of B-type natriuretic peptides as part of screening strategies in cohorts of the general population, the prognostic performance in heart failure patients with preserved left ventricular function and the association with the presence of atrial fibrillation (AF). Furthermore, there are few clinical data on direct comparisons of BNP and NT-proBNP in heart failure. A mechanistic question to be addressed is the influence of (impaired) renal function on the clearance and plasma levels of NT-proBNP, particularly in heart failure patients.

Therefore, this thesis focuses on clarifying those issues.

Aims of this thesis

1. to establish the prognostic value of plasma NT-proBNP in subjects of the general population,

2. to investigate the incremental prognostic properties of plasma NT-proBNP in subjects of the general population with electrocardiographic left ventricular hypertrophy (LVH),

3. to compare the prognostic performance of BNP and NT-proBNP in heart failure patients after discharge for decompensated heart failure.

4. to investigate the prognostic value of BNP and NT-proBNP in heart failure patients with reduced versus those with preserved left ventricular ejection fraction (LVEF)

5. to study the association of NT-proBNP and the presence of atrial fibrillation (AF) in heart failure patients with reduced versus those with preserved LVEF, and in addition the impact of AF on clinical outcome in both LVEF groups,

6. to assess the impact of renal function on the urinary excretion of NT-proBNP in patients with stable chronic heart failure.

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Chapter 2

N-terminal pro-B-type natriuretic peptide independently predicts cardiovascular morbidity and mortality in the general population

Gerard C.M. Linssen, Stephan J.L. Bakker, Adriaan A. Voors, Ron T. Gansevoort, Hans L. Hillege, Paul E. de Jong, Dirk J. van Veldhuisen, Rijk O.B. Gans, Dick de Zeeuw

Eur Heart J. 2010;31:120-127

Abstract

Aims

Natriuretic peptides including N-terminal pro-B-type natriuretic peptide (NT-proBNP) are established biomarkers in heart failure. However, their prognostic value in the general population is less well established. The purpose of our study was to investigate the prognostic properties of NT-proBNP for death and cardiovascular (CV) events in the general population.

Methods and results

In the population-based Prevention of Renal and Vascular End-stage Disease (PREVEND) study, 8383 subjects were prospectively followed for a median period of 7.5 years. There were 4181 (49.9%) males and 4202 (50.1%) females, mean age was 49.3±12.7 years (range 28-75). Median NT-proBNP at baseline was 37.7 pg/mL (IQR 16.8-73.8). All-cause death occurred in 437 (5.2%) subjects and there were 557 CV events. Higher levels of plasma NT-proBNP were related to higher event rates. When adjusted for age, gender, and other relevant covariates, each doubling of NT-proBNP remained significantly associated with a 22% increased risk for all-cause mortality (P<0.001) and a 16% increased risk of CV events (P<0.001).

Conclusions

In this large community-based cohort, plasma NT-proBNP was a strong predictor of death and a wide range of CV events.

Keywords

Cardiovascular diseases, Epidemiology, Natriuretic peptides, Population, Prognosis

Introduction

Natriuretic peptides including brain-type natriuretic peptide (BNP) and its equimolarly secreted N-terminal fragment (NT-proBNP) are established biomarkers for diagnosis, prognosis and management, in particular in patients with established cardiovascular disease and heart failure.[1-8]

In the general population, however, the prognostic value of these peptides is less well established. Wang et al. were the first to describe the prognostic value of BNP in participants of the Framingham Offspring Study.[9] In another community-based cohort from Olmsted County, both BNP and NT-proBNP were shown to predict mortality.[10] Three European groups reported on the predictive value of NT-proBNP in small samples of the general population.[11-13]

In the present study we investigated the independent prognostic value of NT-proBNP in so far the largest sample of the general population, consisting of 8383 subjects. Our cohort is also characterized by a wider age-range of adult subjects (28-75 years) and a long follow-up with a substantially higher number of cardiovascular events compared to the previous studies.

Methods

This study was performed in subjects participating in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study. This project was designed to prospectively investigate the natural course of increased levels of urinary albumin excretion (UAE) and its relation to renal and cardiovascular disease in a large cohort drawn form the general population. Details of this protocol have been described elsewhere.[14,15] In summary, in the period 1997 to 1998, all inhabitants of the city of Groningen, The Netherlands, aged 28 to 75 years, were sent a 1-page postal questionnaire and a vial to collect an early morning urinary sample (N=85,421). Of these subjects, 40,856 responded (47.8%) and sent a vial to a central laboratory where urinary albumin and creatinine concentrations were measured. After exclusion of subjects with type 1 diabetes mellitus (defined as the use of insulin) and pregnant women, all subjects with a UAE of $\geq$ 10 mg/L (N=6000) and a randomly selected control group with UAE <10 mg/L (N=2592) were further investigated in an outpatient clinic and asked to collect two consecutive 24-hour urines. These 8592 subjects form the PREVEND cohort. In 8383 subjects plasma levels of NT-proBNP were measured. They comprise the current study population.

All subjects gave written informed consent. The PREVEND study was approved by the local medical ethical committee, and is conducted in accordance with the guidelines of the Declaration of Helsinki.

Analytical methods

NT-proBNP measurements were performed in plasma on an Elecsys™ 2010 analyser, a commercially available electrochemiluminescent sandwich immunoassay (Elecsys

proBNP, Roche Diagnostics, Mannheim, Germany). The intra- and interassay coefficient of variation were 1.2-1.5% and 4.4-5.0% respectively, with an analytical range of 5-35,000 pg/mL.[16] Conversion of NT-proBNP levels: 100 pg/mL equates to 11.82 pmol/L. Urinary albumin excretion was determined by nephelometry, with a threshold of 2.3 mg/L and intra- and interassay coefficients variation of 2.2% and 2.6%, respectively (BNII, Dade Behring Diagnostica, Marburg, Germany). High-sensitive CRP was also determined by nephelometry with a threshold of 0.175 mg/L and intra- and inter-assay coefficients of less than 4.4 and 5.7% respectively.

Definitions and calculations

Systolic and diastolic blood pressures were calculated as the mean of the last two measurements of the two visits. Hypertension was defined as having a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg and/or use of anti-hypertensive medication. Body mass index (BMI) was calculated as the ratio of weight and height (kg/m^2). Type 2 diabetes was defined as a fasting glucose level of ≥7.0 mmol/L (126 mg/dL) or a non-fasting glucose level of ≥11.1 mmol/L (200 mg/dL) or the use of anti-diabetic drugs. Hypercholesterolemia was defined as a serum cholesterol ≥6.5 mmol/L (251 mg/dL) or a serum cholesterol ≥5.0 mmol/L (193 mg/dL) if a history of myocardial infarction was present or when lipid lowering medication was used. Smoking was defined as current smoking or stopped smoking within the previous year. Histories of myocardial infarction (MI) or cerebrovascular disease were considered present if a participant reported having been hospitalized for at least three days because of these conditions. An elevated CRP was defined as a level >3 mg/L. UAE was calculated as the average urinary albumin excretion in the two consecutive 24-hour urine collections. An estimate of the glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease (sMDRD) formula.[17, 18]

Electrocardiography

Standard 12-lead electrocardiograms were recorded with Cardio Perfect equipment (Cardio Control, Rijswijk, the Netherlands), stored digitally using the computer program MEANS (Modular Electrocardiogram Analysis System). Left ventricular hypertrophy (LVH) was identified using Cornell voltage-duration product, which was calculated as follows: RaVL + SV_3 (with 6 mm added in women) times QRS duration. A threshold of 2440 mm.ms was used to identify LVH.[19, 20]

Cardiovascular events

For cardiovascular outcome we used the combined incidence of cardiovascular morbidity and mortality after the baseline screening. Data on mortality were received through the municipal register. Cause of death was obtained by linking the number of the death certificate to the primary cause of death as coded by the Dutch Central Bureau

of Statistics. Information on hospitalisation for cardiovascular morbidity was obtained from PRISMANT, the Dutch national registry of hospital discharge diagnoses. All data were coded according to the International classification of diseases, 9th revision and the classification of interventions. For this study cardiovascular events were defined as the following; acute myocardial infarction (ICD-code 410), acute and subacute ischemic heart disease (411), subarachnoid hemorrhage (430), intracerebral hemorrhage (431), other intracranial hemorrhage (432), occlusion or stenosis of the precerebral (433) or cerebral arteries (434), coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA), and other vascular interventions as percutaneous transluminal angioplasty (PTA) or bypass grafting of aorta and peripheral vessels. Survival time was defined as the period from the date of urine collection of the participant to the date of first cardiovascular event or January 1st 2006. In case a person had moved to an unknown destination, the date on which the person was removed from the municipal registry was used as census date.

Statistical analyses

Continuous variables with a normal distribution are expressed as means with standard deviation (SD). Variables with a skewed distribution, such as UAE, CRP and NT-proBNP, are given as medians with interquartile range (IQR). Differences in proportions were tested using χ^2 analysis and Fisher's exact test. Differences in continuous variables between quintiles of NT-proBNP levels were tested using weighted ANOVA. For the screening of the PREVEND study we overselected subjects with an elevated UAE to acquire sufficient subjects with microalbuminuria. It should be clear that this is not a simple random sample from an infinite population, where all sampling elementary units have an equal probability of being sampled. Within this context, statistical formulas to calculate population parameter estimates should taken into account the probability of selection. To overcome this oversampling of subjects with elevated UAE a design-based analysis was performed. Due to this statistical weighting method our conclusions can be generalized to the general population. The design-based Cox proportional-hazards regression models evaluating the prognostic properties of NT-proBNP to the risk of death or CV events were built with STATA (Statistical Software release 10.0, StataCorp LP, College Station, Texas, USA). The multivariable model was adjusted for all confounders: age, gender, smoking, medical history, waist-hip ratio, BMI, systolic and diastolic blood pressure, serum cholesterol, serum HDL-cholesterol, serum glucose, eGFR, mean 24 h UAE, CRP and LVH (*Table 1*).

Table 1.Baseline characteristics according to the plasma NT-proBNP levels (total population, n=8383)

Characteristic	Total	Quintiles of NT-proBNP (pg/mL)					*P*-value
Quintile		1	2	3	4	5	
NT-proBNP, min – max		5.0-13.3	13.3-28.2	28.2-48.8	48.8-87.5	87.5-35,000	
Mean		7.4	20.7	37.8	65.1	336.5	
n	8383	1677	1677	1676	1677	1676	
Age, years	49.3±12.7	44.1±9.9	46.2±11.2	48.1±11.9	50.7±12.7	57.4±13.1	<0.001
Female gender (%)	4202 (50.1)	348W (20.7)	705 (42.0)	986 (58.9)	1123 (67.0)	1040 (62.1)	<0.001
Smoking, n (%)	3160 (37.8)	645 (38.6)	664 (39.8)	647 (38.7)	614 (36.7)	590 (35.3)	0.058
Medical history							
Diabetes, n (%)	310 (3.8)	64 (3.9)	52 (3.2)	47 (2.8)	51 (3.1)	96 (5.8)	<0.001
Myocardial infarction, n (%)	513 (6.2)	47 (2.9)	57 (3.5)	62 (3.8)	86 (5.2)	261 (15.9)	<0.001
Hypertension, n (%)	2642 (32.0)	396 (24.1)	390 (23.6)	434 (26.2)	560 (33.9)	862 (52.2)	<0.001
Hypercholesterolemia, n (%)	2179 (26.4)	456 (27.6)	390 (23.7)	396 (24.1)	421 (25.5)	516 (31.3)	<0.001
Stroke, n (%)	78 (1.0)	6 (0.4)	11 (0.7)	14 (0.9)	18 (1.1)	29 (1.8)	0.001
Waist-hip ratio	0.88±0.10	0.91±0.08	0.88±0.09	0.87±0.10	0.88±0.10	0.88±0.10	<0.001
BMI, kg/m^2	26.1±4.2	26.5±3.9	26.0±4.3	25.8±4.2	26.0±4.4	26.3±4.3	0.18
Systolic BP, mm Hg	129.1±20.3	128.1±14.8	126.1±17.7	125.4±18.6	128.3±20.8	137.6±25.7	<0.001
Diastolic BP, mm Hg	74.0±9.8	74.8±8.4	73.4±9.3	72.6±9.5	73.3±10.0	75.9±11.1	0.006
Serum cholesterol, mmol/L	5.6±1.1	5.8±1.1	5.6±1.2	5.6±1.1	5.6±1.1	5.7±1.1	0.001
Serum HDL-cholesterol, mmol/L	1.3±0.4	1.2±0.3	1.3±0.4	1.4±0.4	1.4±0.4	1.4±0.4	<0.001
Serum glucose, mmol/L	4.9±1.2	5.0±1.3	4.9±1.2	4.8+1.0	4.8±1.0	5.0±1.3	0.20
eGFR, mL/min/1.73 m^2	80.7±14.7	85.4±13.7	83.2±13.7	80.7±13.7	79.4±14.5	74.7±15.4	<0.001
Mean 24 h UAE, mg/24 h[a]	9.5(6.3-17.9)	9.2(6.5-16.3)	9.0(6.3-15,6)	8.7(6.0-15.1)	9.4(6.1-17.2)	11.7(6.8-29.8)	<0.001
CRP, mg/L[a]	1.3(0.6-3.0)	1.1(0.5-2.4)	1.1(0.5-2.6)	1.2(0.5-2.8)	1.4(0.6-3.1)	2.0(0.9-4.4)	<0.00
LVH, n (%)	420 (5.1)	57 (3.4)	59 (3.5)	69 (4.1)	69 (4.1)	166 (9.9)	<0.001

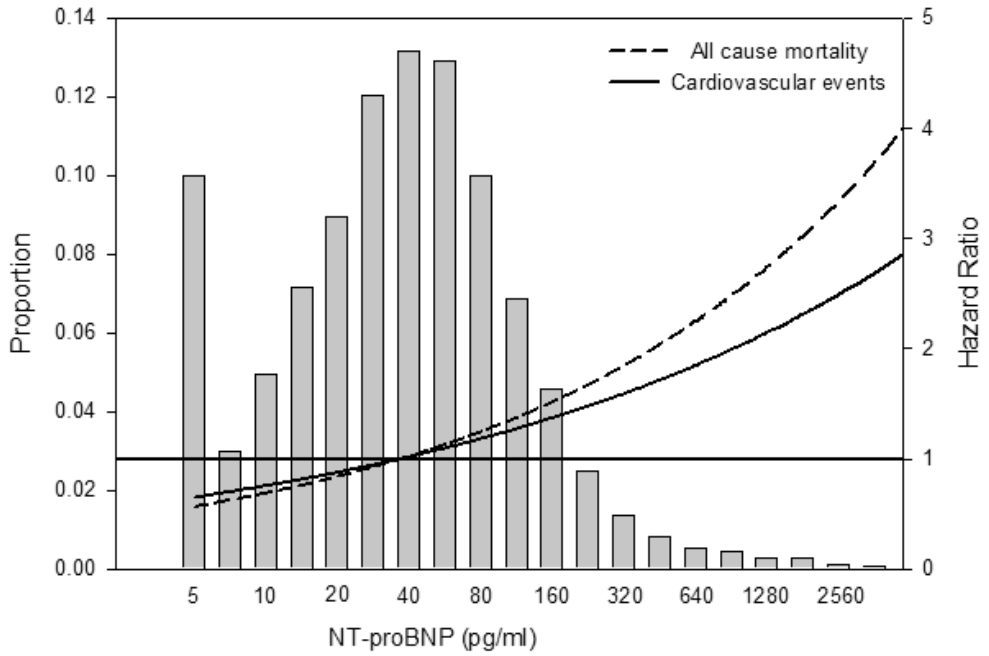
BP indicates blood pressure; BMI, body mass index; UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate by simplified Modification of Diet in Renal Disease (sMDRD) formula; LVH, left ventricular hypertrophy was identified on standard 12-lead electrocardiogram. Conversion of N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels: 100 pg/mL equates to 11.82 pmol/L. All continuous variables are presented as mean±SD. [a]Continuous variable is presented as median value (25th-75th percentiles).

Results are summarized by hazard (risk) ratios (HR) with 95% confidence intervals (CI). NT-proBNP showed a log-linear functional shape with the response variable and was transformed to a 2-log scale. This means that risk estimates should be interpreted as the relative risk if values of NT-proBNP were doubled (e.g. 10 to 20 pg/mL). All reported probability values are 2-tailed and $P<0.05$ was considered statistically significant. The independent contribution or NT-proBNP was explored crude, age and sex adjusted and by modelling in a mutually adjusted model. In addition, we calculated the incremental value of NT-proBNP beyond CRP by means of Harrel's C concordance statistics. Analyses were performed using the Statistical Package for Social Sciences software (SPSS version 14.0.1 for Windows, SPSS Inc., Chicago, Illinois, USA) and STATA software (STATA version 10.0, College Station, Texas, USA).

Results

A total of 8383 subjects were followed for a median of 7.5 years (IQR 7.3-7.9). The median NT-proBNP level at baseline was 37.7 pg/mL (IQR 16.8-73.8). *Figure 1* shows the frequency-distribution of plasma levels of NT-proBNP. The majority of subjects (83.4%) had a level below 100 pg/mL (11.8 pmol/L). Baseline characteristics of the participants according to quintiles of plasma NT-proBNP are presented in *Table 1*. The population consisted of 4181 (49.9%) males and 4202 (50.1%) females. Mean age was 49.3±12.7 years (28-75). Individuals in the highest quintile of NT-proBNP levels were generally older, more often female, and more often had a history of hypertension and/or myocardial infarction, hypercholesterolemia and stroke. Furthermore, subjects in the highest quintile had higher BP, serum cholesterol, UAE and CRP levels, while they had lower values of eGFR and more often LVH on the ECG at baseline in comparison to subjects in the lower four quintiles (P for all <0.001).

Figure 1. Frequency distribution of plasma levels of N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP) and multivariable adjusted hazard ratios on the risk of cardiovascular events and all-cause mortality.



Values below the detection limit are reported as 5 pg/mL.

All-cause mortality and cardiovascular events

A total of 437 (5.2%) subjects died and there were 557 CV events during follow-up. *Table 2* shows the numbers of all prespecified endpoints according to quintiles of NT-proBNP levels. In the fifth quintile of NT-proBNP, about half of the total number of events occurred. In *Figure 2* Kaplan-Meier curves are plotted for CV events by quintiles of NT-proBNP extrapolated to the original screening sample numbers. CV outcome of subjects in the highest quintile of NT-proBNP (>87.5 pg/mL (10.3 pmol/L)) was worse in comparison to the lower four quintiles. However, there were no statistically significant differences with regard to CV outcome between the first four quintiles. The majority of CV events were of cardiac origin.

Five year incidences of CV morbidity/mortality were 3.50% (95% CI 3.10-3.97), with cerebral and cardiac event rates of 0.77% (95% CI 0.60-1.00) and 2.73% (95% CI 2.38-3.16) respectively.

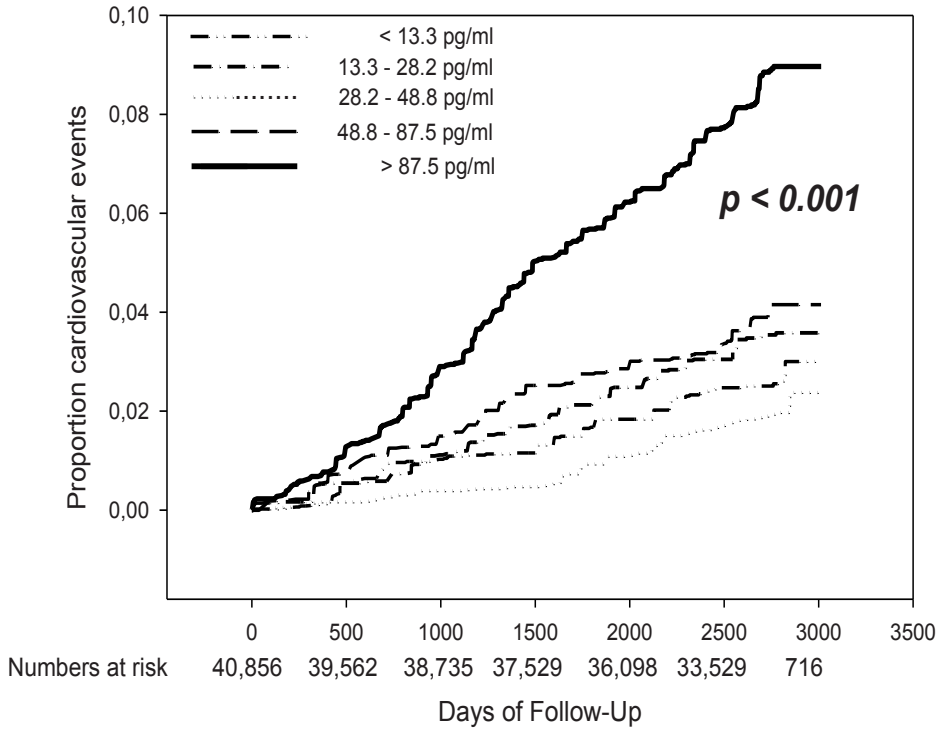
Table 2 . Events according to quintiles of the N-terminal pro-B-type natriuretic peptide level

Event	Number of events	Quintiles of NT-proBNP (pg/mL)				
Quintile		1	2	3	4	5
NT-proBNP min – max		5.0-13.3	13.3-28.2	28.2-48.8	48.8-87.5	87.5-35,000
All-cause death	437	25	55	57	71	229
Cardiovascular events	557	62	62	82	99	252
Cardiac morbidity	385	52	47	54	69	163
Myocardial infarction	147	25	23	21	21	57
Ischemic heart disease	111	8	11	15	23	54
PTCA	78	11	9	11	16	31
CABG	49	8	4	7	9	21
Cardiac mortality	24	0	2	3	0	19
Cerebral morbidity[a]	116	10	9	19	26	52
Cerebral mortality	4	0	1	0	0	3
Peripheral morbidity[b]	28	0	3	6	4	15

[a]Cerebral morbidity is defined as CVA and arterial disease, carotid desobstruction, and cerebral (subarachnoid or intracerebral or other intracranial) hemorrhage.

[b]Peripheral morbidity is defined as peripheral arterial or aorta surgery, and percutaneous transluminal angioplasty.

Figure 2. Kaplan-Meier plot for cardiovascular events by quintiles (Q) of N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP).



Doubling of NT-proBNP was univariably associated with a 1.56-fold increased risk of all-cause mortality (*P*<0.001; *Table 3*), a 1.37-fold increased risk of CV events (*P*<0.001; *Table 3*) and a 1.38 increased risk of non-cardiovascular death (*P*<0.001; *Table 3*). When adjusted for age, gender, and all other baseline characteristics listed in *Table 1*, doubling of NT-proBNP was still significantly associated with a 1.22-fold increased risk of all-cause mortality (*P*<0.001; *Table 3*) and a 1.16-fold increased risk of cardiovascular events (*P*<0.001; *Table 3*). However, doubling of NT-proBNP was not associated with non-cardiovascular death (HR 1.07; *P*=0.45; *Table 3*).

Multivariable hazards ratios on the risk of CV events and all-cause death are presented in *Figure 1*. For reference, a NT-proBNP concentration of 40 pg/mL, which is approximately the median value, was defined as a HR of 1.0. *Figure 3* shows that at a similar level of NT-proBNP male subjects are at higher risk for mortality and CV events than female subjects. There was however no significant influence of gender on the relationship between NT-proBNP and prognosis. Finally, only marginal model improvements in the fully adjusted model were observed in Harrel's C concordance statistics regarding CRP alone versus CRP and NT-proBNP: 0.838 versus 0.841, respectively (*P* = NS).

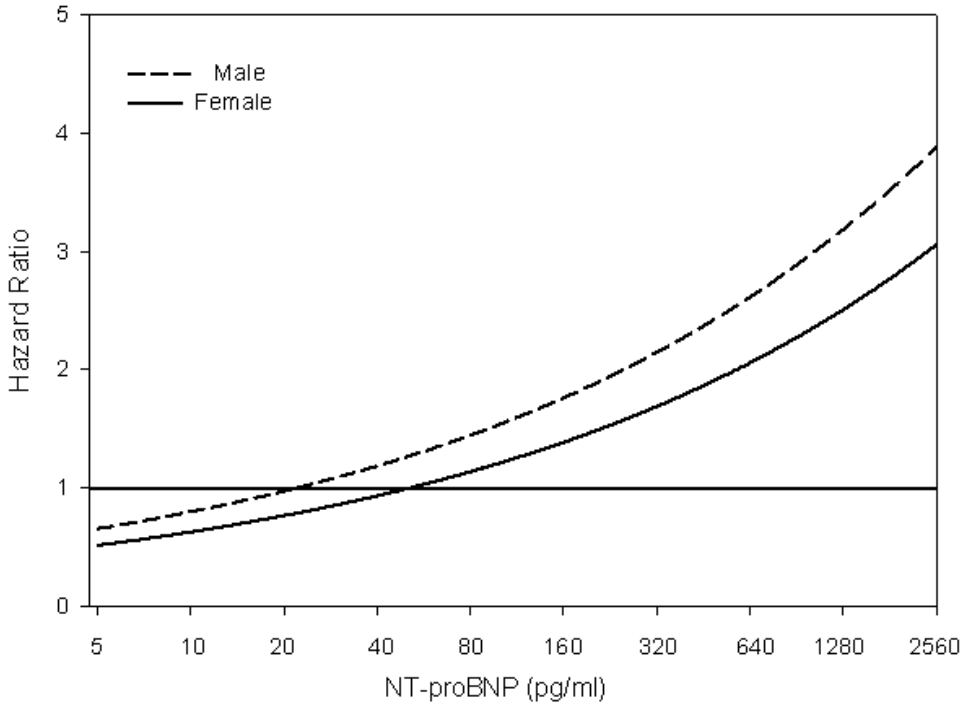
Table 3. Hazard ratios for all-cause mortality, cardiovascular mortality, and non-cardiovascular mortality according to doubling of N-terminal pro-B-type natriuretic peptide

	Hazard ratio	T	95% CI	P-value
For all-cause mortality				
Unadjusted model	1.56	10.07	1.43–1.70	<0.001
Model 1	1.27	4.88	1.16-1.41	<0.001
Model 2	1.22	3.89	1.10-1.35	<0.001
For cardiovascular events				
Unadjusted model	1.37	6.85	1.25-1.50	<0.001
Model 1	1.22	4.19	1.11-1.33	<0.001
Model 2	1.16	2.78	1.05-1.29	<0.005
For non-cardiovascular mortality				
Unadjusted model	1.38	4.77	1.20-1.57	<0.001
Model 1	1.11	1.41	0.95-1.28	0.16
Model 2	1.07	0.76	0.90-1.27	0.45

Model 1: age and gender adjusted model.

Model 2: multivariate model adjusted for all characteristics as presented in *Table 1*.

Figure 3. Multivariable adjusted hazard ratios on the risk of all-cause mortality and cardiovascular events in female and male subjects according to the level of N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP).



Discussion

The main finding of the present study is that plasma NT-proBNP independently predicted all-cause mortality and cardiovascular events in the general population. Our large PREVEND cohort is characterized by a wide age-range (28-75 years) and more than 60.000 subject-years of follow-up, which is considerably more than any other comparable study to date.

Particularly in the highest quintile of NT-proBNP [plasma level >87.5 pg/mL (10.3 pmol/L)] markedly higher event rates during follow-up were found in comparison to the lower four quintiles. Kaplan-Meier survival curves indicated that the risk of mortality and cardiovascular events was particularly increased in patients with NT-proBNP levels of >87.5 pg/mL. This might suggest a cut-off level. However, it should be noted that the fifth quintile showed a less favourable cardiovascular risk profile including a substantial higher mean NT-proBNP concentration when compared with the other quintiles. The adjusted models demonstrated a gradual increased risk of mortality and cardiovascular events with increasing levels of NT-proBNP, without a clear cut-off.

Each doubling of NT-proBNP was associated with a 56% increase in all-cause mortality and a 37% increase in CV events. After adjustment for age, gender and other relevant covariates, the increased risks remained significant, 22% and 16%, respectively. Interestingly, neither CRP nor eGFR and mean 24 h UAE influenced the prognostic value of NT-proBNP.

In three studies of the general population, NT-proBNP was found to be predictive for CV events and mortality.[11-13] First, in a population-based study of 626 participants aged 50 to 89 years free of heart or renal failure from a community in Copenhagen, the adjusted HR for mortality during 5 years of follow-up for values above the 80th percentile of NT-proBNP was 1.96 (95% CI 1.21-3.19) and for first major CV event 3.24 (95% CI 1.80-5.79), respectively.[11] In another study Laukkanen *et al.*[12] reported on the predictive power of NT-ANP and NT-proBNP with respect to CV events and mortality in a sample of 905 men (age 46-65 years) from eastern Finland. The third study was a community-based sample of 2656 individuals (41, 51, 61, or 71 years of age) from Denmark, where CV risk prediction improved by using NT-proBNP.[13] In the Olmsted County study in 1991 subjects from the general population, aged ≥ 45 years, both NT-proBNP and BNP were evaluated as biomarkers for predicting mortality.[10] In their multivariable model the HR per 1-SD increase in Log Variable of NT-proBNP for all-cause mortality during 7 years of follow-up was 1.44 (CI 1.08-1.94, P=0.014). In the Framingham Offspring Study, in which 3346 subjects participated, the level of BNP independently predicted death, heart failure, atrial fibrillation, and stroke during a mean follow-up period of 5.2 years.[9] In selected populations with an increased risk, (NT-pro)BNP can be applied for further risk stratification.[21-24] In the previous community-based studies the rates of all-cause mortality ranged from 0.6 to 3% per year.[9-12] The highest mortality rate was found in the study from Copenhagen in which subjects where older (mean age of 68 years).[11]

In our PREVEND study all-cause death occurred in 0.7% of subjects per year during a median follow-up period of 7.5 years. Taken both the wider age range (28-75 years) and the lower mean age of the participants of our study also into consideration, our cohort comprises a representative sample of the community.

In the reported studies, different natriuretic peptide assays and antibodies were used. These differences in precision and performance of analytical methods may have influenced the predictive value of those peptides. Furthermore, the magnitude of the effects of NT-proBNP on mortality and cardiovascular outcome differs between studies. We analysed the effects of doubling of NT-proBNP, while in previous studies several other methods were used.[11-13]

Although NT-proBNP was associated with both cardiovascular and non-cardiovascular mortality, in multivariable analysis, NT-proBNP was only associated with cardiovascular mortality. Therefore, increased NT-proBNP in the general population seems to be associated with an increased risk of predominantly cardiovascular disease, and might therefore reflect underlying silent or overt cardiovascular disease. Slight elevations of NT-proBNP may represent subtle cardiac remodelling. Elevated natriuretic peptides reflect increased atrial or ventricular stretch from pressure or volume overload. An increased left ventricular filling pressure in the setting of diastolic dysfunction may be the underlying mechanism of the association between elevated natriuretic peptides and mortality in the general population.[21-25] Additional mechanisms, in which natriuretic peptides play a role in vascular function and remodelling, may also be important. Besides myocardial stretch and ischemia, other factors including endothelin, angiotensin II and tumor necrosis factor α have been found to stimulate secretion of BNP in vitro.[26,27] Both cardiac myocytes and fibroblasts secrete BNP which leads to fibrosis through induction of matrix metalloproteinases.[28] The increased vascular reactivity and myocardial alterations enhanced by local and circulating factors may progress to cardiovascular disease.[29] Subclinical myocardial ischemia, hypertrophy and fibrosis induce elevated cardiac filling pressures which result in increased myocardial stretch enhancing synthesis and release of B-type natriuretic peptides. Furthermore, ischemic or injured myocardial tissue releases additional BNP irrespective of hemodynamic factors.[30,31]

Risk stratification using biomarkers will help to identify those subjects in the community who may benefit most from advanced diagnostic testing and therapeutic intervention. However, whether specific preventive strategies or treatment may be of benefit for subjects with increased NT-proBNP remain to be addressed before this biomarker can be applied for routine screening purposes.[32-34]

Limitations

The present study has several limitations. We measured NT-proBNP only once and without correction for potential variability in concentrations. The PREVEND cohort is predominantly white, and our findings may not be representative for non-whites. However, the finding that the percentage of all deaths in the present study that is classified as being due to CV disease is in line with previous prospective studies of subjects of the general population. Echocardiography was not part of our study design. It may have provided additional information in the early detection of CV disease.

Conclusions

In our large community-based cohort, plasma NT-proBNP was a strong predictor of the risk of death and a wide range of cardiovascular events. Higher values might reflect subclinical CV disease such as LVH, diastolic dysfunction or even asymptomatic LV systolic dysfunction.

Acknowledgments

The authors acknowledge the Trial Coordination Center, Groningen, the Netherlands.
We are grateful to Dade Behring Diagnostica, Marburg, Germany; and Roche Diagnostics, Mannheim, Germany for providing tests, assay kits and technical support.

Funding

The PREVEND study was financially supported by grant E.013 of the Netherlands Kidney Foundation.
Prof. van Veldhuisen and Prof. Voors are Clinical Established Investigators of the Netherlands Heart Foundation (grant D97.017 and grant 2006T037).

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Chapter 3

Left ventricular hypertrophy in the general population only predicts cardiovascular events when NT-proBNP is elevated

Gerard C.M. Linssen, Stephan J.L. Bakker, Adriaan A. Voors, Ron T. Gansevoort, Paul E. de Jong, Dick de Zeeuw, Rijk O.B. Gans, Dirk J. van Veldhuisen, Hans L. Hillege

Abstract

Purpose

Left ventricular hypertrophy (LVH) is a frequent finding on routinely performed electrocardiography (ECG), and is related to an increased cardiovascular risk. The purpose of our study was to investigate the added value of the use of NT-proBNP for predicting cardiovascular (CV) events in subjects with LVH on their ECG.

Methods

We investigated 8292 participants of the population-based Prevention of Renal and Vascular End-stage Disease (PREVEND) study. There were 4129 (49.8%) males and 4163 (50.2%) females, mean age was 49±13 years (range 28-75). In 420 (5.1%) subjects, LVH was identified on baseline ECG. Time to first major CV event was analysed.

Results

LVH was associated with higher plasma levels of NT-proBNP at baseline, median 61.8 pg/mL (IQR 25.1-182.6) versus no LVH, median 36.9 pg/mL (IQR 16.5-71.6), (P<0.001). During follow-up for 10.4 years (IQR 8.1-10.8), a total of 808 CV events occurred in 548 (6.6%) of subjects. The majority of CV events were cardiac: 584 of which 62 were cardiac deaths. There were 185 cerebral and 39 peripheral events. LVH was related to higher CV event rates, 70 in 50 (11.9%) subjects with LVH versus 738 in 498 (6.3%) subjects without LVH, hazard ratio (HR) 1.94 (95% CI 1.25 – 3.03, P<0.002). In subjects with LVH and NT-proBNP <100 pg/mL, event rate was identical to those without LVH and NT-proBNP <100 pg/mL. However, in subjects with NT-proBNP >100 pg/mL, subjects with LVH did worse than those without LVH.

Conclusions

LVH on ECG is only predictive for CV events in subjects with elevated NT-proBNP. Therefore, when LVH is found on ECG, measurement of NT-proBNP might further help to risk stratify these subjects.

Keywords

Cardiovascular diseases, Left ventricular hypertrophy, Natriuretic peptides, Population, Prognosis

Introduction

Currently, B-type natriuretic peptides (BNP and NT-proBNP) are widely used in the diagnostic assessment and prognostic evaluation of cardiovascular (CV) diseases, particularly heart failure and ischemic syndromes.[1-3] Recently, we demonstrated that plasma NT-proBNP independently predicted all-cause mortality and cardiovascular events in a large cohort of the general population.[4]

Left ventricular hypertrophy (LVH) is a subclinical manifestation of cardiovascular (CV) end-organ damage which may evolve to ventricular dysfunction, heart failure, and sudden cardiac death. The presence of LVH is an established risk factor for future CV events.[5] LVH is associated with myocardial fibrosis, increased LV stiffness and diastolic dysfunction, which together contribute to an increased gene expression and secretion of myocardial B-type natriuretic peptides into the circulation.[6]

The identification of LVH on the ECG may therefore signal increased CV risk. However, the specificity of ECG criteria is not optimal. Also, some subjects with LVH might do better than others. Natriuretic peptides might be helpful to further improve risk stratification of patients with LVH on their ECG, and might potentially reduce the burden of additional investigations, such as echocardiography.

Therefore, we evaluated the added value of NT-proBNP on risk stratification in a subgroup of a community-based cohort, who had LVH according to a simple and readily available 12-lead ECG.

Methods

Study population

This study was performed in subjects participating in the prospective Prevention of Renal and Vascular End-stage Disease (PREVEND) study. This project sought to investigate the natural course of increased levels of urinary albumin excretion rate (UAE) and its relation to renal and cardiovascular disease in a large cohort from the community. Details of this protocol have been described elsewhere.[7,8] In summary, in the period 1997 to 1998, all inhabitants of the city of Groningen, the Netherlands, aged 28 to 75 years, were sent a 1-page postal questionnaire and a vial to collect an early morning urinary sample (N=85,421). Of these subjects, 40,856 responded (47.8%) and sent a vial to a central laboratory where urinary albumin was measured. After exclusion of subjects with type 1 diabetes mellitus (defined as the use of insulin) and pregnant women, all subjects with a UAE of $\geq$ 10 mg/L and a randomly selected control group with UAE <10 mg/L were invited for detailed evaluation in an outpatient clinic, and N=6000 and N=2592, respectively, responded. These 8592 subjects form the PREVEND cohort. In 8292 subjects plasma levels of NT-proBNP were measured and complete electrocardiographic data were available.

Study design

The screening program in the outpatient clinic consisted of two visits within one week. At the first visit, participants completed a self-administered extended questionnaire regarding demographics by a trained nurse. Furthermore, blood pressure and anthropometric measurements (weight and height; waist and hip circumference) were done. Subjects were asked to collect 24-hour urine on two consecutive days. The second visit comprised of electrocardiographic recordings, blood pressure measurements and taking fasting blood samples. Measurements of urinary volume, albumin, and creatinine concentration were performed on each collection.

All subjects gave written informed consent. The PREVEND study was approved by the local medical ethical committee, and is conducted in accordance with the guidelines of the Declaration of Helsinki.

Analytical methods

NT-proBNP measurements were performed in plasma on an Elecsys™ 2010 analyser, a commercially available electrochemiluminescent sandwich immunoassay (Elecsys proBNP, Roche Diagnostics, Mannheim, Germany). The intra- and interassay coefficient of variation were 1.2-1.5% and 4.4-5.0% respectively, with an analytical range of 5-35,000 pg/mL.[9] Conversion of NT-proBNP levels: 100 pg/mL equates to 11.82 pmol/L. UAE was determined by nephelometry, with a threshold of 2.3 mg/L and intra- and interassay coefficients variation of 2.2% and 2.6%, respectively (BNII, Dade Behring Diagnostica, Marburg, Germany). High-sensitive CRP was also determined by nephelometry with a threshold of 0.175 mg/L and intra- and inter-assay coefficients of less than 4.4 and 5.7% respectively. Creatinine assessment in urine was determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY, USA), an automatic enzymatic method. The intra- and interassay coefficients of variation were 0.9% and 2.9%, respectively. Plasma glucose and cholesterol, and serum creatinine were also determined by this enzymatic method.

Definitions and calculations

Systolic and diastolic blood pressures were calculated as the mean of the last two measurements of the two visits. Hypertension was defined as having a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg and/or use of anti-hypertensive medication. Body mass index (BMI) was calculated as the ratio of weight and height (kg/m^2). Obesity was defined as BMI greater than 30 kg/m^2. Type 2 diabetes was defined as a fasting glucose level of ≥7.0 mmol/L (126 mg/dL) or a non-fasting glucose level of ≥11.1 mmol/L (200 mg/dL) or the use of anti-diabetic drugs. Hypercholesterolemia was defined as a serum cholesterol ≥6.5 mmol/L (251 mg/dL) or a serum cholesterol ≥5.0 mmol/L (193 mg/dL) if a history of myocardial infarction was present or when lipid lowering medication was used. Smoking was defined as

current smoking or stopped smoking within the previous year. Histories of myocardial infarction (MI) or cerebrovascular disease were considered present if a participant reported having been hospitalized for at least three days because of these conditions. An elevated CRP was defined as a level >3 mg/L. UAE was calculated as the average UAE in the two consecutive 24-hour urine collections. An estimate of the glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease (sMDRD) formula.[10, 11]

Electrocardiography

Standard 12-lead electrocardiograms were recorded with Cardio Perfect equipment (Cardio Control, Rijswijk, the Netherlands), stored digitally using the computer program MEANS (Modular Electrocardiogram Analysis System). Left ventricular hypertrophy (LVH) was identified using Cornell voltage-duration product, which was calculated as follows: RaVL + SV_3 (with 6 mm added in women) times QRS duration. A threshold of 2440 mm.ms was used to identify LVH.[12,13]

Cardiovascular events

For cardiovascular outcome we used the combined incidence of cardiovascular morbidity and mortality after the baseline screening. Data on mortality and cause of death (primary cause) was obtained by record linkage of the PREVEND database with the Dutch Central Bureau of Statistics. Information on hospitalisation for cardiovascular morbidity was obtained from PRISMANT, the Dutch national registry of hospital discharge diagnoses. All data were coded according to the International classification of diseases, 9th revision and the classification of interventions. For this study cardiovascular events were defined as the following; acute myocardial infarction (ICD-code 410), acute and subacute ischemic heart disease (411), subarachnoid hemorrhage (430), intracerebral hemorrhage (431), other intracranial hemorrhage (432), occlusion or stenosis of the precerebral (433) or cerebral arteries (434), coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA), and other vascular interventions as percutaneous transluminal angioplasty (PTA) or bypass grafting of aorta and peripheral vessels. Survival time was defined as the period from the date of urine collection of the participant to the date of first cardiovascular event or January 1st 2009. In case a person had moved to an unknown destination, the date on which the person was removed from the municipal registry was used as census date.

Statistical analyses

Continuous variables with a normal distribution are expressed as means with standard deviation (SD). Variables with a skewed distribution, such as UAE, CRP and NT-proBNP, are given as medians with interquartile range (IQR). Differences in proportions were tested using χ^2 analysis and Fisher's exact test. Differences in continuous variables between

quintiles of NT-proBNP levels were tested using weighted ANOVA. For the screening of the PREVEND study we overselected subjects with an elevated UAE to acquire sufficient subjects with microalbuminuria. To correct for oversampling of subjects with elevated UAE a design-based analysis was performed. Due to this statistical weighting method our conclusions can be generalized to the general population. Time to first major CV event was analysed. The design-based Cox proportional-hazards regression models used to evaluate the prognostic properties of NT-proBNP for risk of CV events were built with STATA (Statistical Software release 10.0, StataCorp LP, College Station, Texas, USA). The multivariable model was adjusted for age, gender, smoking, medical history, waist-hip ratio, BMI, systolic and diastolic blood pressure, serum cholesterol, serum HDL-cholesterol, serum glucose, eGFR, mean 24 h UAE and CRP as potential confounders (*Table 1*).

Results are summarized by hazard (risk) ratios (HR) with 95% confidence intervals (CI). NT-proBNP showed a log-linear functional shape with the response variable and was transformed to a 2-log scale. This means that risk estimates should be interpreted as the relative risk per doubling of NT-proBNP were doubled (e.g. 10 to 20 pg/mL). All reported probability values are 2-tailed and $P<0.05$ was considered statistically significant. The independent contribution or NT-proBNP was explored crude, age and sex adjusted and by modelling in a multivariable adjusted model.

Analyses were performed using the Statistical Package for Social Sciences software (SPSS version 16.0 for Windows, SPSS Inc., Chicago, Illinois, USA) and STATA.

Results

The population from the community consisted of 4129 (49.8%) males and 4163 (50.2%) females. Mean age was 49±13 years (28-75). Using the ECG criterium of the Cornell voltage-duration product 420 (5.1%) subjects were identified as having LVH at baseline. Characteristics according to the presence or absence of LVH on the ECG are presented in *Table 1*. Subjects with LVH were significantly older, had more often a history of hypertension and myocardial infarction, and had higher blood pressure. Also, serum HDL-cholesterol, glucose and mean UAE were higher in subjects with LVH in comparison to those without LVH. Furthermore, the presence of LVH was associated with lower eGFR. CRP levels were not different between both groups.

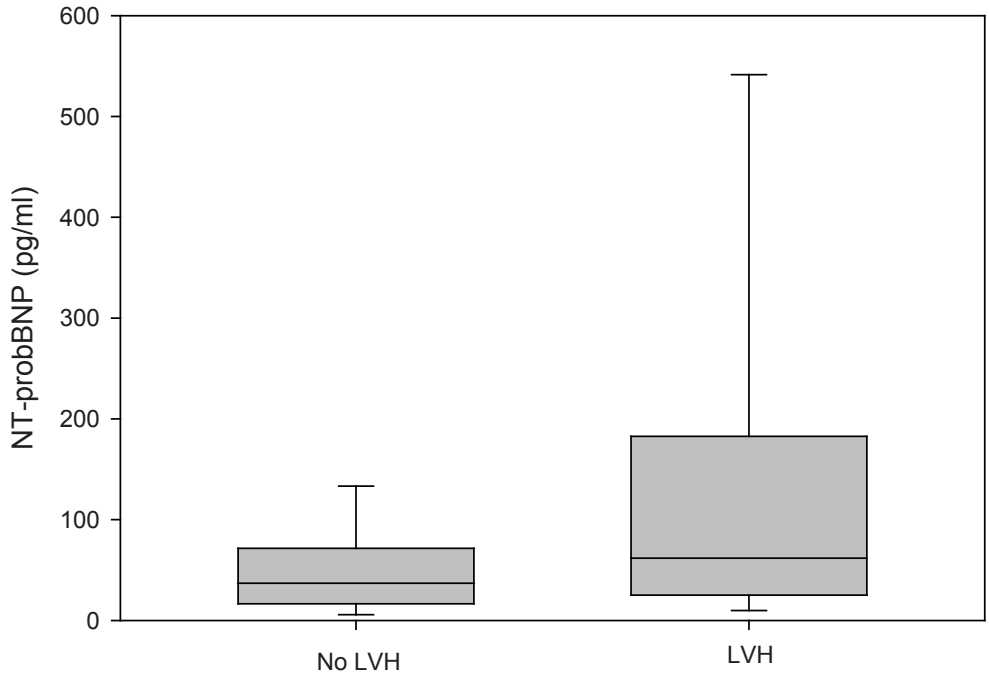
Presence of LVH was associated with higher plasma levels of NT-proBNP at baseline, median 61.8 pg/mL (IQR 25.1-182.6) versus absence of LVH, median NT-proBNP 36.9 pg/mL (IQR 16.5-71.6) ($P<0.001$), respectively (*Figure 1*).

Table 1 Baseline characteristics of study participants with and without left ventricular hypertrophy (LVH) on ECG (total population, n=8292)

Characteristic	No LVH	LVH	*P*-value
N (%)	7872 (94.9)	420 (5.1)	
Age, years	49±13	53±14	<0.001
Female gender (%)	3960 (50.3)	203 (48.3)	0.458
Smoking, n (%)	2991 (38.1)	140 (33.4)	0.053
Medical history			
Diabetes, n (%)	282 (3.6)	25 (6.0)	0.018
Myocardial infarction, n (%)	430 (5.6)	74 (18.0)	<0.001
Hypertension, n (%)	2379 (30.7)	220 (53.0)	<0.001
Hypercholesterolemia, n (%)	2032 (26.3)	124 (29.8)	0.055
Stroke, n (%)	71 (0.9)	6 (1.5)	0.292
Waist-hip ratio	0.88±0.09	0.88±0.10	0.499
BMI, kg/m2	26.1±4.2	25.9±4.4	0.331
Systolic BP, mm Hg	128±20	140±26	<0.001
Diastolic BP, mm Hg	74±10	77±11	<0.001
Serum cholesterol, mmol/L	5.6±1.1	5.7±1.1	0.489
Serum HDL-cholesterol, mmol/L	1.3±0.4	1.4±0.4	0.034
Serum glucose, mmol/L	4.9±1.2	5.0±1.6	0.006
eGFR, mL/min/1.73 m^2	80.8±14.6	78.6±16.3	0.002
Mean 24 h UAE, mg/24 h[a]	9.3 (6.3-17.4)	11.5 (7.5-28.3)	<0.001
CRP, mg/L[a]	1.3 (0.6-3.0)	1.4 (0.5-2.9)	0.951
NT-proBNP, pg/mL[a]	36.9 (16.5-71.6)	61.8 (25.1-182.6)	<0.001

BP indicates blood pressure; BMI, body mass index; UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate by simplified Modification of Diet in Renal Disease (sMDRD) formula; LVH, left ventricular hypertrophy was identified on standard 12-lead electrocardiogram. Conversion of N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels: 100 pg/mL equates to 11.82 pmol/L. All continuous variables are presented as mean±SD. [a]Continuous variable is presented as median value (25^{th}-75^{th} percentiles).

Figure 1. Plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in 420 subjects with left ventricular hypertrophy (LVH) versus those without LVH.



Data are presented as medians with interquartile range and 5 – 95% interval.

LVH and cardiovascular events in the general population

A total of 808 CV events occurred in 548 (6.6%) subjects during a median follow-up of 10.4 years (IQR 8.1-10.8). Numbers of prespecified endpoints comparing participants with and without LVH are shown in *Table 2*. The majority of CV events were cardiac: 584 of which 62 were cardiac deaths. In addition, there were 185 cerebral and 39 peripheral events. Presence of LVH was related to higher CV event rates, 70 in 50 (11.9%) subjects with LVH versus 738 in 498 (6.3%) subjects without LVH. The associated hazard ratio (HR) was 1.94 (95% CI 1.25 – 3.03, $P<0.003$).

Also, presence of LVH was related to higher cardiac event rates; the univariably associated hazard ratio (HR) for non-fatal cardiac events was 1.54 (95% CI 0.93 – 2.54, $P=0.093$) and the HR for cardiac death was 5.75 (95% CI 2.32 – 14.23, $P<0.001$).

There were no significant differences in the risk of cerebral and peripheral events, respectively, between subjects with and without LVH.

Table 2 Cardiovascular events (CV) according to the presence or absence of left ventricular hypertrophy (LVH); and hazard ratios (HR) of the presence of LVH (total population, n=8292)

CV event	Total no. of events	No LVH (n=7872)	LVH (n=420)	HR	T	95% CI	*P*-value
	808	**738**	**70**				
Cardiac morbidity	522	483	39	1.54	1.68	0.93 – 2.54	0.093
Myocardial infarction	202	186	16	1.74	1.38	0.79 – 3.80	0.168
Ischemic heart disease	166	153	13	1.10	0.21	0.47 – 2.57	0.831
PTCA	90	83	7	2.67	1.74	0.89 – 8.05	0.081
CABG	64	61	3	0.53	-1.02	0.16 – 1.78	0.307
Cardiac mortality	62	48	14	5.75	3.78	2.32 – 14.23	<0.001
Cerebral morbidity[a]	178	167	11	1.07	0.13	0.42 – 2.70	0.894
Cerebral mortality	7	5	2	4.01	1.42	0.59 – 27.25	0.155
Peripheral morbidity[b]	39	35	4	1.26	0.40	0.42 – 3.81	0.686

[a]Cerebral morbidity is defined as CVA and arterial disease, carotid desobstruction, and cerebral (subarachnoid or intracerebral or other intracranial) hemorrhage.

[b]Peripheral morbidity is defined as peripheral arterial or aorta surgery, and percutaneous transluminal angioplasty.

NT-proBNP and cardiovascular events in subjects with LVH

In *Figure 2* Kaplan-Meier curves are plotted for CV events by tertiles of plasma NT-proBNP levels at baseline in subjects with LVH. CV outcome of subjects in the highest tertile of NT-proBNP (>118 pg/mL, equates to 13.9 pmol/L) was worse in comparison to the lower two tertiles. There were no statistically significant differences with regard to CV outcome between the first two tertiles.

Each doubling of NT-proBNP was univariably associated with a 45% increased risk of CV events (*P*<0.001; *Table 3*). When adjusted for age, gender, and all other baseline characteristics listed in *Table 1*, doubling of NT-proBNP was still significantly associated with a 32% increased risk of cardiovascular events (*P*=0.004; *Table 3*).

The frequency-distribution of plasma levels of NT-proBNP in subjects with LVH and multivariable adjusted hazards ratios on the risk of CV events are presented in *Figure 3*. For reference, in the Cox regression analyses, HR at a NT-proBNP concentration of 70 pg/mL (8.3 pmol/L), was defined as 1.0.

Figure 2. Kaplan-Meier plot for cardiovascular events in 420 subject with left ventricular hypertrophy (LVH) by tertiles of N-terminal pro-B-type natriuretic peptide (NT-proBNP).

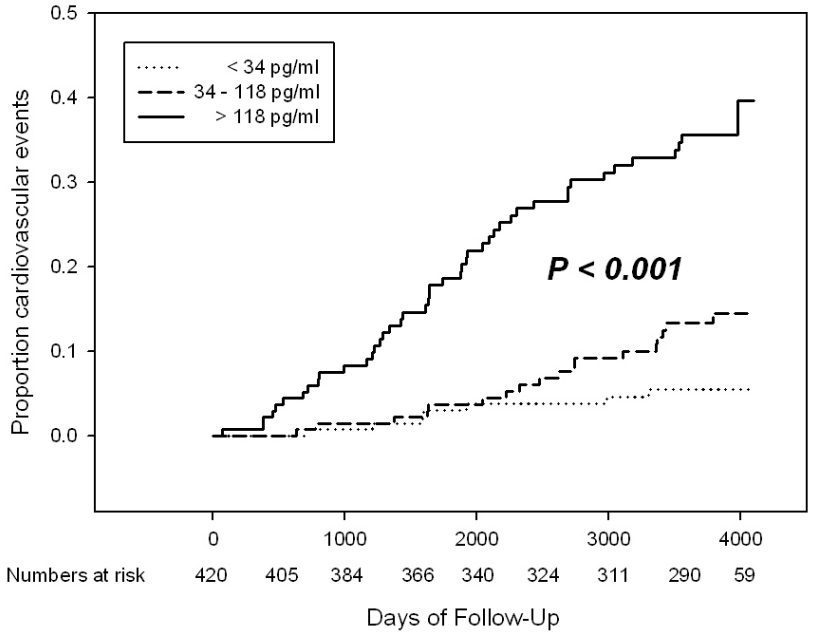


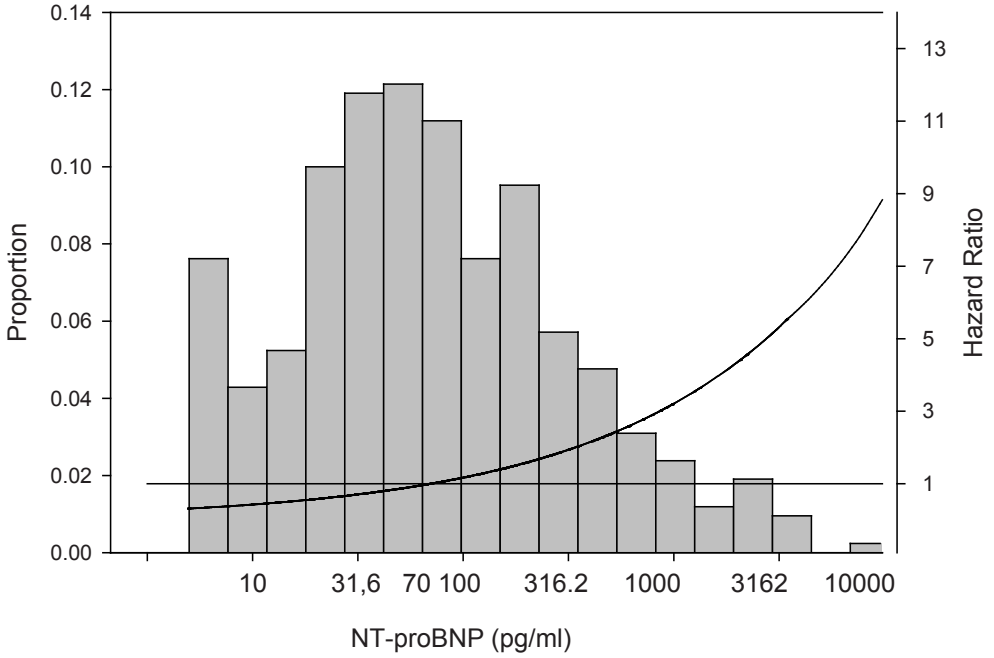
Table 3 Hazard ratios (HR) for cardiovascular events in 420 subjects with left ventricular hypertrophy (LVH) according to doubling of N-terminal pro-B-type natriuretic peptide (NT-proBNP)

	HR	Z	95% CI	*P*-value
Unadjusted model	1.45	7.17	1.31 – 1.61	<0.001
Model 1	1.21	3.02	1.07 – 1.37	0.003
Model 2	1.32	2.84	1.09 – 1.59	0.004

Model 1: Age and gender adjusted model

Model 2: Multivariate model adjusted for all characteristics as presented in Table 1

Figure 3. Frequency distribution of plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and multivariable adjusted hazard ratios on the risk of cardiovascular events in 420 subjects with left ventricular hypertrophy (LVH).



Plasma levels of NT-proBNP are plotted on a logarithmic scale.

Values below the detection limit are reported as 5 pg/mL.

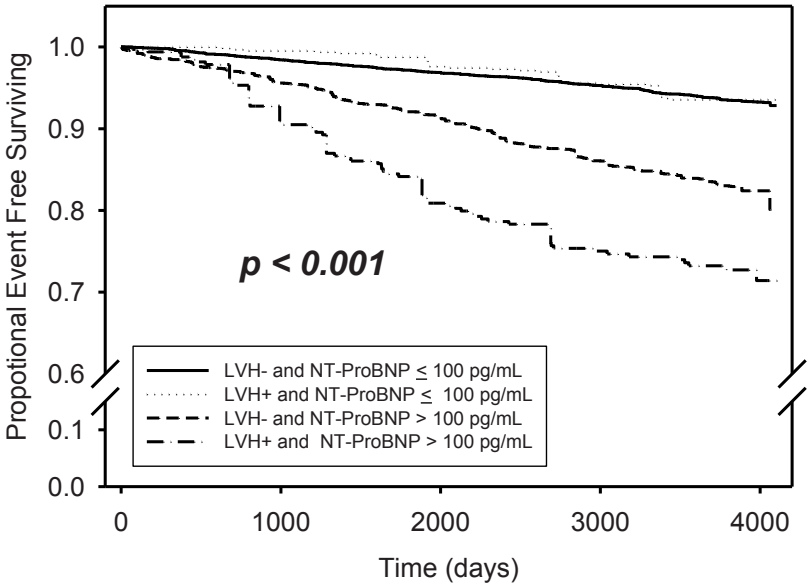
Additional outcome analyses

In *Figure 4* Kaplan-Meier curves are plotted for CV events in four (2x2) subgroups of subjects from the PREVEND cohort: those with LVH versus no LVH, which are subdivided by those with NT-proBNP > 100 pg/mL versus ≤ 100 pg/mL. This value is close to the lower margin of the highest tertile of NT-proBNP in our LVH group.

Subjects with LVH but with plasma NT-proBNP levels ≤100 pg/mL have a favorable CV event free survival similar to those without LVH and NT-proBNP levels ≤100 pg/mL. On the other hand, subjects without LVH, but with NT-proBNP levels >100 pg/mL have worse CV outcome when compared to subjects with NT-proBNP ≤100 pg/mL.

The combination of LVH on ECG and a NT-proBNP level >100 pg/mL was associated with the highest probability of CV events during long-term follow-up.

Figure 4. Kaplan-Meier plot for cardiovascular events in four categories of subjects (2x2): LVH (LVH+) versus no LVH (LVH-), and subdivided in N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≤100 versus >100 pg/mL (n=420).



Discussion

The main finding of the present study in a large community-based cohort is that LVH on ECG is only predictive for CV-events in patients who have an elevated NT-proBNP. In other words, when patients present with LVH and have a low NT-proBNP, their CV outcome is similar to patients without LVH on ECG. Therefore, NT-proBNP is of additional value in patients presenting with LVH on ECG. Furthermore, the presence of LVH was associated with an increased risk of cardiac events, but not of cerebral and peripheral vascular events.

Left ventricular hypertrophy is associated with adverse cardiac outcome

There is compelling evidence that left ventricular hypertrophy (LVH) is an important risk factor for mortality and future CV events.[5] In our present analysis of the PREVEND cohort, electrocardiographic LVH was associated particularly to major cardiac events. Our finding that LVH was not related to both cerebral and peripheral vascular outcome may be explained by the fact that LVH itself reflects cardiac organ damage unrelated to atherosclerosis and is thereby not significantly related to more atherosclerosis-related vascular damage in other domains.[14] Interestingly, half of the participants with LVH did not have hypertension.

The added value of (NT-pro)BNP in subjects presenting with LVH on ECG

Elevations of NT-proBNP or BNP reflect predominantly increased myocardial wall stress, but are also found in acute ischemic syndromes, stable coronary heart disease, valvular heart disease, pulmonary hypertension, vascular disease and stroke.[1,2] Concentrations of these circulating natriuretic peptides are much lower in apparently healthy individuals. However, variation of (NT-pro)BNP within the "reference range" for diagnosing heart failure can still predict a wide range of CV diseases. Subtle changes of (NT-pro)BNP may indicate subclinical disease. In subjects with LVH, stretch-mediated (NT-pro)BNP release may reflect myocardial fibrosis, increased LV stiffness, diastolic dysfunction, and also ischemia and LV remodelling leading to elevated filling pressures. Recently, we reported on the strong predictive value of plasma NT-proBNP for all-cause mortality and cardiovascular events in the PREVEND cohort of the general population.[4] The present analysis of this cohort is the first to describe that subjects with LVH on ECG and a low NT-proBNP have a similar risk to subjects without LVH and a low NT-proBNP. It should be noted, that the adjusted models demonstrated a gradual increased risk of CV events with increasing levels of NT-proBNP, without a clear cut-off. In our study, the median values of NT-proBNP in both the subjects with LVH and those without LVH were far below NT-proBNP levels of patients with (suspected) heart failure.

In a previous systematic review and meta-analysis of 11 prospective studies in the general populations (27,785 participants; 1271 CV disease cases; average follow-up ranging from 2.0 to 12.8 years) increments of BNP or NT-proBNP were associated with increased CV disease risk.[15] It was concluded that these biomarkers only yielded modest incremental improvements in risk discrimination for subsequent CV disease.

In the present analysis of the PREVEND cohort assessing the prespecified subgroup with LVH identified on the ECG, we found that elevated plasma levels of NT-proBNP at baseline were strong and independent predictors of future major CV events. In that way, an increased level of NT-proBNP may serve as an early biological warning signal for adverse outcome. Inherent to the use of biomarkers for risk management is how to choose the optimal cut-point for preventive or therapeutic actions. In general, cut-off levels simplify clinical application; however this binary translation of the continuous

process of cardiovascular disease evolution inevitably leads to loss of information. Furthermore, the cut-points are specific for the cohort and endpoints studied and do not allow generalization to other populations. Nevertheless, natriuretic peptides emerge as good candidate markers for identification of subclinical CV disease and prediction of future adverse events.[16]

Whether specific interventions, therapies or preventive strategies in subjects with LVH and elevated levels of NT-proBNP (or BNP) improve CV outcome beyond heart failure remains to be addressed in further studies.

In current guidelines measurement of natriuretic peptides is not recommended for CV risk assessment in asymptomatic adults.[17,18] Further research is warranted to clarify whether measurements of circulating concentrations of B-type natriuretic peptides can usefully enhance stratification of CV disease beyond traditional risk factors. In addition, both multiple biomarker testing strategies and novel markers of CV risk are promising; however require structural exploration of their use.[19-22] For now, the role of B-type natriuretic peptides in defining therapeutic strategies in the general population is still uncertain. In other words, the questions to be addressed are how we should respond to various risk categories based on natriuretic peptides and what is the effect of the corresponding clinical decisions and CV outcome, respectively. Furthermore, there is no evidence in asymptomatic adults that knowledge of their NT-proBNP or BNP level is of value in motivating behavioural changes towards a healthy lifestyle. In addition, we need more data from low- and intermediate-risk populations to build evidence and allow more confident extension of application of these biomarkers to primary prevention settings.

Limitations

The present study has several limitations. In the screening phase of the PREVEND study subjects with microalbuminuria were overselected. To correct for oversampling, we performed design-based analyses. Therefore, the results can be generalized to the general population. The PREVEND cohort is predominantly white, and our findings may not be representative for other populations. However, the finding that the percentage of all deaths in the present study that is classified as being due to CV disease is in line with previous prospective studies of subjects of the general population. We measured NT-proBNP only once and without correction for potential variability in concentrations. Echocardiography was not part of our study design. This implied that several subjects with LVH may not have been detected or falsely identified. However, the computerised electrocardiogram analysis avoided intra- and inter-observer bias, and echocardiography in large scale population studies is unfeasible.

Strength of the PREVEND study is that we report on a large sample of the general population with detailed information on characteristics of the participants (e.g. medication, ECG, UAE, NT-proBNP) and morbidity and mortality.

Conclusions

In this large cohort of the general population, plasma NT-proBNP was independently associated with CV events in subjects with LVH on ECG. The presence of LVH on ECG is only predictive for CV events in subjects with elevated NT-proBNP. The combined use of ECG to identify LVH and measurement of plasma NT-proBNP at baseline, respectively, may enhance long-term CV risk stratification in the community. This strategy might reduce the need for advanced investigations.

Acknowledgments

The authors acknowledge the Trial Coordination Center, Groningen, the Netherlands. We are grateful to Dade Behring Diagnostica, Marburg, Germany; and Roche Diagnostics, Mannheim, Germany for providing tests, assay kits and technical support.

PREVEND Study Group

In addition to the authors, the PREVEND investigators are as follows: Department of Internal Medicine (Division of Nephrology): G.J. Navis, MD, PhD; Department of Internal Medicine (Division of Endocrinology): B.H.R. Wolffenbuttel, MD, PhD; R.P.F. Dullaart, MD, PhD; Department of Cardiology: P. van der Harst, MD, PhD; Department of Clinical Epidemiology: R.P. Stolk, PhD; Department of Clinical Pharmacology: W.H. van Gilst, PhD; Department of Geriatric Medicine: J.P.J. Slaets, MD, PhD; G. Izaks, MD, PhD; Department of Pharmacoepidemiology and Pharmacoeconomics: L.W.T. de Jong-van den Berg, PhD; M.J. Postma, PhD, S.T. Visser, PhD. University of Groningen, Groningen, the Netherlands.

Funding

The PREVEND study was financially supported by grant E.013 of the Netherlands Kidney Foundation.

Prof. van Veldhuisen and Prof. Voors are Clinical Established Investigators of the Netherlands Heart Foundation (grant D97.017 and grant 2006T037).

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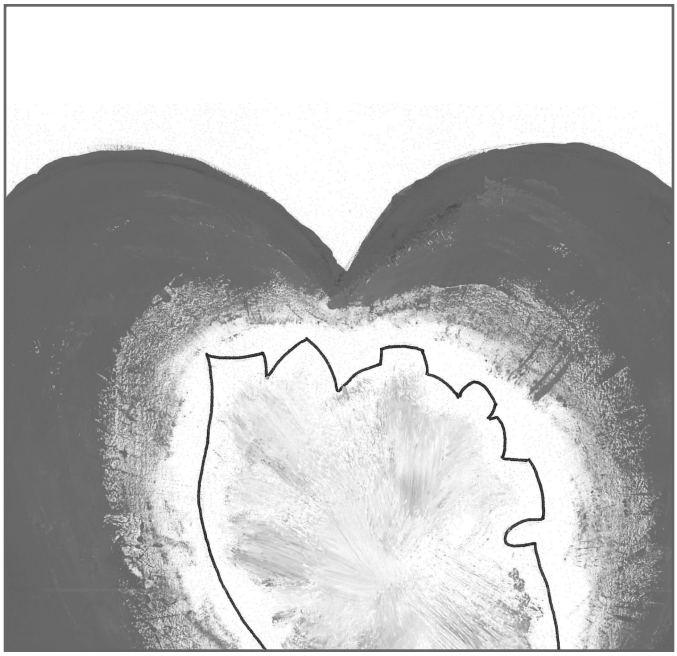
Chapter 4

Direct comparison of the prognostic value of BNP and NT-proBNP measurements at hospital discharge after an admission for decompensated heart failure



Gerard C.M. Linssen, Tiny Jaarsma, Hans L. Hillege, Adriaan A. Voors, Dirk J. van Veldhuisen

Abstract

Background

B-type natriuretic peptides provide important prognostic information. The purpose of our present study was to directly compare the prognostic performance of BNP versus NT-pro-BNP measurements in a large population of heart failure (HF) patients at hospital discharge after an admission for decompensated HF.

Methods

BNP and NT-proBNP were measured in 563 stable HF patients before discharge. All patients were followed for a fixed time period of 18 months. Endpoints of interest were time to death and rehospitalization for HF.

Results

Patients were in NYHA class II (47%) or III/IV (53%) at discharge and the mean age of the patients was 71±11 years, 217 (39%) females, mean LVEF was 0.33±14 and 234 (42%) had an ischemic etiology of HF. Multivariate odds ratios of the primary endpoint for doubling of baseline levels of BNP and NT-proBNP were 1.46 (95% CI 1.19-1.80, *P*<0.001) and 1.45 (95% CI 1.18-1.78, *P*<0.001), respectively. The multivariably adjusted areas under the receiver-operating characteristic (ROC) cure (AUC), for prediction of the primary endpoint for doubling of BNP and NT-proBNP were 0.69 and 0.68, respectively. Direct comparison of the prognostic value of BNP and NT-proBNP did not reveal significant differences.

Conclusions

Both BNP and NT-proBNP at discharge for a HF hospitalization are equally strong and independent predictors of all-cause death and HF rehospitalization.

Keywords

Heart failure, B-type natriuretic peptides, Prognosis

Introduction

Hospitalization for acute heart failure (HF) syndromes portends a poor prognosis in patients with chronic HF.[1] Brain natriuretic peptides (BNP) and its equimolarly secreted amino-terminal fragment (NT-proBNP) are strong independent predictors of mortality and cardiovascular (CV) events in patients with heart failure (HF).[2-7] Therefore, these biomarkers can help to identify patients at risk for death or HF hospitalization.[8-12] Although both natriuretic peptides are frequently used, direct comparative studies on the prognostic value of BNP and NT-proBNP are scarce. Since BNP and NT-proBNP differ with regard to their biological activity and half-life, in vitro stability and clearance mechanisms, different prognostic values can be expected. The large ValHeFT-study compared the prognostic value of BNP and NT-proBNP in a large group of patients with stable chronic HF.[13] The predictive value of NT-proBNP appeared to be better than the predictive value of BNP. This study was done in the chronic setting, which is markedly different from the acute setting. After hospital discharge, a substantial number of patients suffer from early unfavorable events, particularly re-admission and death. Therefore, identification of subjects at high risk for adverse events at hospital discharge is of utmost importance. However, there are no studies comparing the predictive effects of BNP and NT-proBNP in HF patients just before discharge.

Therefore, the purpose of our present study was to directly compare the prognostic performance of BNP versus NT-pro-BNP measurements in a large population of HF patients at hospital discharge after an admission for decompensated HF. Both the prognostic value and the predictive accuracy of the measurements at discharge of plasma levels of both peptides were evaluated.

Methods

Patient population and study design

This analysis was performed as part of the Coordinating study evaluating Outcomes of Advising and Counselling in Heart Failure (COACH) study, a multicenter, randomized, open trial with blinded endpoint evaluation, in which 1023 patients were enrolled. It was designed to compare basic support and intensive support in patients with CHF to a control group receiving ”usual” care, as described in detail before.[14] All patients had been admitted to the hospital with symptoms of HF, New York Heart Association (NYHA) functional class II-IV. Patients were >18 years of age and had evidence of structural underlying heart disease, as shown by cardiovascular imaging. Both patients with an impaired and those with a preserved left ventricular ejection fraction could participate. Before discharge from the hospital (i.e. before inclusion into the study), patients had to be stable on standard medication for HF, at the discretion of the physician and if tolerated. Patients were recruited during a period of 28 months (October 2002 to February 2005) and all patients were followed for a fixed time period of 18 months. Primary endpoints were time to death or rehospitalization for HF, and the number of days lost to death or

hospitalization. Secondary (major) endpoints were all-cause mortality, CV mortality; hospitalizations (all-cause, CV, HF). The Medical Ethics Committee approved the study protocol and all patients provided written informed consent. Institutional review board approval was required for all 17 participating Dutch centers.

The primary results of the COACH study have been recently published.[15] Briefly, neither moderate nor intensive disease management by a HF nurse reduced the combined endpoint of HF hospitalization and mortality compared to standard follow-up. In addition, there was a nonsignificant, however potentially relevant reduction of mortality, accompanied by a slight increase in the number of short hospitalizations in both intervention groups.

In the current analyses, we investigated HF patients enrolled in the COACH study, in which measurements of plasma levels of both BNP and NT-proBNP at hospital discharge for decompensated chronic heart failure (baseline) were available. Endpoints of interest were all-cause mortality and HF (re)hospitalization during 18 months follow-up.

Laboratory analyses and calculations

Serum creatinine was determined from the blood drawn shortly before hospital discharge, in the local laboratory at each center. Serum creatinine was measured by Jaffé alkaline picrate assay. Estimated GFR (eGFR) was calculated using the simplified Modification of Diet in Renal Disease (sMDRD, mL/min per 1.73 m^2) formula: 186.3 x (serum creatinine)$^{1.154}$ x (age)$^{-0.203}$ x 0.742 (if patient is female) x 1.212 (if patient is black).[16,17]

Of the 1023 patients included in the COACH study, 563 patients had both BNP and NT-proBNP plasma levels available. The main reason for missing BNP and NT-proBNP data was temporary unavailability of the necessary laboratory facilities, usually in the starting phase of the study. Blood was collected shortly before discharge from hospital between 8:00 AM and 4:00 PM, after patients had been clinically stabilized and recovered enough to return to their homes. Ten millilitres of whole blood was taken from an antecubital vein and collected into tubes containing potassium ethylenediaminetetraacetic acid (EDTA; 1 mg/mL blood) when patients were in a supine position. The tubes were centrifuged for 10 minutes (2500 x *g*) and the plasma was separated and stored in polyepropene tubes at -70ºC to -80ºC.

BNP measurement: BNP levels were determined on site in whole blood within 4 hours after blood collection. In the majority of patients BNP levels were determined in plasma at the Core Laboratory at the University Medical Center Groningen. All measurements were performed using a fluorescence immunoassay kit (Triage®, Biosite Incorporated, San Diego, CA). Details on the system provided by the manufacturer indicated the analytical sensitivity of the assay is less than 5.0 pg/mL. The system has been extensively validated.[18,19] The measurable range of BNP assays was 5.0 – 5000.0 pg/mL. To convert BNP to picomoles per liter, divide by 3.47.

NT-proBNP measurement: All measurements were performed in plasma on an Elecsys™ 2010 analyser, a commercially available electrochemiluminescent sandwich immunoassay (Elecsys proBNP, Roche Diagnostics, Mannheim, Germany). The intra- and interassay coefficients of variation were 1.2-1.5% and 4.4-5.0% respectively, with an analytical range of 5-35,000 pg/mL.[20] To convert NT-proBNP to picomoles per liter, divide by 8.46.

Statistical analyses

Continuous variables with a normal distribution are expressed as means with standard deviation (SD). Nominal variables are expressed as *n* (%). Levels of BNP and NT-proBNP with a skewed distribution are given as medians with interquartile range (IQR). Differences in continuous variables were evaluated by Student's t-test or Mann-Whitney-U tests, depending on normality of data. Categorical clinical variables were compared with the Fisher's exact test or chi-square test. To realize a constant variance, natriuretic peptide values were logarithmically transformed. BNP levels were correlated with NT-proBNP levels using Spearman's rank correlation coefficient.

The primary endpoint was time to first major event (HF hospitalization or death). To estimate the size of the effect, odds ratios (OR) with 95 percent confidence intervals (CI) were calculated with the use of logistic regression models. A stepwise approach was used. From logistic regression analysis the predictive values of BNP and NT-proBNP were determined and the area under the receiver operating characteristics (ROC) curves (AUC) for quantification of the predictive accuracy was calculated. An ROC area of 0.5 signifies no discriminatory value, while an area of 1.0 means perfect discrimination for prediction of those with and without an endpoint during follow-up.

Furthermore, a direct comparison of single levels in the regression models in COACH-patients was part of this analysis.

All reported probability values are 2-tailed and $P<0.05$ was considered statistically significant. Analyses were performed using STATA software (STATA version 10.0, College Station, Texas, USA).

Results

Baseline characteristics

The study group at baseline comprised 563 HF patients: 217 (39%) females, the mean age of the patients was 71±11 years. Patients were in NYHA class II (47%) or III/IV (53%) at discharge, mean LVEF was 0.33±0.14 and 234 (42%) had an ischemic etiology of HF. There were no significant differences in baseline characteristics between patients who participated in this study and in the main COACH cohort. In *Table 1* baseline characteristics of the study group (n=563) at hospital discharge are presented.

Table 1.Baseline characteristics of the study group at hospital discharge.

	Study group (n=563)
Female gender	217 (39%)
Age (years)	71±11
NYHA class III or IV*	294 (53%)
LVEF	0.32±0.14
Body mass index (kg/m^2)	26±5
Etiology of heart failure	
Ischemic heart disease	234 (42%)
Non-ischemic heart disease	329 (58%)
Previously hospitalized for HF	192 (34%)
Comorbidities	
Hypertension	249 (44%)
Atrial fibrillation	258 (46%)
Diabetes	167 (30%)
Stroke	51 (9%)
COPD	156 (28%)
Medication	
ACE-I and/or ARB	463 (82%)
ß-Blockers	375 (67%)
Diuretics**	538 (96%)
Laboratory values	
Hemoglobin (mmol/L)	8.2±1.3
eGFR (mL/min/1.73 m^2)	54±20
BNP (pg/mL)†	447 (196-906)
NT-proBNP (pg/mL)†	2528 (1289-5615)

Abbreviations: ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BNP = brain natriuretic peptide; BP = blood pressure; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; NYHA = New York Heart Association.

SI conversion factors: To convert NT-proBNP to picomoles per liter, divide by 8.46; BNP to picomoles per liter, divide by 3.47; hemoglobin to grams per liter, divide by 0.62.

*NYHA class at hospital discharge. **Includes loop diuretics, thiazides, and aldosterone antagonists.

All continuous variables are presented as mean±SD, if † is present continuous variable is presented as median value (25th-75th percentiles).

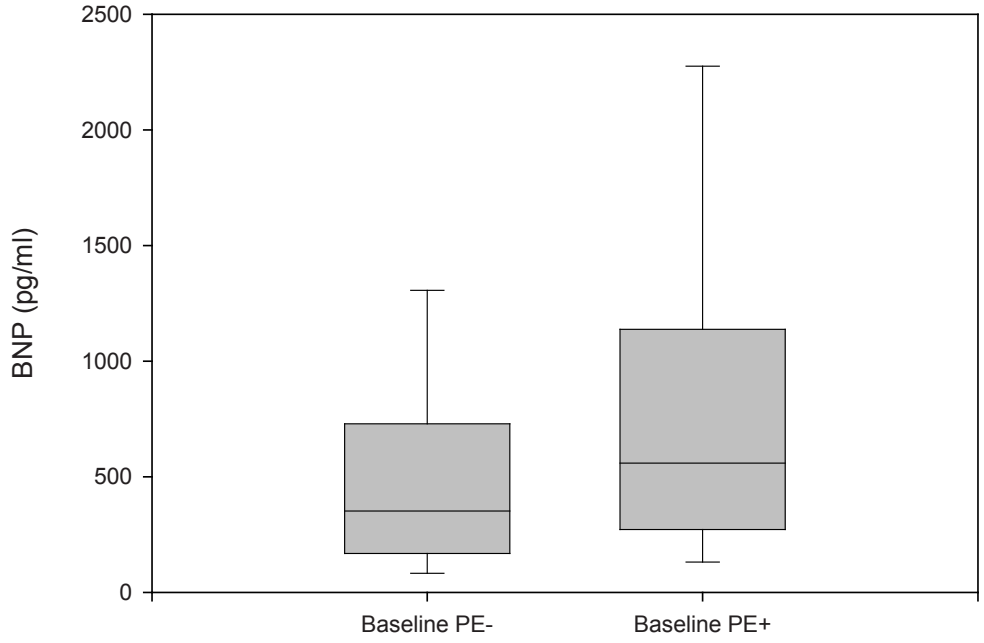
BNP, NT-proBNP and outcome

At hospital discharge after an admission for decompensated HF, median (25^{th}-75^{th} percentiles) BNP and NT-proBNP levels in the 563 study patients were 447 (196-906) and 2528 (1289-5615) pg/mL, respectively, see *Table 1*. The ratio of the median NT-proBNP to the median BNP level at hospital discharge was 5.66.

We found a strong association between BNP and NT-proBNP concentrations (correlation coefficient 0.82, *P* <0.001).

BNP at baseline was significantly (*P*<0.05) related to: NYHA class, LVEF, BMI, HF underlying disease (ischemic vs. non-ischemic). NT-proBNP at baseline was significantly related to age, NYHA class, LVEF, BMI, HF underlying disease (ischemic vs. non-ischemic), hemoglobin and eGFR.

Figure 1. BNP levels at hospital discharge in heart failure patients who reached the primary endpoint versus those who remained free of this endpoint.



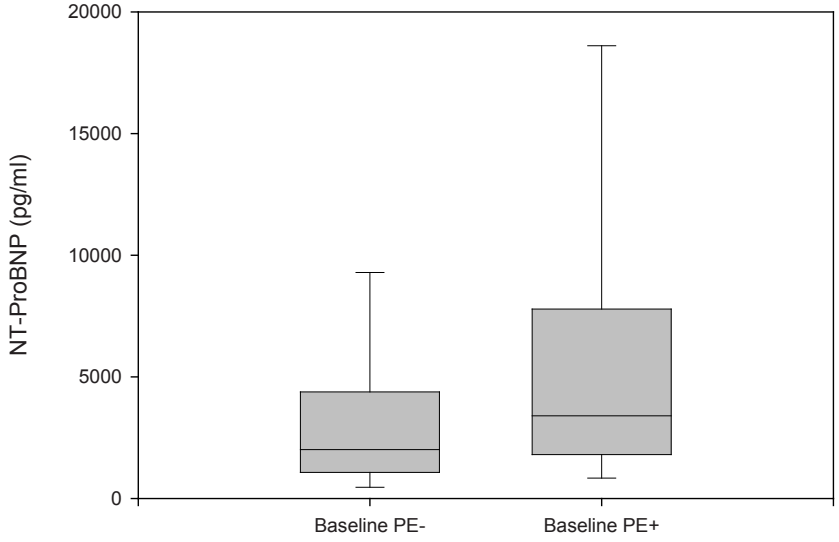
Data are presented as medians with interquartile range and 5 – 95% interval.

P for comparison <0.001.

PE indicates primary endpoint.

The baseline median BNP and NT-proBNP levels were higher in patients (n=236, 42%) who reached the primary endpoint compared to those (n=337, 58%) who remained free of this endpoint: 559 vs. 352 pg/mL, *P*<0.001; and 3396 vs. 2011 pg/mL, *P*<0.001, respectively (*Figures 1 and 2*).

Figure 2. NT-proBNP levels at hospital discharge in heart failure patients who reached the primary endpoint versus those who remained free of this endpoint.

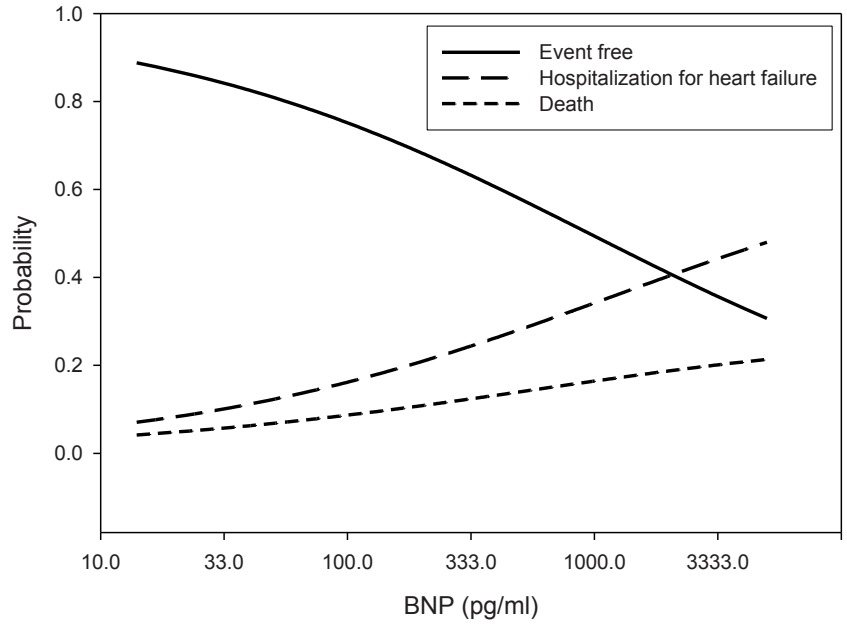


Data are presented as medians with interquartile range and 5 – 95% interval.

P for comparison <0.001.

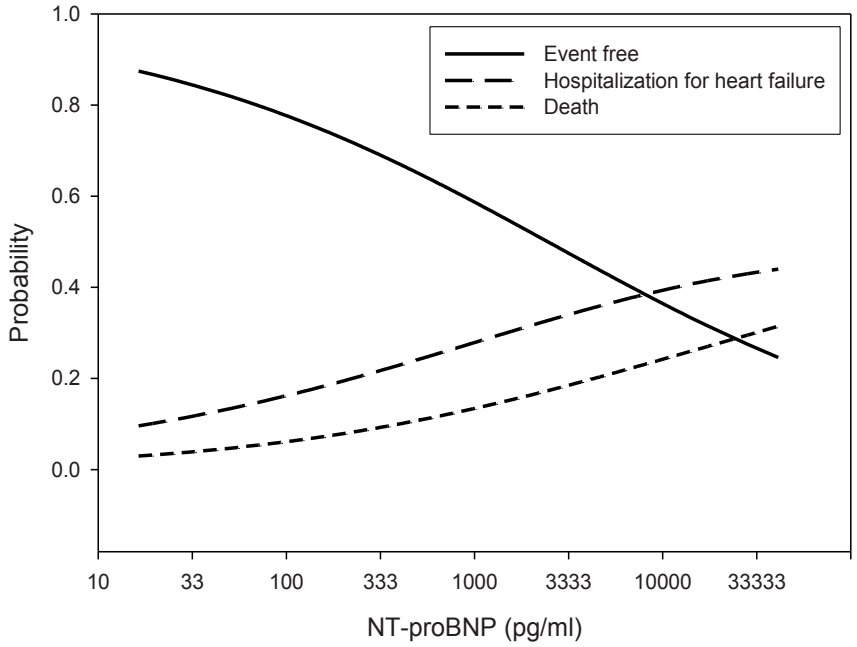
PE indicates primary endpoint.

Figure 3. Multivariable adjusted probability of outcome according to the BNP level at hospital discharge (on a log transformed scale)**.**



The multivariably adjusted probability for event free survival and for the separate endpoints (HF hospitalization and all-cause death) according to the baseline BNP and NT-proBNP levels, respectively, are presented in *Figures 3 and 4*.

Figure 4. Multivariable adjusted probability of outcome according to the NT-proBNP level at hospital discharge (on a log transformed scale)**.**



Prognostic value of a single predischarge measurement of BNP and NT-proBNP
Unadjusted, age- and gender adjusted and multivariate odds ratios (OR) of the primary endpoint for doubling of baseline levels of BNP and NT-proBNP are presented in *Table 2 and 3*. Multivariate odds-ratios (adjusted for age, NYHA class, LVEF, BMI, HF underlying disease (ischemic vs. non-ischemic), eGFR) were 1.46 (95% CI 1.19-1.80, $P<0.001$) and 1.45 (95% CI 1.18-1.78, $P<0.001$), respectively for BNP and NT-proBNP. In addition, both BNP and NT-proBNP were independent predictors of the separate endpoints HF hospitalization and all-cause death.

Table 2.Odds ratios for outcome according to doubling of B-type natriuretic peptide (BNP) at hospital discharge for heart failure.

	Odds ratio	95% CI	*P*-value
For primary endpoint			
Unadjusted model	1.30	1.16-1.45	<0.001
Model 1	1.29	1.15-1.45	<0.001
Model 2	1.46	1.19-1.80	<0.001
For HF hospitalization			
Unadjusted model	1.24	1.09-1.41	<0.001
Model 1	1.25	1.09-1.41	<0.001
Model 2	1.42	1.20-1.68	<0.001
For all-cause death			
Unadjusted model	1.41	1.20-1.66	<0.001
Model 1	1.40	1.19-1.66	<0.001
Model 2	1.37	1.12-1.69	0.003

Model 1: Age and gender adjusted model

Model 2: Multivariate model adjusted for significant covariates: age, NYHA class, LVEF, BMI, HF underlying disease (ischemic vs. non-ischemic), and eGFR

Table 3.Odds ratios for outcome according to doubling of N-terminal pro-B-type natriuretic peptide (NT-proBNP) at hospital discharge for heart failure.

	Odds ratio	95% CI	*P*-value
For primary endpoint			
Unadjusted model	1.34	1.20-1.49	<0.001
Model 1	1.31	1.17-1.46	<0.001
Model 2	1.45	1.18-1.78	<0.001
For HF hospitalization			
Unadjusted model	1.23	1.10-1.40	<0.001
Model 1	1.22	1.08-1.38	<0.001
Model 2	1.33	1.13-1.56	<0.001
For all-cause death			
Unadjusted model	1.55	1.33-1.82	<0.001
Model 1	1.50	1.28-1.76	<0.001
Model 2	1.45	1.17-1.78	<0.001

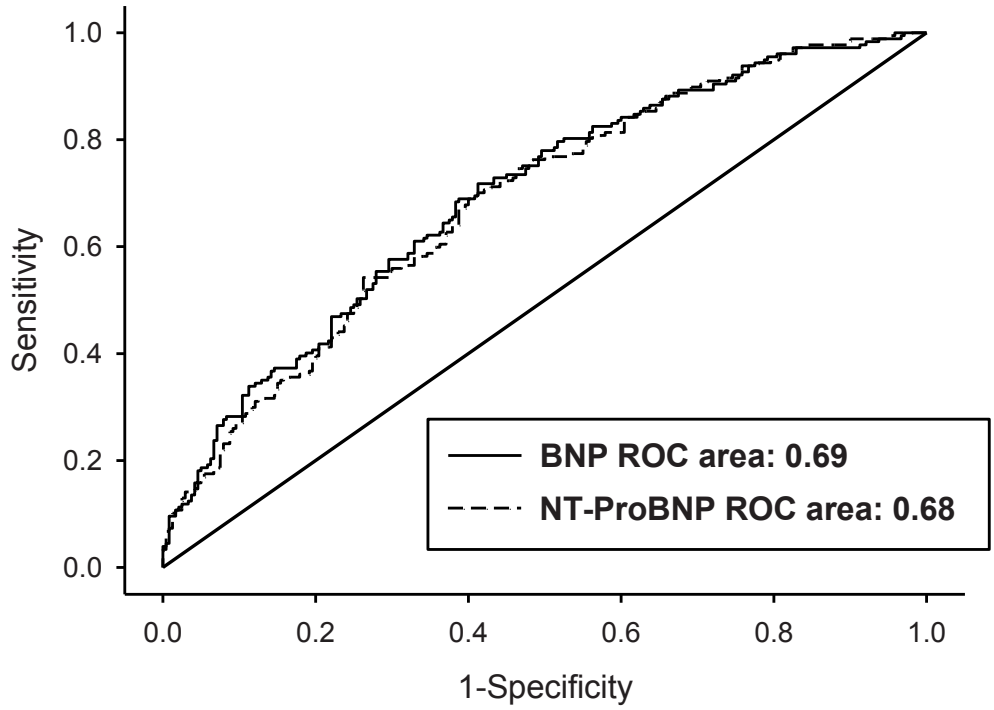
Model 1: Age and gender adjusted model

Model 2: Multivariate model adjusted for significant covariates: age, NYHA class, LVEF, BMI, HF underlying disease (ischemic vs. non-ischemic), and eGFR

Predictive accuracy of BNP versus NT-proBNP

The areas under the receiver-operating characteristic (ROC) cure (AUC) for prediction of the primary endpoint, calculated for each doubling of BNP and NT-proBNP were 0.69 and 0.68 respectively. The corresponding, multivariably adjusted ROC-curves for each doubling of BNP and NT-proBNP are plotted in *Figure 5*. There were no significant differences in AUC between BNP and NT-proBNP.

Figure 5. Receiver operating characteristics (ROC) curves (multivariable adjusted) of discharge levels of BNP and NT-proBNP levels in predicting hospitalization for HF or death, both at 18 months.



Discussion

The main finding of the present study is that both B-type natriuretic peptides are equally strong and independent predictors of outcome at hospital discharge. Direct comparison of the predictive accuracy of BNP and NT-proBNP did not reveal significant differences.

In the past ten years many clinical studies provided compelling evidence that plasma levels of (NT-pro)BNP correlate with hemodynamic parameters, severity and prognosis of HF patients.[2] Rational use of these peptides is currently advocated in patients with HF in several clinical settings: on admission for decompensated heart failure, after a major treatment effect, at hospital discharge when euvolemia is reached, and during

ambulatory follow-up.[21,22] A single measurement of a B-type natriuretic peptide provides strong and independent prognostic information in patients with heart failure. Euvolemia reached at hospital discharge is an important point of time for measurement of BNP or NT-proBNP, of which concentrations could serve as targets for optimal fluid status or markers of disease evolution in addition to clinical parameters during follow-up, setting the stage for biomarker-guided therapy. Importanty, a recent meta-analysis of 6 randomized controlled trials showed that titration of medical therapy using serial BNP or NT-proBNP levels was associated with a significant reduction in all-cause mortality (hazard ratio was 0.69, 95% CI 0.55-0.86) compared to usual care in patients with chronic HF.[23] However, the evidence for the use of these biomarkers in guidance of HF drug therapy to improve clinical outcome needs to be assessed in a adequately powered randomized controlled trial.

BNP versus NT-proBNP in heart failure

Plasma levels of the biological active BNP and inactive N-terminal fragment of BNP are closely correlated with each other in HF patients, as confirmed by the results of our study. The Valsartan Heart Failure Trial (Val-HeFT) study group provided a direct comparison of the prognostic value of BNP and NT-proBNP in 3916 patients with chronic and stable HF.[13] They found that both peptides were the most powerful independent markers of outcome in HF, but NT-proBNP was superior to BNP in predicting mortality and morbidity or hospitalization for HF. We found that the prognostic performance of BNP and NT-proBNP at the time of hospital discharge were comparable. In previous studies, however, patient and assay related factors influence both BNP and NT-proBNP concentrations.[24-26] In head-to-head comparisons, distinct discrepancies in individual patients demonstrate that both markers are clinically not completely equivalent.[27] Furthermore, BNP was found to be more sensitive to rapid hemodynamic changes in acute heart failure than NT-proBNP.[28] For purposes of disease monitoring in heart failure both peptides were reported as comparably useful.[29]

The influence of biological variation of BNP and NT-proBNP levels

The intra-individual biological variation and analytical assay variances of BNP and NT-proBNP affect the interpretation of single and serial test results in patients with CHF. In order to qualify for clinical relevance, intraindividual changes of concentrations of B-type natriuretic peptides during follow-up of CHF patients should exceed the magnitude of reported variances of 25-50%.[30-32]

In addition, the analytical performance and clinical results of test methods differ greatly and are also strongly dependent of population characteristics, co-morbidity and confounding factors.[33-38] The variation in plasma levels of analytes also reflects differences in half-life and mechanisms of metabolism and clearance.

Taken together, the plasma levels of these peptides determined by different assays are not interchangeable with regard to the interpretation and significance of test results. These factors influence the determination of the importance of serial changes of B-type natriuretic peptides levels. These issues should be taken into account while applying serial testing for risk stratification and (long-term) monitoring of HF patients. This confers an important limitation of the utilization of BNP and NT-proBNP in HF management.

Study limitations

The present analysis was observational in design and is therefore only hypothesis-generating. In the current retrospective analysis of a randomized controlled trial, we only included medical therapy at hospital discharge. In that way, modifications in the drug treatment and non-pharmacological therapy during follow-up were not accounted for in our analysis. The COACH study was powered for the primary composite endpoint, time to hospitalization for HF or all-cause mortality, but not for the separate, secondary endpoint all-cause mortality.

Conclusions

Both BNP and NT-proBNP at discharge for a HF hospitalization are equally strong and independent predictors of all-cause death and HF rehospitalization.

Funding sources

The COACH study was supported by a large program grant from the Netherlands Heart Foundation (grant 2000Z003). Prof. van Veldhuisen and Prof. Voors are Clinical Established Investigators of the Netherlands Heart Foundation (grant D97.017 and grant 2006T037).

Additional unrestricted grants were obtained from Biosite Europe, France (Brain Natriuretic Peptide [BNP]), Roche Diagnostics, The Netherlands (N-terminal-proBNP), and Novartis Pharma BV, The Netherlands.

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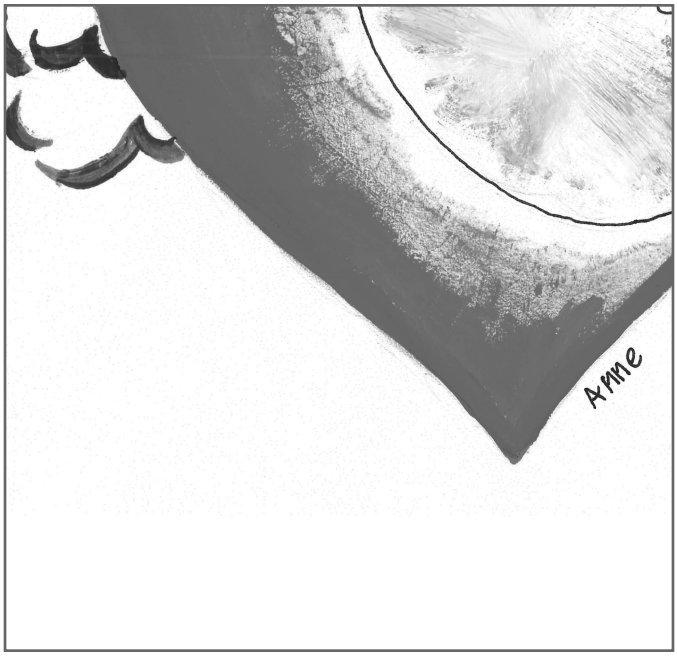
Chapter 5

B-type natriuretic peptides and outcome in heart failure patients with preserved and reduced ejection fraction



Dirk J. van Veldhuisen, Gerard C.M. Linssen, Tiny Jaarsma, Wiek H. Van Gilst, Arno W. Hoes, Jan G.P. Tijssen, Adriaan A. Voors, Hans L. Hillege

Abstract

Background

Diagnosis and management of patients with heart failure with preserved ejection fraction (HFPEF) is difficult, and treatment options are limited. Natriuretic peptides, like brain natriuretic peptide (BNP) and N-terminal (NT-)proBNP are useful biomarkers, but data in HFPEF are scarce.

Methods

We studied 615 patients with mild to moderate HF (mean age 70 years, mean left ventricular (LV)EF 33%), who were followed for 18 months. BNP and NT-proBNP concentrations were measured at baseline, and were related to the primary outcome, i.e. a composite of all-cause mortality and HF hospitalization, and to mortality alone. HFPEF (n=155) was defined as LVEF >40%.

Findings

There were 257 patients (42%) who had a primary endpoint and 171 (28%) who died. BNP/NT-proBNP levels were higher in patients with reduced LVEF (median 502 pg/mL and 3266 pg/mL, respectively) than in those with HFPEF (340 pg/mL and 1950 pg/mL, respectively; both $P<0.001$). BNP/NT-proBNP were strong predictors of outcome, but LVEF was not. Importantly, if similar levels of BNP and NT-proBNP were compared across the whole spectrum of LVEF, and also for LVEF ≤40% versus >40%, the associated risk of adverse outcome was at least as high in HFPEF patients as in HF patients with reduced LVEF.

Interpretation

Although BNP/NT-proBNP levels are lower in HFPEF than in HF with reduced LVEF, for a given BNP/NT-proBNP level, the outcome in patients with HFPEF is at least as poor as in those with reduced LVEF. This finding should be taken into account in the clinical decision making in HFPEF.

Keywords

Chronic heart failure, Natriuretic peptides, HFPEF, Prognosis

Introduction

Heart failure with preserved ejection fraction (HFPEF) is an increasingly large medical and epidemiological problem.[1-4] Although older studies reported that HFPEF patients in general had a better prognosis than HF patients with a reduced LVEF [5], more recent data indicate that mortality in HFPEF patients is in fact similar.[3,4] While survival has improved over the last 10-20 years in HF patients with reduced LVEF, no change was observed in HFPEF patients. Patients with HFPEF are generally older, more often women, and have more comorbidities.[3,4]

A large number of trials have been conducted in HF patients and reduced EF, examining angiotensin converting enzyme (ACE) inhibitors, beta-blockers, angiotensin receptor blockers (ARBs) and aldosterone receptor blockers.[1,6] These trials reported significant reductions in morbidity and mortality which led to strong recommendations for these drugs in current HF guidelines. In comparison, only few trials have been conducted in HFPEF, and none of the treatments was convincingly shown to improve outcome, and therefore none has received a recommendation for HFPEF in current HF guidelines. [2,6,7]

Methodological issues may play a role in the disappointing results from trials in HFPEF, and many trials enrolled patients only a "preserved" LVEF combined with rather "soft" criteria related to symptoms of HF, which means that a proportion of them may not have had HF.[7] Symptoms of HF such as dyspnea and fatigue are aspecific and may be secondary to other diseases such as anaemia, obesity and chronic obstructive pulmonary disease (COPD).[8,9] One way to overcome this problem, is to employ strict echocardiographic criteria[7], and by using such criteria one third of patients enrolled in a large-scale trial indeed had no echocardiographic signs of diastolic dysfunction.[10] However, there are many different definitions, and measurement of these parameters requires experienced technicians, which has often not been very useful.[7]

Another and potentially more useful approach to define the presence of HF in patients with HFPEF would be to use natriuretic peptides, i.e. brain natriuretic peptide (BNP) or N-terminal (NT-)proBNP. These biomarkers are now used on a large scale and have been proven to be of value in the diagnosis and in the management of HF patients with reduced LVEF.[11] Recent work has shown that these natriuretic peptides may also be used in patients with HFPEF, both for diagnostic and for prognostic purposes.[11-13]

The aim of the present study was therefore to study BNP and NT-proBNP concentrations in one HF cohort which included a wide range of LVEF. Given the fact that BNP and NT-proBNP can be considered reliable markers of the severity of HF, we compared the prognostic value of similar levels of these peptides across the whole range of LVEF, i.e. to examine the prognostic value of specific values of BNP or NT-proBNP across the whole range of LVEF.

Methods

Patients

All patients in the present study participated in the Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure (COACH) (ISRCNT98675639), of which the methods and the main outcome results have been reported in detail.[14,15] COACH was a multicenter randomized trial to evaluate the effect of two levels of a disease management program (basic support and intensive support) versus care as usual. Patients were randomized before discharge, i.e. at the end of a hospitalization for HF, when they were clinically stable. BNP/NT-proBNP measurements were taken at this time.

Patients had to be ≥18 years of age, and were in New York Heart Association functional class II-IV; they had to have evidence of underlying structural heart disease. The primary outcome was a composite of hospitalization for HF or all-cause mortality. A total of 1023 patients were included in the main study, and follow-up was performed at 1, 3, 6, 12 and 18 months after discharge. Hospitalization for HF was defined as an unplanned overnight stay in a hospital (different dates for admission and discharge) as a result of progression of HF, or directly related to HF. All events were adjudicated by and independent end-point committee. Of the 17 participating centers in COACH, all but one agreed to collect additional blood samples. The study followed the principles outlined in the Declaration of Helsinki. Ethical approval, both for the main study and for the present substudy, was obtained from the Medical Ethical Committee, and all subjects gave their written informed consent.

Measurement of BNP and NT-proBNP

Plasma BNP and NT-pro BNP were measured as described in detail before.[16] In short, plasma BNP was measured using a fluorescence immunoassay kit (Triage®, Biosite Incorporated, San Diego, CA, USA) which was validated before. The measurable range of BNP assays was 5.0-5,000 pg/mL. To convert BNP to picomoles per liter, divide by 3.47. NT-proBNP was measured using a commercially available electrochemiluminescent sandwich immunoassay (Elecsys proBNP, Roche Diagnostics, Mannheim, Germany). The analytical range of the NT-proBNP assays was 5.0-35,000 pg/mL. To convert NT-proBNP to picomoles per liter, divide by 8.46.

Statistical analysis

Data are given as mean ± standard deviation when normally distributed, as median and interquartile range when distributed not normally or skewed, and as frequencies and percentages for categorical variables. Associations between baseline variables were evaluated by means of 1-way ANOVA, the Kruskal-Wallis test, and $\chi 2$ or Fisher exact tests, when appropriate. LVEF was divided into 5 categories (≤20, 21-30, 31-40, 41-50, ≥51%) to assess relationships between baseline characteristics and LVEF. The

prevalences of NT-proBNP, BNP are presented in categories for descriptive purposes but were measured continuously in statistical tests.

To evaluate the association between NT-proBNP, BNP and the risk of all-cause mortality and hospitalization for worsening HF defined as time to first event, we calculated unadjusted, age- and sex-adjusted, and multivariable-adjusted hazard ratios (HRs), 95% confidence intervals (CIs), and 2-sided probability values using Cox proportional hazards regression models.

In multivariable models, we mutually adjusted for all important predictors of cardiovascular mortality and morbidity. These variables, in the order of strength of association with the risk of all-cause mortality and hospitalization for worsening HF, were history of cerebrovascular accident (stroke), estimated glomerular filtration rate (eGFR), previous hospitalization for HF, age, serum sodium, diabetes, NYHA functional class, LVEF, use of diuretics, use of beta-blockers, COPD, (history of) hypertension, body mass index, atrial fibrillation/flutter, use of angiotensin converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs), history of myocardial infarction, underlying heart disease, depressive symptoms, and diastolic and systolic blood pressure. Depressive symptoms were assessed using the Centre for Epidemiological Studies Depression Scale (CES-D), which contains a 20-item questionnaire, and a score of ≥16 is considered as having depressive symptoms.[17]

To assess the shape of the association between natriuretic peptides and the risk of all-cause mortality and hospitalization for worsening HF, we introduced terms with common transformations of BNP and NT-proBNP inclusive of linear, quadratic, linear plus quadratic, logarithmic, squared root, and exponential in multivariable models. The natriuretic peptides showed a log-linear functional shape with the response variables and were transformed to a 2-log scale. This means that risk estimates should be interpreted as the relative risk if values of BNP or NT-proBNP were doubled (e.g. from 10 to 20 pg/mL). In the multivariable models evaluating BNP and NT-proBNP, we additionally examined for interaction (P<0.10) of the effect of BNP and NT-proBNP with LVEF on all-cause mortality and hospitalization for worsening HF. The risk estimates of the adjusted analyses were graphically presented for increasing LVEF with different levels of BNP and NT-proBNP. For reference BNP and NT-proBNP concentrations of 250 and 1250 pg/ml were chosen (based on values in the current HF guidelines[1]), conditionally with a LVEF of 40%.

The assumption of proportionality of hazards was checked by means of Schoenfeld residuals, using procedure 'stphtest' in STATA, which is based on the methods described by Grambsch and Therneau. No severe deviations from parallelism were evident. The assumption of linearity was checked graphically by studying the smoothed marginal residuals from the null model plotted against the covariate variables. The linearity assumptions were satisfied.

The internal validity of the regression model was assessed by the bootstrap

resampling technique. A resampling analysis with 250 iterations was performed to identify the variables that entered into 50% of the Cox regression models, with $P<0.05$ for retention of variables. A second series of 250 iterations was performed with only the variables that were retained in the first iteration. This second analysis was used to assess robustness of the estimated hazard ratios and confidence intervals (CIs) in the presented mutually adjusted multivariate analysis.

Statistical analyses were performed using SPSS version 16.0 (Chicago, Illinois) and STATA version 11.0 (College Station, Texas). A two-sided *P*-value <0.05 was considered to be significant. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

The present study population (*Table 1*) consisted of 615 HF patients in whom LVEF and BNP measurements at baseline were available. In 451 of these 615 patients, NT-proBNP levels were also measured. Baseline characteristics of this population of 615 patients were comparable to those of the complete COACH cohort (n=1023).

BNP and NT-proBNP baseline measurements were available in 132 and 106 patients with LVEF ≤20%, resp., in 199 and 150 patients with LVEF 21-30%, in 129 and 90 patients with LVEF 31-40%, in 81 and 54 patients with LVEF 41-50%, and in 74 and 51 patients with LVEF ≥51%.

Association between LVEF, clinical characteristics and BNP/NT-proBNP

Patients with higher LVEF were older, more often female, and they had a higher systolic blood pressure. Also, their body mass index was higher, and haemoglobin levels were lower in patients with higher LVEF. With regard to comorbidities, the incidence of obesity, (history of) hypertension, and anaemia all increased in patients with higher LVEF (all $P<0.05$), while a trend for more COPD was observed ($P=0.05$). Depression, diabetes, and (history of) stroke were not significantly different between the groups.

Use of HF medication was different for ACE inhibitors and beta-blockers, and these drugs were less often used in those with higher LVEF. Diuretics were used by almost all patients and digoxin in about one third of the population.

Median levels of both BNP and NT-proBNP decreased as LVEF increased (both $P<0.001$ for trend, *Table 1*). In the higher LVEF groups there was a higher proportion of patients with low BNP/NT-proBNP, whereas in the lower LVEF groups most patients were in the highest BNP/NT-proBNP groups. In *Figure 1*, the following division in three categories was made for BNP: low, 0-250; middle, 250-750, and high, >750 pg/mL, and for NT-proBNP: low, 0-1250; middle, 1250-3750; and high, >3750 pg/mL. BNP/NT-proBNP levels were higher in patients with reduced LVEF (median 502 pg/mL and 3266 pg/mL, respectively) than in those with HFPEF (340 pg/mL and 1950 pg/mL, respectively; both $P<0.001$).

Table 1.Baseline characteristics of the study population.

	All patients (n=615)	LVEF ≤20% (n=132)	LVEF 21-30% (n=199)	LVEF 31-40% (n=129)	LVEF 41-50% (n=81)	LVEF >50% (n=74)	*P* for trend
Age, year	70±12	67±12	70±12	71±11	75±10	73±11	<0.001
Female gender, %	38	32	37	35	41	55	0.002
NYHA class, %							0.029
II	48	44	47	43	53	60	
III/IV	52	56	53	57	47	40	
LVEF - median, %	33	17	26	36	45	59	
Heart rate, bpm	74±14	76±14	75±12	77±16	71±11	72 ±13	0.031
Systolic BP, mmHg	118±21	111±19	115±19	122±22	124±22	124±22	<0.001
Diastolic BP, mmHg	69±12	68±11	68±12	71±15	69±14	68±11	0.719
BMI, kg/m^2	27±5	25±5	26±5	27±6	26±5	28±6	0.001
Hemoglobin, g/l	12.8±1.9	13.4±1.8	12.9±1.9	12.7±2.1	12.5±1.9	12.1±2.0	<0.001
Sodium, mEq/l	139±4	139±4	138±4	139±5	139±4	138±4	0.503
eGFR, ml/min/1.73 m^2	56±22	58±19	55±23	57±24	51±19	54±20	0.044
Natriuretic peptides							
BNP, median (IQR), pg/mL	463 (212-918)	534 (275-1130)	502 (243-1120)	447 (215-798)	424 (179-828)	256 (112-598)	<0.001
NT-proBNP*, median (IQR), pg/mL	2549 (1368-5906)	3371 (1801-7278)	3266 (1516-7694)	2365 (1218-6340)	2231 (804-4745)	1563 (758-3565)	<0.001

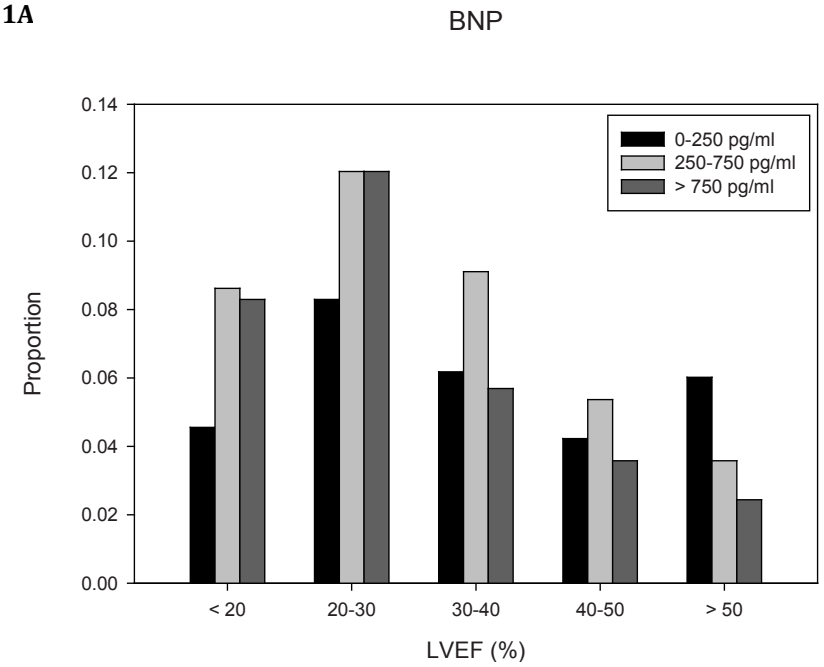
Table 1. continued

Medical history, %							
Previous HF-hospitalization	34	23	33	40	35	41	0.010
Primary cause of HF, %							
Ischemic	42	38	42	44	49	34	0.828
Non-ischemic	58	62	58	56	51	66	
Comorbidities, %							
Atrial fibrillation/flutter**	36	31	31	39	48	41	0.010
Obesity***	22	14	21	23	26	33	0.002
Diabetes	27	20	34	23	25	30	0.599
Hypertension	42	31	40	45	52	49	0.001
Stroke	10	11	10	8	16	8	0.920
COPD	26	21	28	25	22	39	0.050
Anaemia	38	26	35	40	42	49	0.007
Depressive symptoms****	39	42	34	39	48	39	0.296
Medication, %							
ACE-I	74	78	79	76	59	64	<0.001
ARB	12	13	11	7	16	14	0.693
ACE-I and/or ARB	84	89	88	83	74	74	<0.001
Beta-blocker	66	79	68	61	58	50	<0.001
Diuretic	97	97	98	95	95	97	0.606
Digoxin	32	33	31	33	35	34	0.652

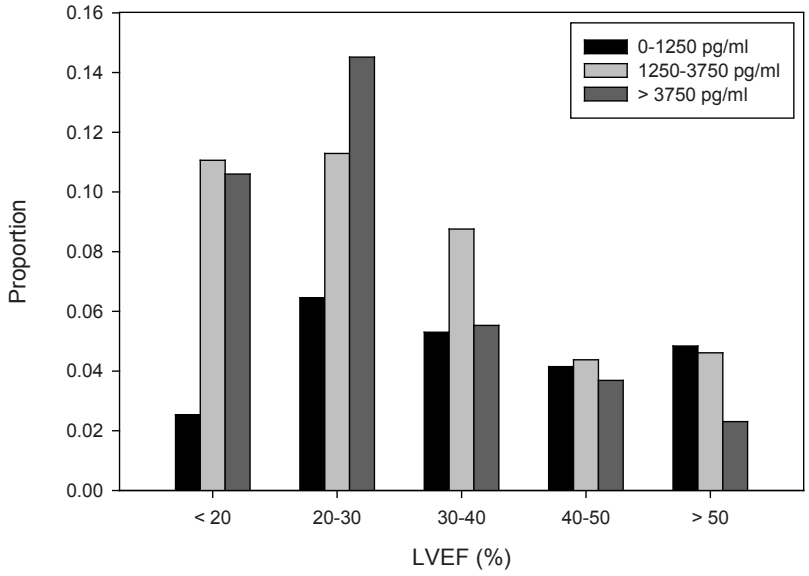
*NT-proBNP available in 451 patients (see text). **Atrial fibrillation/flutter on baseline ECG. ***Obesity defined as BMI ≥ 30 kg/m^2. ****Assessed by the CES-D score in which of ≥16 was used to define depressive symptoms[17]. BMI = body mass index; IQR = interquartile range. Other abbreviations: see text.

Figure 1. Distribution of patients in the 5 LVEF groups for BNP (1A) and NT-proBNP (1B).

1A



1B



Association between BNP/NT-proBNP and outcome

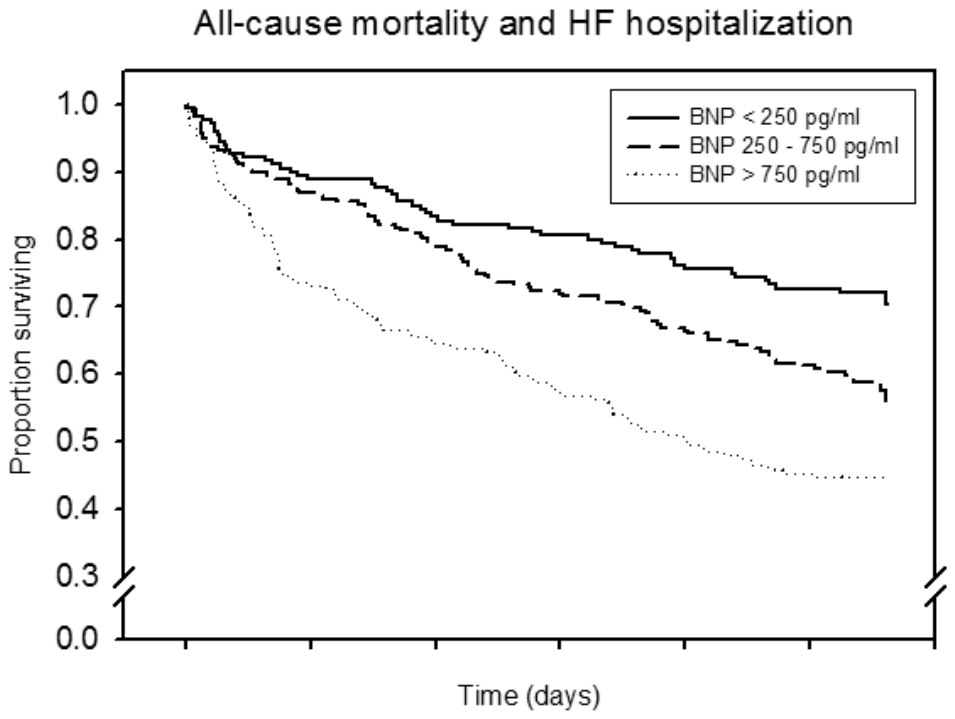
During the 18 month study, the primary endpoint (all-cause mortality and HF hospitalization) occurred in 257 patients (42%), and there were 171 (28%) patients who died.

LVEF was not associated with the primary composite endpoint and there were no significant differences between the 5 LVEF groups. The highest incidence was 51% in patients with LVEF 41-50%, and the lowest incidence was 33% in patients with LVEF 31-40%. LVEF was also not associated with all-cause mortality alone and varied from 22% in patients with LVEF 31-40% to 33% in those with LVEF 41-50%.

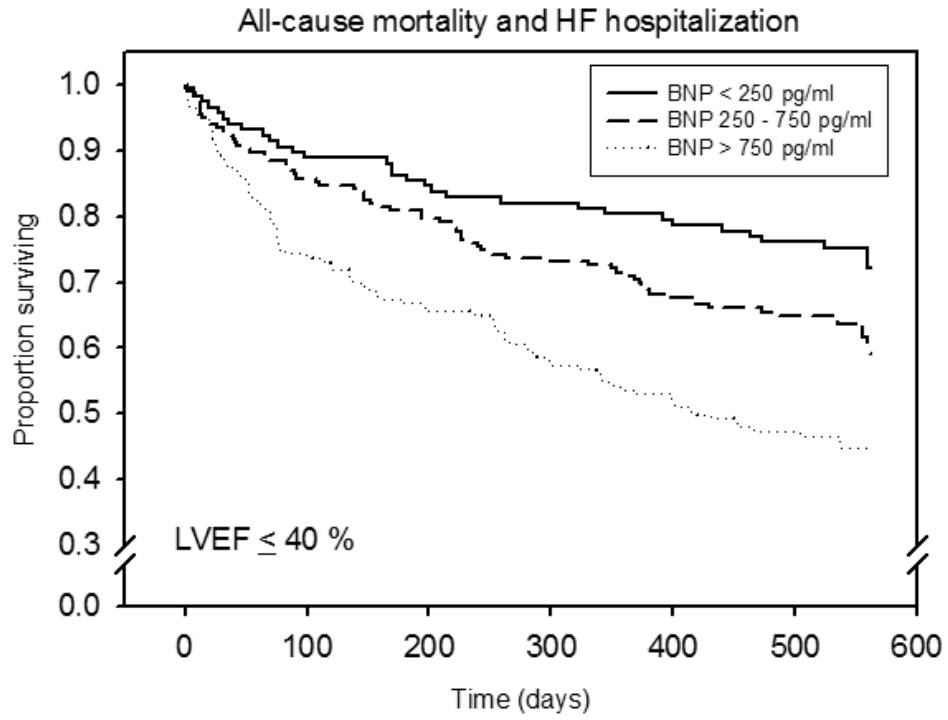
BNP and NT-proBNP were strong predictors for outcome, both in the whole population, as well as in the 2 subgroups of patients with LVEF ≤40% and in those with LVEF >40%. *Figure 2* shows the Kaplan-Meier survival curves for the composite primary endpoint for BNP, for all patients (*Figure 2A*), for patients with LVEF ≤40% (*Figure 2B*), and for patients with LVEF >40% (*Figure 2B*). Similar survival curves were observed for NT-proBNP in these 3 groups (data not shown). The association between BNP was also examined for all cause-mortality alone in the 3 LVEF groups (shown in *Figures 3A-3C*).

Figure 2. Effect of BNP on the primary endpoint (all-cause mortality and HF hospitalizations) in all patients (2A), in patients with LVEF ≤40% (2B), and in patients with LVEF >40% (2C).

2A



2B


All-cause mortality and HF hospitalization
BNP < 250 pg/ml
BNP 250 - 750 pg/ml
BNP > 750 pg/ml
Proportion surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.0
LVEF ≤ 40 %
0
100
200
300
400
500
600
Time (days)

2C

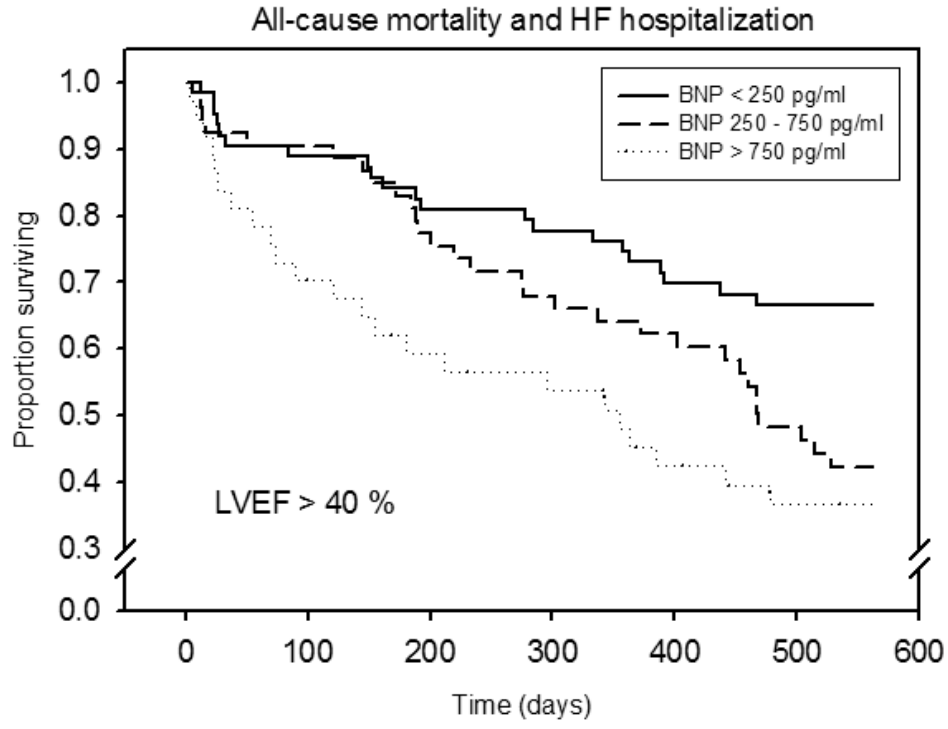
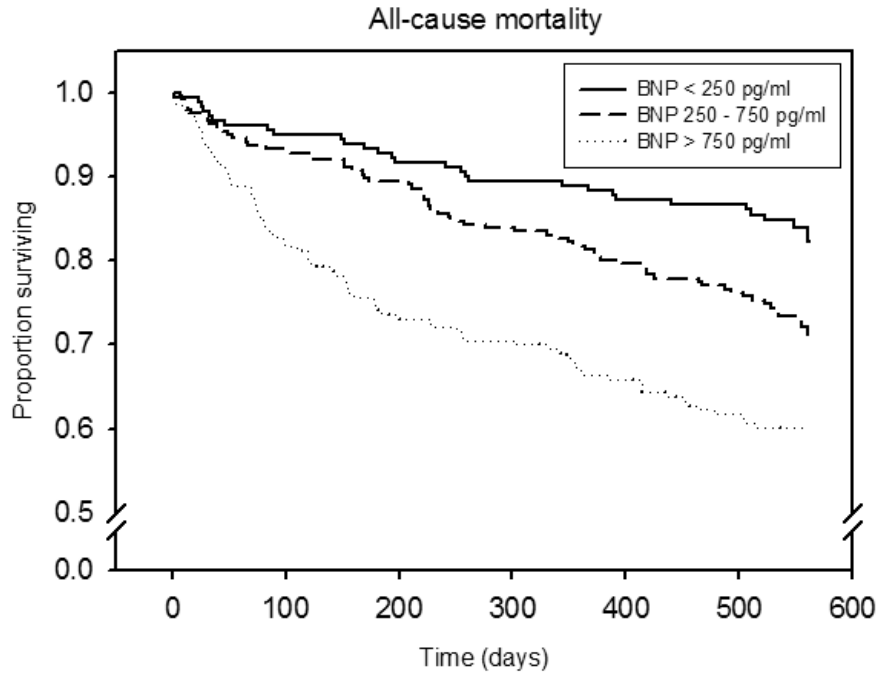
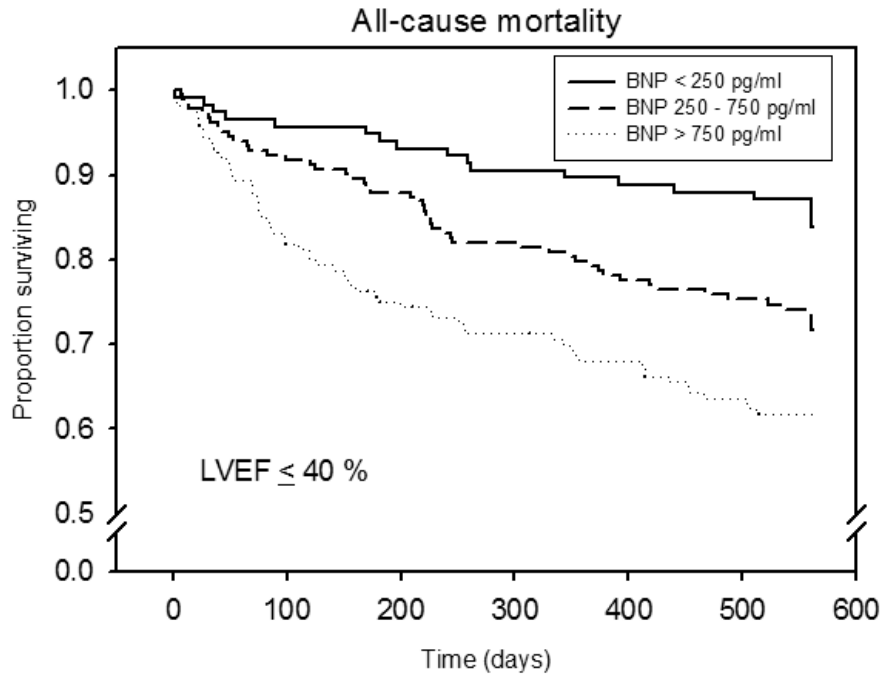

All-cause mortality and HF hospitalization
BNP < 250 pg/ml
BNP 250 - 750 pg/ml
BNP > 750 pg/ml
Proportion surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.0
LVEF > 40 %
0
100
200
300
400
500
600
Time (days)

Figure 3. Effect of BNP on all-cause mortality in all patients (A), in patients with LVEF ≤40% (B), and in patients with LVEF >40% (C).

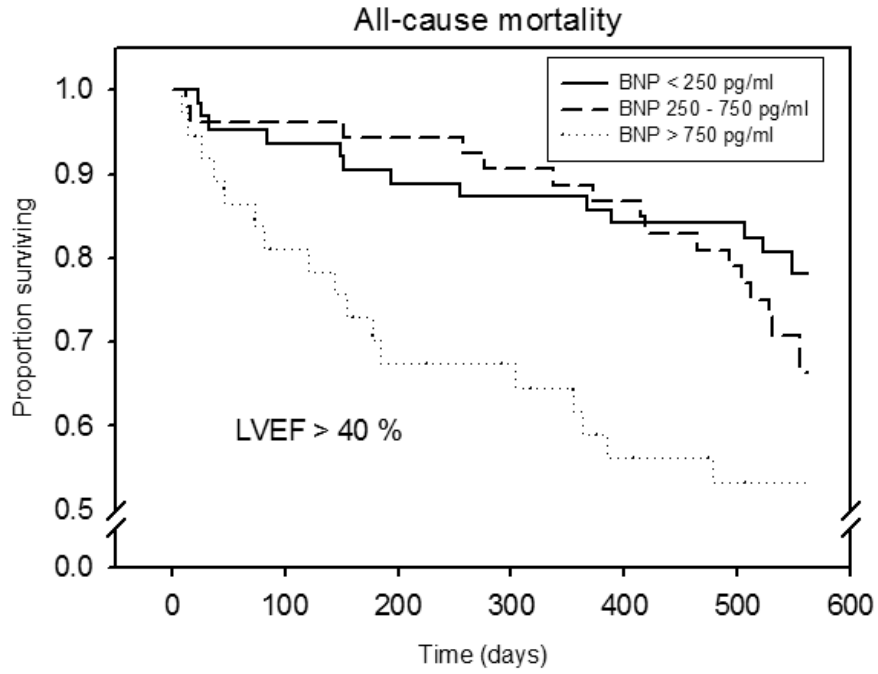
3A



3B



3C



Doubling of BNP and NT-proBNP remained significantly associated with the primary outcome and with all-cause mortality after adjustment for LVEF, age and sex, and in the multivariably adjusted analysis (*Table 2*). When adjusted for LVEF, age, sex, and other relevant covariates, doubling of BNP and NT-proBNP was still significantly associated with a 1.24 and 1.25-fold risk of the composite of all-cause mortality and HF hospitalization, respectively (both *P*<0.001, Table 2), and a 1.35 and 1.37-fold increased risk of all-cause mortality alone (both *P*<0.001, *Table 2*).

Table 2 Hazard ratios for outcome according to doubling of BNP and NT-proBNP.

BNP

All-cause mortality and HF hospitalization				
	HR	**95% CI**	**Z**	***P*-value**
BNP; unadjusted	1.29	1.19-1.41	5.96	<0.001
Adjusted for LVEF	1.32	1.21-1.45	6.33	<0.001
Adjusted for LVEF, age and sex	1.31	1.20-1.43	5.93	<0.001
Multivariably adjusted	1.24	1.12-1.37	4.20	<0.001

Table 2 continued

All-cause mortality				
	HR	**95% CI**	**Z**	***P*-value**
BNP; unadjusted	1.41	1.27-1.57	6.19	<0.001
Adjusted for LVEF	1.43	1.27-1.60	6.27	<0.001
Adjusted for LVEF, age and sex	1.41	1.26-1.58	5.95	<0.001
Multivariably adjusted	1.35	1.18-1.53	4.55	<0.001

NT-proBNP

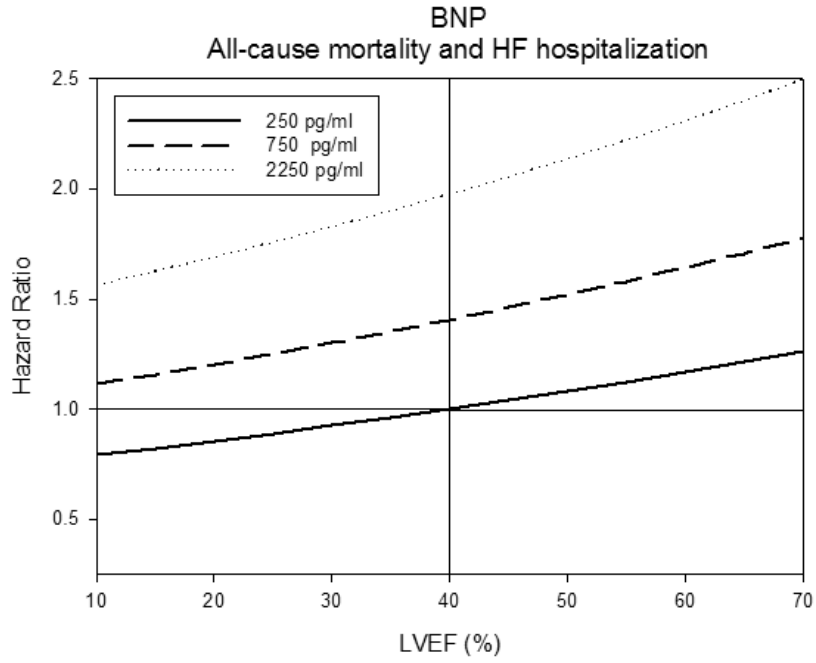
All-cause mortality and HF hospitalization				
	HR	**95% CI**	**Z**	***P*-value**
BNP; unadjusted	1.33	1.21-1.45	6.20	<0.001
Adjusted for LVEF	1.36	1.25-1.50	6.64	<0.001
Adjusted for LVEF, age and sex	1.34	1.22-1.47	6.04	<0.001
Multivariably adjusted	1.25	1.12-1.40	3.86	<0.001

All-cause mortality				
	HR	**95% CI**	**Z**	***P*-value**
BNP; unadjusted	1.45	1.30-1.63	6.44	<0.001
Adjusted for LVEF	1.47	1.31-1.65	6.53	<0.001
Adjusted for LVEF, age and sex	1.43	1.27-1.61	5.84	<0.001
Multivariably adjusted	1.37	1.18-1.59	4.19	<0.001

When we determined risk estimates of LVEF on outcome across the whole spectrum of LVEF for several specific BNP and NT-proBNP values, there were no statistically significant changes, neither for the primary composite endpoint of all-cause mortality and HF hospitalization EF (*Figure 4*) nor for all-cause mortality alone (*Figure 5*). For the composite primary endpoint, the hazard ratio for specific BNP/NT-proBNP values slightly increased with higher LVEF but this was not statistically significant (for BNP: HR 1.01 (CI 1.00-1.02), *P*=0.199; for NT-proBNP: HR 1.01 (CI 0.99-1.03), *P*=0.098), while for mortality alone no trends were observed (BNP: HR 1.00 (CI 0.99-1.02) P=0,691; NT-proBNP: HR 1.00 (CI 0.99-1.02), *P*=0.507). Subsequent interaction analyses did not show any statistically significant interaction between LVEF and BNP or NT-proBNP. The additional sensitivity analyses showed similar results (data not shown).

Figure 4. Risk estimates of LVEF on the primary endpoint (all-cause mortality and HF hospitalizations) for specific levels of BNP (A) and NT-proBNP (4).

4A



4B

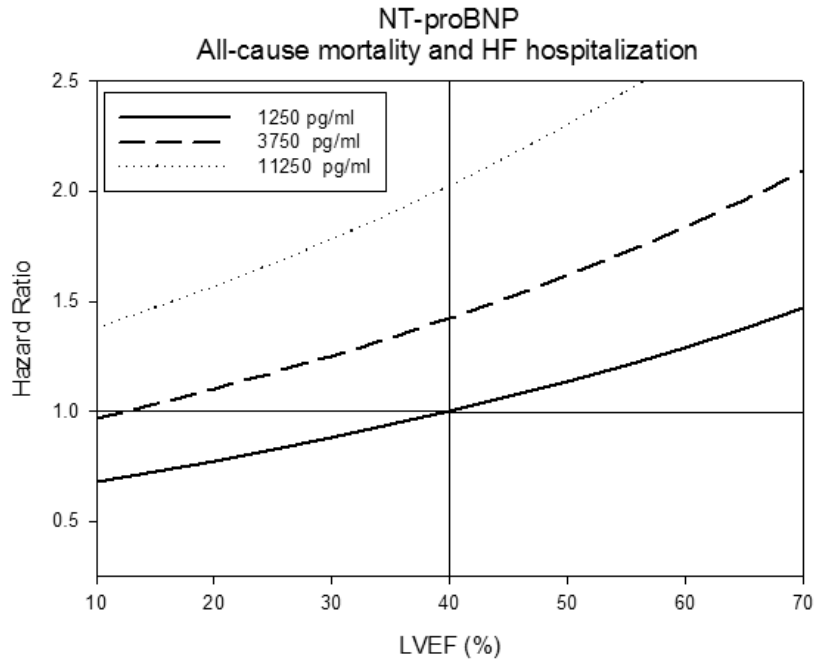
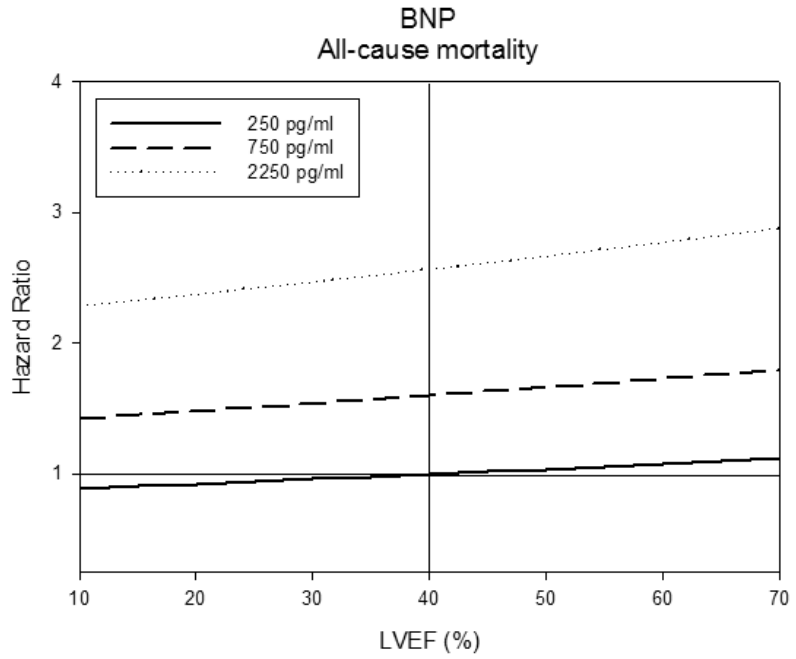
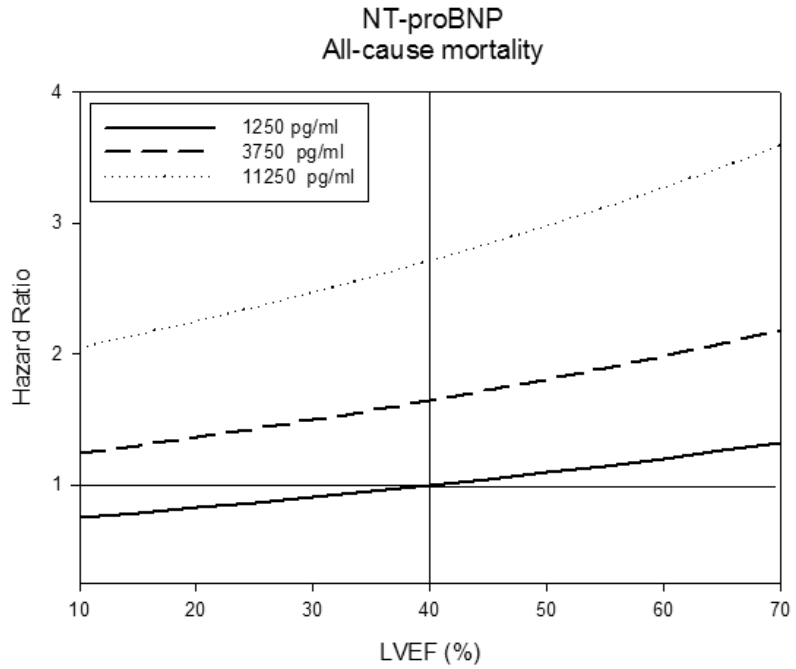


Figure 5. Risk estimates of LVEF on all-cause mortality for specific levels of BNP (A) and NT-proBNP (B).

5A



5B



Discussion

Patients with HFPEF overall have lower levels of the natriuretic peptides BNP and NT-proBNP, than HF patients with low LVEF. The most important and novel finding of the present study, however, is that for a given BNP/NT-proBNP level, the associated risk of all-cause mortality and HF hospitalization is at least similar in patients with HFPEF as in those with low LVEF. BNP and NT-proBNP are currently used on a large scale in the management of HF patients. The findings from the present study are new, and may have important clinical implications, since they suggest that if the severity and prognosis of HF patients is assessed (both clinically and in research) BNP or NT-proBNP can and should be used, irrespective of LVEF.

Other studies have also reported lower levels of BNP and NT-proBNP in patients with HFPEF than in HF patients with reduced LVEF.[11] This reflects a lesser degree of myocardial stretch and/or pressure overload, but may also be related to a larger proportion of patients who do not have heart failure, compared to HFREF patients. In fact, patients in these higher LVEF groups more often had obesity, anaemia, and COPD. Interestingly, all these three diseases have been reported to mimic HF.[8,9] Therefore, one may speculate that in some patients in the higher LVEF groups, who were thought to have HF, their complaints may in fact have been due to these co-morbidities. Consequently, BNP/NT-proBNP levels will most likely be normal or only moderately elevated.

Despite the fact that BNP and NT-proBNP were overall lower in the present study in patients with HFPEF than in those with reduced LVEF, the associated risk for reaching the primary endpoint was at least similar for a given BNP/NT-proBNP. This is the most important finding from the present study, and it may have significant clinical implications. For a long time it has been assumed that morbidity and mortality in HFPEF patients would be lower than in HF patients with lower LVEF.[5,18] The present findings indicate, however, that first, for a given BNP/NT-proBNP level, which suggest a similar severity of HF, the associated risk is at least the same, and this was true for patients with low, intermediate and high natriuretic petide levels. In other words, if a patient truly has HFPEF (confirmed by an elevated BNP/NT-proBNP level), his/her prognosis is not better than for a HF patient with a low LVEF. Secondly, it supports the notion that (elevated) BNP/NTproBNP levels should be used as an (additional) inclusion in HFPEF trials, as has been suggested before.[11,13] By using such criteria in HFPEF, patients who do not really have HF can be excluded, thereby increasing the chance of getting a favorable result in an (pharmacological) intervention trial.

HFPEF is a large medical problem, which is increasing in prevalence in the Western world,[2-4] but treatment for these patients is difficult. Despite the fact that ACE inhibitors, ARBs and beta-blockers are not recommended for HFPEF in current HF guidelines,[1,19] they are used by many patients with HFPEF (also in the present study), which may also be related to the fact that many of the patients are receiving these drugs for hypertension or diabetes.[9] The evidence for the use of these drugs in HFPEF, however,

is not conclusive. In a trial of 850 elderly patients with HFPEF (LVEF ≥40%), the ACE inhibitor perindopril did not cause a significant effect on the primary endpoint of mortality and HF hospitalizations.[20] This was partly related to the fact that there were many premature withdrawals, leading to an underpowered study, although the effect by one year was of borderline significance (*P*=0.055). In a much larger study of 3023 patients with HFPEF (LVEF >40%), the ARB candesartan caused a 14% reduction of the (adjusted) primary endpoint of cardiovascular death or HF hospitalization, which just failed statistical significance (*P*=0.051), and this effect was mainly attributed the effect on hospitalizations.[21] In the I-PRESERVE study of 4128 patients with HFPEF (LVEF ≥45%) examining another ARB, irbesartan, there was no effect on the primary outcome of mortality or cardiovascular hospitalization (hazard ratio 0.95)[22]. Patients in I-PRESERVE had low levels of NT-proBNP (median 341 pg/mL)[11] , and according to current HF guidelines (which state that HF is unlikely when NT-proBNP are <400 pg/mL)[1] , many of them would not fulfil these criteria. With regard to beta-blockers; no large-scale trial has so far been conducted in HFPEF patients. The only available data on outcome were collected in a study with nebivolol, in which a prespecified substudy showed a similar treatment effect of this beta-blocker in 752 patients with an LVEF ≥35%, as in the 1359 patients with LVEF <35%.[23] Currently, there are several ongoing trials in patients with HFPEF, and their results must be awaited.[7]

Limitations

The present study has some limitations. First, the number of patients studied was relatively small, particularly for those with HFPEF (LVEF >40%), and also it may be argued that LVEF of 45% or even 50% should be used as a cut-off. We chose a LVEF of 40% for practical purposes, and because many other large trials used this, but also because otherwise the number of patients with "HFPEF" would become small. Second, systematic echocardiographic evaluations to examine diastolic dysfunction were not done, but it has been shown that BNP/NT-proBNP correlates with indices of diastolic dysfunction, and that it has a similar accuracy of diagnosing HF as in HF patients with systolic dysfunction.[11,24]

Conclusions

For a given BNP/NT-proBNP level, the outcome in patients with HFPEF is similar as in those with reduced LVEF. Overall BNP/NT-proBNP levels, however, are lower in HFPEF than in HF with reduced LVEF, which may possibly be related to the fact, that a proportion of patients with "assumed" HFPEF may in fact not have HF. These findings may have important implications in the clinical decision making and design of trials in HFPEF.

Funding: The COACH trial was supported by a Program Grant from the Netherlands Heart Foundation (Grant 2000Z003). Additional unrestricted funding for diagnostic kits and analyzers was obtained from Biosite France (BNP) and Roche Diagnostics, The Netherlands (NT-proBNP).

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Chapter 6

Clinical and prognostic effects of atrial fibrillation in heart failure patients with reduced and preserved left ventricular ejection fraction

Gerard C.M. Linssen, Michiel Rienstra, Tiny Jaarsma, Adriaan A. Voors, Isabelle C. van Gelder, Hans L. Hillege, Dirk J. van Veldhuisen

Eur J Heart Fail. 2011;13:1111-1120

Abstract

Aims

Atrial fibrillation (AF) is common in heart failure (HF), but only few data regarding the prognostic relevance of AF are available in HF-PEF. We aimed to study the clinical impact of AF versus sinus rhythm (SR) in stabilized HF patients with reduced (HF-REF) and in those with preserved left ventricular ejection fraction (HF-PEF).

Methods and results

We studied 927 patients with stable HF, of whom 336 (36%) had AF. N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations were measured at baseline and patients were followed for 18 months. We compared time to first HF (re-)hospitalization or death between patients with AF and SR.

AF was present at baseline in 215 (35%) patients with HF-REF (mean LVEF 0.25±0.08) and in 121 (40%) patients with HF-PEF (mean LVEF 0.50±0.09). Plasma NT-proBNP levels were similar in AF and SR patients (median 2,398 versus 2,532 pg/mL, $P = 0.74$). AF was independently associated with elevated NT-proBNP levels in HF-PEF, but not in HF-REF patients (multivariable B = 0.33, $P = 0.047$ and B = 0.03; $P = 0.89$, respectively). After 18 months of follow-up, the presence of AF was an independent predictor of death or HF hospitalization in HF-PEF (multivariable hazard ratio 1.49 (95% CI 1.04-2.14), $P = 0.03$), but not in HF-REF patients (1.05 (CI 95% 0.80-1.38), $P = 0.72$).

Conclusion

AF is equally common in patients with HF-PEF and HF-REF. In HF-PEF, but not in HF-REF patients, AF was associated with higher NT-proBNP levels and was independently related to death or HF hospitalization.

Keywords

Heart failure, Atrial fibrillation, Natriuretic peptides, Prognosis, Ageing

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in patients with heart failure (HF), and its prevalence is increased in parallel to the severity of HF, ranging from 10 to 50%.[1-5]. It is widely acknowledged that HF promotes AF and that AF worsens HF prognosis.[6-13] AF can precipitate acute HF and may facilitate the progression of HF in several ways. Due to rapid heart rates, an irregular ventricular rhythm, loss of atrioventricular synchrony, and an increase of mitral and tricuspid regurgitation, the presence or onset of AF may further decrease cardiac output and aggravate HF.[14,15] In addition, filling of the left ventricle might be impaired during AF, due to loss of the "atrial kick". This might be particularly important in HF patients with preserved left ventricular ejection fraction (HF-PEF), since the main problems in these patients are an impaired relaxation and elevated filling pressures.[16-21] These haemodynamic changes may be reflected by higher plasma levels of B-type natriuretic peptide (BNP) and its inactive metabolite N-terminal pro-B-type natriuretic peptide (NT-proBNP).[22]

However, there are few data on the clinical and prognostic relevance of AF in HF-PEF versus HF patients with reduced left ventricular ejection fraction (HF-REF). Therefore, the purpose of our present study was to investigate the clinical and prognostic effects of AF (versus sinus rhythm) in stabilized HF-REF and HF-PEF patients at hospital discharge for decompensated HF.

Methods

Patient population and study design

The present study is a substudy of the Coordinating study evaluating Outcomes of Advising and Counselling in Heart Failure (COACH) study, a Dutch multicenter, and randomized, open trial with blinded endpoint evaluation. The study design and main results have been published before.[23-25] Briefly, 1023 patients were randomized, during hospitalization because of HF, to a usual care, basic support and intensive support group. All patients had been admitted to the hospital with symptoms of HF, New York Heart Association (NYHA) functional class II-IV and had evidence of structural underlying heart disease, as shown by cardiovascular imaging. Reduced LV systolic function was defined as an LVEF <40% (HF-REF); and preserved LV systolic function was defined as an LVEF ≥40% (HF-PEF) on standard transthoracic echocardiography. In the current post-hoc analyses, 927 patients with interpretable echocardiograms were included. A structured echocardiogram report was used.

The following echocardiographic criteria were used to diagnose HF-PEF: LVEF ≥ 40% (or 45% as cutoff used in additional statistical analyses) and normal or mildly depressed LV systolic function.

LA dilation assessed by 2D echocardiography was defined as maximal LA antero-posterior dimension > 40 mm on parasternal long-axis view, and RA dilatation was defined as maximal RA medio-lateral dimension > 46 mm on apical four- chamber view, respectively.

Before discharge from the hospital (i.e. before inclusion into the study), patients had to be stable on standard heart failure medication for HF, at the discretion of the physician and if tolerated, including angiotensin-converting enzyme inhibitors (ACE-I) and/or angiotensin receptor blockers (ARB); and diuretics, β-blockers, and, if indicated, digoxin. All patients were studied from hospital discharge for 18 months. In the present study we analysed the primary composite endpoint of HF hospitalization or death from any cause, and the individual components HF hospitalization and all-cause mortality. All reported endpoints were referred to and adjudicated by an independent Clinical Event Committee. Demographic and clinical data were collected from medical records and patient interview. The Medical Ethics Committee approved the study protocol and all patients provided written informed consent.

Definition of atrial fibrillation

AF was diagnosed on a standard 12-lead electrocardiogram (ECG). The index ECG was performed at hospital discharge after stabilization of decompensated HF as judged by the clinical physician. The investigators were asked to report the heart rhythm and ventricular rate on the ECG.

Laboratory analyses

Serum creatinine was determined from the blood drawn shortly before hospital discharge, in the local laboratory at each center. Estimated glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease (sMDRD, ml/min per 1.73 m^2) formula: 186.3 x (serum creatinine)$^{1.154}$ x (age)$^{-0.203}$ x 0.742 (if patient is female) x 1.212 (if patient is black).[26,27]

After patients had been clinically stabilized and recovered enough to be discharged from hospital, blood for NT-proBNP measurement was collected shortly before discharge between 8:00 AM and 4:00 PM. Ten millilitres of whole blood was taken from an antecubital vein and collected into tubes containing potassium ethylenediaminetetraacetic acid (EDTA; 1 mg/ml blood) when patients were in a supine position. The tubes were centrifuged for 10 minutes (2500 x *g*) and the plasma was separated and stored in polyepropene tubes at -70ºC to -80ºC. All NT-proBNP measurements were performed in plasma on an Elecsys™ 2010 analyser, a commercially available electrochemiluminescent sandwich immunoassay (Elecsys proBNP, Roche Diagnostics, Mannheim, Germany). The intra- and interassay coefficients of variation were 1.2-1.5% and 4.4-5.0% respectively, with an analytical range of 5-35,000 pg/mL.[28] To convert NT-proBNP to picomoles per liter, divide by 8.46.

Statistical analyses

Baseline descriptive statistics are presented as the mean ± standard deviation (SD) or median (range) for continuous variables and as numbers with percentages for categorical variables. Differences between variables in HF patients with LVEF <40% versus LVEF ≥40% were evaluated by Students t-test or Mann-Whitney U-test, depending on normality of the data, for continuous data and by Fisher exact test or Chi-square test for categorical data.

Linear regression analyses were performed to determine risk indicators of the NT-proBNP levels. To realize a constant variance, NT-proBNP values were logarithmically transformed. All patient characteristics were included. Kaplan–Meier estimates of interest were performed to study the occurrence of the primary composite endpoint during follow-up according to the underlying rhythm on the ECG at horpital discharge as reported by the investigator, AF or sinus rhythm in both patient groups. In addition, Kaplan-Meier curves were constructed on the individual endpoints of the composite endpoint; and all-cause mortality and HF hospitalization.

Adjusted hazard ratios (HR) were calculated using Cox proportional hazards regression models. Additional analyses were performed investigating HF patients with LVEF <45% versus those with LVEF ≥45%. Linearity of the continuous variables with respect to the response variable was assessed by determining the quartiles of their distribution. In case of a linear trend in the estimated risk ratios the variable was introduced in the model as continuous. If no linearity was demonstrated, the variable was further categorized. All patient characteristics and NT-proBNP were tested. All univariate variables with $P < 0.1$ were investigated in a multivariate model. In the multivariate model a variable was excluded when $P \geq 0.05$. A stepwise approach was used.

To evaluate the robustness of the presented results, a number of additional assessments were conducted: a full blown mutually adjusted analyses without taking into account NT-proBNP in view of missing measurements. Furthermore, propensity score analyses, both with and without division of the score into deciles, were performed. In addition, we explored by means of the c-statistics if differences in the selection process of prognostic parameters resulted in differences in overall discrimination. We calculated and tested c-statistics of the different models using bootstrapping techniques with selection of variables of the forced stepwise regression analyses versus variables selected by means of the backward regression analyses.

Analyses were performed using Statistical Package for Social Sciences software (SPSS version 16.0 for Windows, SPPS Inc., Chicago, Illinois) and STATA software (version 10.0, StataCorp LP, College Station, Texas, USA).

Table 1.Baseline characteristics by left ventricular ejection fraction groups comparing atrial fibrillation and sinus rhythm at hospital discharge.

	LVEF <40% (n = 623)			LVEF ≥40% (n = 304)		
	Atrial fibrillation (n = 215)	Sinus rhythm (n = 408)	P-value	Atrial fibrillation (n = 121)	Sinus rhythm (n = 183)	P-value
Female gender	65 (30%)	152 (37%)	0.09	53 (43%)	74 (40%)	0.64
Age, years	71 ± 10	68 ± 13	0.001	75 ± 9	72 ± 11	0.001
NYHA functional class			0.86			0.71
II	100 (47%)	200 (50%)		63 (53%)	105 (57%)	
III	105 (50%)	191 (47%)		50 (42%)	71 (39%)	
IV	6 (3%)	12 (3%)		6 (5%)	7 (4%)	
Randomized treatment strategy			0.88			0.93
Care as usual	65 (30%)	130 (32%)		42 (35%)	63 (34%)	
Basic support	70 (33%)	134 (33%)		40 (33%)	64 (35%)	
Intensive support	80 (37%)	144 (35%)		39 (32%)	56 (31%)	
Systolic blood pressure, mmHg	116 ± 19	114 ± 20	0.40	124 ± 20	125 ± 24	0.61
Diastolic blood pressure, mmHg	70 ± 12	67 ± 11	0.008	69 ± 12	68 ± 14	0.54
Heart rate, bpm	74 ± 14	76 ± 13	0.21	74 ± 14	72 ± 13	0.18
Body mass index, kg/m^2	27 ± 6	26 ± 5	0.05	28 ± 5	27 ± 6	0.97
Duration of heart failure, years	0.4 (0-29)	0.2 (0-30)	0.002	1.1 (0-35)	0.3 (0-34)	0.03
History of atrial fibrillation	174 (81%)	84 (21%)	<0.001	108 (89%)	44 (24%)	<0.001
History of myocardial infarction	85 (40%)	194 (48%)	0.06	27 (22%)	81 (44%)	<0.001
PCI	21 (10%)	47 (12%)	0.51	8 (7%)	21 (12%)	0.15
CABG	38 (18%)	65 (16%)	0.58	16 (13%)	30 (16%)	0.45
Valvular dysfunction	126 (59%)	218 (53%)	0.24	78 (65%)	100 (55%)	0.10
Valve surgery	12 (6%)	20 (5%)	0.72	7 (6%)	8 (4%)	0.58

Comorbidities						
Hypertension	92 (43%)	153 (38%)	0.23	62 (51%)	86 (47%)	0.48
Diabetes	54 (25%)	113 (28%)	0.51	32 (26%)	55 (30%)	0.52
Tromboembolic event	33 (15%)	63 (15%)	1.00	24 (20%)	24 (13%)	0.15
COPD	53 (25%)	95 (23%)	0.69	30 (25%)	59 (32%)	0.20
Medication						
ACE-I or ARB	189 (88%)	356 (87%)	0.90	94 (78%)	136 (74%)	0.59
ß-Blockers	149 (69%)	289 (71%)	0.71	66 (55%)	120 (66%)	0.06
Diuretics*	206 (96%)	390 (96%)	1.00	118 (98%)	174 (95%)	0.38
Digoxin	127 (59%)	72 (18%)	<0.001	61 (50%)	25 (14%)	<0.001
Calcium antagonists	25 (12%)	44 (11%)	0.79	29 (24%)	41 (22%)	0.78
Nitrates	52 (24%)	125 (31%)	0.09	34 (28%)	74 (40%)	0.03
Statins	69 (32%)	176 (43%)	0.008	29 (24%)	80 (44%)	0.001
Antiplatelet therapy	21 (10%)	172 (42%)	<0.001	12 (10%)	90 (49%)	<0.001
Oral anticoagulant therapy	200 (93%)	207 (51%)	<0.001	104 (86%)	61 (33%)	<0.001
Antiarrhythmics	32 (15%)	42 (10%)	0.12	12 (10%)	11 (6%)	0.27
Laboratory values						
NT-proBNP, pg/ml	3,045 (220-35,000)	3,068 (135-35,000)	0.50	1,800 (122-27,494)	1,898 (39-35,000)	0.84
eGFR, ml/min/1.73 m^2	54 ± 20	58 ± 23	0.04	57 ± 19	56 ± 22	0.81
Serum sodium, mEq/l	138 ± 5	138 ± 5	0.89	139 ± 4	139 ± 4	0.25
Haemoglobin, mmol/l	8.5 ± 1.1	8.4 ± 1.2	0.31	8.4 ± 1.2	8.2 ± 1.3	0.39

*Includes loop diuretics, thiazides, and aldosterone antagonists.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; NYHA = New York Heart Association; PCI = percutanuous coronary intervention.

Table 1. continued

	LVEF <40% (n = 623)			LVEF ≥40% (n = 304)		
	Atrial fibrillation (n = 215)	Sinus rhythm (n = 408)	P-value	Atrial fibrillation (n = 121)	Sinus rhythm (n = 183)	P-value
Echocardiography						
Left atrium dilated	176 (88%)	256 (73%)	<0.001	81 (78%)	89 (55%)	<0.001
LVEF	0.26 ± 0.08	0.25 ± 0.08	0.12	0.51 ± 0.09	0.51 ± 0.09	0.60
Diastolic dysfunction	36 (25%)	94 (32%)	0.18	24 (30%)	48 (35%)	0.55
Right atrium dilated	112 (62%)	103 (33%)	<0.001	57 (58%)	38 (25%)	<0.001
Right ventricle function			0.12			0.006
Reasonable	31 (18%)	49 (16%)		14 (15%)	17 (12%)	
Moderate	35 (20%)	54 (17%)		18 (19%)	9 (6%)	
Impaired	12 (7%)	9 (3%)		- (0%)	4 (3%)	

*Includes loop diuretics, thiazides, and aldosterone antagonists.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; NYHA = New York Heart Association; PCI = percutanuous coronary intervention.

Results

Patient characteristics

In total 591 (64%) patients with sinus rhythm and 336 (36%) patients with AF were studied. Plasma NT-proBNP levels were similar in AF and SR patients (median 2,398 versus 2,532 pg/mL, *P* = 0.74). Baseline characteristics of the study patients are presented in *Table 1*. In patients with HF-REF group (mean LVEF 0.25±0.08), 215 (35%) had AF on the ECG at hospital discharge, compared with 121 (40%) in patients with HF-PEF (mean LVEF 0.50±0.09) (*P* between groups = non-significant). In both groups, patients with AF were older, had a longer duration of HF history, more often a history of AF, more often dilated atria, used more often digoxin and oral anticoagulant therapy, and less often statins and antiplatelet therapy in comparison to patients with sinus rhythm (*Table 1*). There were no significant differences in the use of ACE-I or ARB, β-blockers and diuretics or in the presence of diastolic LV dysfunction on echocardiographic evaluation between patients with AF and those with sinus rhythm. There were no significant differences in heart rate between AF and SR patients in both groups.

Table 2.Multivariable analysis on the determinants of N-terminal prohormone B-type natriuretic peptide within left ventricular ejection fraction groups.

	Univariable B (95% CI)	P-value	Multivariable B (95% CI)	P-value
HF patients with LVEF <40%				
Atrial fibrillation at discharge	*0.10 (-0.14 to 0.35)*	*0.40*	*0.03 (-0.33 to 0.38)*	*0.89*
Dilated right atrium	0.32 (0.07 to 0.58)	0.01	0.46 (0.12 to 0.80)	0.008
eGFR, ml/min/1.73 m^2	-0.02 (-0.02 to -0.01)	<0.001	-0.01 (-0.02 to -0.01)	<0.001
Haemoglobin, g/dL	-0.31 (-0.40 to -0.21)	<0.001	-0.26 (-0.40 to -0.11)	0.001
HF patients with LVEF ≥40%				
Atrial fibrillation at discharge	*0.16 (-0.21 to 0.53)*	*0.40*	*0.33 (0.01 to 0.66)*	*0.047*
ß-Blockers	0.36 (-0.01 to 0.74)	0.06	0.40 (0.06 to 0.74)	0.02
Diuretics	0.98 (0.23 to 1.74)	0.01	0.80 (0.09 to 1.50)	0.03
Diastolic blood pressure, mmHg	-0.02 (-0.04 to -0.01)	0.003	-0.02 (-0.03 to -0.00)	0.01
Body mass index, kg/m^2	-0.07 (-0.10 to -0.03)	<0.001	-0.05 (-0.08 to -0.02)	0.003
eGFR, ml/min/1.73 m^2	-0.02 (-0.03 to -0.01)	<0.001	-0.01 (-0.02 to -0.01)	0.001
Hemoglobin, g/dL	-0.20 (-0.33 to -0.07)	0.003	-0.16 (-0.29 to -0.03)	0.01
LVEF	-0.03 (-0.05 to -0.01)	0.003	-0.03 (-0.05 to -0.01)	0.005

CI = confidence interval; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone B-type natriuretic peptide.

B-type natriuretic peptides and atrial fibrillation in HF-REF and HF-PEF patients

There were no differences in plasma levels of NT-proBNP between patients with AF and those with sinus rhythm, in both LVEF groups (*P* for all non-significant), see *Table 1*. However, AF was an independent determinant of elevated NT-proBNP levels (multivariable B = 0.33 (95% CI 0.01-0.66), *P* = 0.047) in HF-PEF patients, but not in HF-REF patients (multivariable B = 0.03 (95% CI -0.33-0.38), *P* = 0.89)(*Table 2*). Furthermore, body mass index, eGFR and LVEF were independent determinants of NT-proBNP levels in both HF-REF and HF-PEF groups (*Table 2*). Dilated right atrium, eGFR and haemoglobin independently determined NT-proBNP levels in the HF-REF group. Use of β-blockers and diuretics, diastolic blood pressure, body mass index, eGFR, hemoglobin and LVEF were also independently associated with NT-proBNP levels in the HF-PEF group.

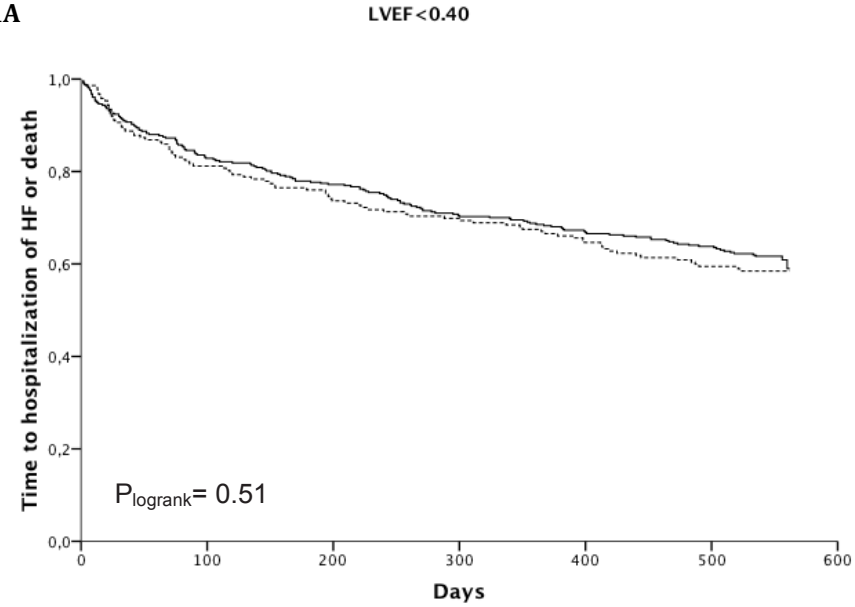
On additional analyses, the median plasma levels of NT-proBNP were similar in the HF patients with LVEF ≥40% and LVEF ≥45%. In HF patients with LVEF ≥40%, comparing AF vs. SR: median NT-proBNP was 1800 (IQR 955-3564) vs. 1898 (IQR 661-3915) pg/mL, *P* = 0.84 (*Table 1*); and in HF patients with LVEF ≥45%, comparing AF vs. SR: median NT-proBNP was 1805 (IQR 906-3311) vs. 1866 (IQR 585-3956) pg/mL; *P* = 0.65.

Table 3.Outcomes of heart failure patients by left ventricular ejection fraction groups with atrial fibrillation vs. sinus rhythm.

	LVEF <40% (n = 623)		LVEF ≥40% (n = 304)	
	Atrial fibrillation (n = 215)	Sinus rhythm (n = 408)	Atrial fibrillation (n = 121)	Sinus rhythm (n = 183)
Death or hospitalization of heart failure	88 (41%)	158 (39%)	58 (48%)	64 (35%)
Hospitalization				
All causes	115 (53%)	227 (56%)	70 (58%)	104 (57%)
Cardiovascular causes	87 (41%)	170 (42%)	57 (47%)	77 (42%)
Heart failure	49 (23%)	109 (27%)	39 (32%)	43 (24%)
Number of hospitalizations				
All causes	244	425	147	256
Cardiovascular causes	163	277	93	160
Heart failure	83	148	45	76
All-cause death	63 (29%)	99 (24%)	35 (29%)	43 (24%)

Figure 1. (1A) Time to hospitalization for heart failure or death in patients with reduced left ventricular ejection fraction – patients in sinus rhythm (solid line) and atrial fibrillation (dashed line). **(1B) Time to hospitalization for heart failure or death in patients with preserved left ventricular ejection fraction –** patients in sinus rhythm (solid line) and atrial fibrillation (dashed line).

1A



1B

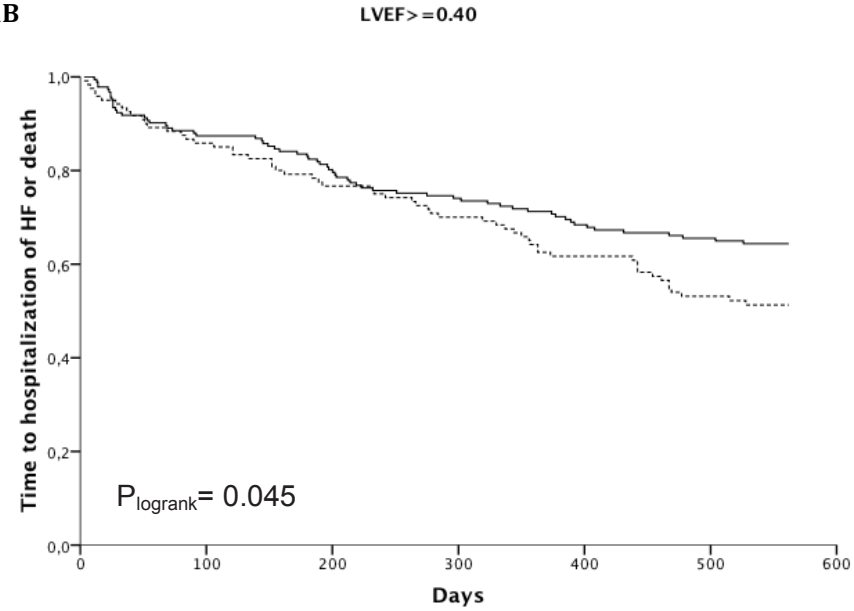


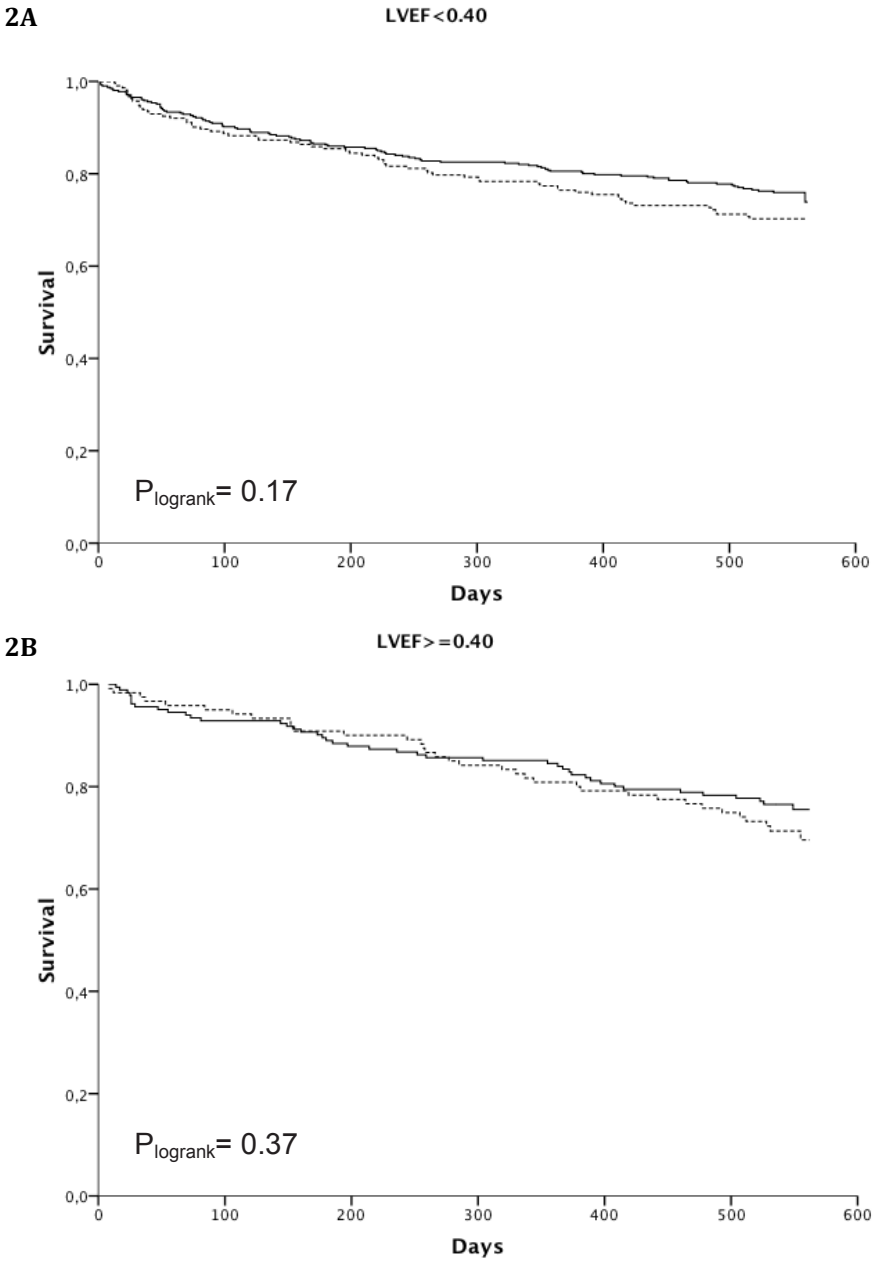
Table 4.Predictors of outcome (hospitalization for heart failure or death) in heart failure patients with left ventricular ejection fraction <40% and ≥40%.

	Univariable HR (95% CI)	P-value	Multivariable HR (95% CI)	P-value
HF patients with LVEF <40%				
Atrial fibrillation at baseline	*1.09 (0.84-1.42)*	*0.51*	*1.05 (0.80-1.38)*	*0.72*
NYHA class III vs. II	1.62 (1.24-2.10)	<0.001	1.28 (0.97-1.68)	0.08
NYHA class IV vs. II	3.23 (1.77-5.89)	<0.001	2.78 (1.51-5.12)	0.001
Myocardial infarction	1.87 (1.45-2.41)	<0.001	1.54 (1.19-2.01)	0.001
Duration of HF, years	1.06 (1.04-1.08)	<0.001	1.05 (1.02-1.07)	<0.001
eGFR, per 1 ml/min/1.73 m^2	0.98 (0.98-0.99)	<0.001	0.99 (0.98-0.10)	0.003
Haemoglobin, g/dL	0.81 (0.73-0.89)	<0.001	0.81 (0.72-0.90)	<0.001
Valvular dysfunction	1.49 (1.15-1.93)	0.002	1.32 (1.01-1.74)	0.05
Diabetes	1.69 (1.30-2.20)	<0.001		
Stroke	1.54 (1.13-2.09)	0.007		
COPD	1.42 (1.07-1.86)	0.01		
ACE-I or ARB	0.71 (0.50-1.00)	0.05		
Nitrates	1.52 (1.17-1.98)	0.002		
Statines	1.24 (0.96-1.59)	0.01		
Antiplatelet therapy	1.37 (1.06-1.78)	0.02		
Antiarrhythmics	1.40 (0.98-1.99)	0.06		
Age, years	1.02 (1.01-1.04)	<0.001		
Sodium >139 mEq/l	0.79 (0.62-1.02)	0.07		
NT-proBNP, 1,000 pg/mL	1.03 (1.02-1.04)	<0.001		

HF patients with LVEF ≥40%				
Atrial fibrillation at baseline	*1.44 (1.01-2.05)*	*0.046*	*1.49 (1.04-2.14)*	*0.03*
Diastolic blood pressure >70 mm Hg	0.61 (0.42-0.87)	0.006	0.67 (0.46-0.96)	0.03
eGFR, ml/min/1.73 m^2	0.98 (0.97-0.99)	<0.001	0.98 (0.97-0.99)	<0.001
Hemoglobin, g/dl	0.75 (0.65-0.86)	<0.001	0.85 (0.73-0.98)	0.02
Valvular dysfunction	1.87 (1.27-2.75)	0.001	1.51 (1.02-2.23)	0.04
Diabetes	1.53 (1.06-2.22)	0.02		
Stroke	1.84 (1.20-2.82)	0.005		
Nitrates	1.38 (0.96-1.97)	0.08		
Age, years	1.03 (1.01-1.05)	0.003		
Duration of HF, years	1.04 (1.00-1.07)	0.04		
NT-proBNP, 1,000 pg/mL	1.09 (1.04-1.13)	<0.001		
NYHA class III vs. II	1.85 (1.28-2.67)	0.001		
NYHA class IV vs. II	2.14 (0.97-4.70)	0.06		

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CI = confidence interval; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; NYHA = New York Heart Association.

Figure 2. (2A) All-cause mortality in heart failure patients with reduced left ventricular ejection fraction – patients in sinus rhythm (solid line) and atrial fibrillation (dashed line). **(2B). All-cause mortality in heart failure patients** w**ith preserved left ventricular ejection fraction –** patients in sinus rhythm (solid line) and atrial fibrillation (dashed line).



Clinical outcome and atrial fibrillation in HF-REF and HF-PEF patients

During a follow-up of 18 months, 368 of 927 patients (40%) reached the primary endpoint (hospitalization for HF or death) and was similar in HF-PEF (n = 122; 40%) and HF-REF (n = 246; 40%) patients. All-cause mortality rates were also equal (26% in both groups) and rehospitalization rates for HF were 25% in the HF-REF and 27% in the HF-PEF group. In the HF-REF group, 88 (41%) patients with AF and 158 (39%) patients with sinus rhythm reached the primary composite endpoint (*P* logrank = 0.51), see *Table* 3. However in the HF-PEF group, 58 (48%) patients with AF and 64 (35%) patients with SR reached the primary composite endpoint. (*P* logrank = 0.045) (*Figures 1A and 1B*). Interestingly, after adjustment for univariate variables (with $P < 0.1$), AF was independently associated with a higher risk of reaching the primary endpoint only in the HF-PEF group (HR 1.49 (1.04-2.14); $P = 0.03$) and not in the HF-REF group (HR 1.05 (0.80-1.38); $P = 0.72$), see *Table 4*.

In a full blown mutually adjusted analyses without taking into account NT-proBNP due to the large number of missing measurements (almost 50%), AF remained in the model with a comparable point estimate and confidence interval 1.62 (1.02 – 2.57) vs 1.49 (1.04-2.14).

Similar findings were observed with the propensity score analyses whether or not the propensity score was divided into deciles; 1.61 (1.01 – 2.55) vs 1.61 (1.01-2.56).

The coefficient of c-statistics of the forced entry model was: 0.67 (0.63-0.72) and not significantly different from the observed coefficient of stepwise regression analysis: 0.68 (0.63-0.73), respectively.

In both groups, there were no significant differences between AF and sinus rhythm regarding all-cause mortality, *P* logrank = 0.17 and 0.37, respectively (*Figures 2A and 2B*). Also, in both groups, there were no significant differences between AF and sinus rhythm regarding hospitalization for HF, *P* logrank = 0.46 and 0.10, respectively. Lastly, there were no significant differences between AF and sinus rhythm in the occurrence of the separate endpoints hospitalizations for all-causes, cardiovascular causes, and the number of hospitalizations, respectively (*Table 3*).

Additional outcome analyses

Although we used 40% as a cutoff for preserved versus impaired LVEF, in clinical practice guidelines 45% is also often used. Therefore, we investigated the primary outcome and separate endpoints for LVEF <45% versus ≥45% (see *Supplementary material. Table S5*). The independent predictors of the primary endpoint in 226 HF patients with LVEF ≥45% were similar to those for 304 HF patients with LVEF ≥40%. AF was independently associated with a 56% ($P = 0.04$) higher risk of reaching the primary endpoint in the HF with LVEF ≥45% and an only 8% higher risk in patients with LVEF <45% ($P = 0.55$), see S*upplementary material, Table S6*.

Discussion

AF is highly prevalent in a broad spectrum of patients with HF. In patients that were hospitalised for acute heart failure, presence of AF just before discharge was related to elevated levels of NT-proBNP and an increased risk of death or HF-hospitalization in HF-PEF patients, but not in HF-REF patients.

Atrial fibrillation and HF often coexist, although a causal relationship between these conditions has not been fully determined.[5] In the ADHERE registry[29], AF is present in one third of HF patients, which is comparable to the prevalence in our study. The EuroHeart Failure Survey reported in 24% of patients the presence of chronic AF, 25% in those with LVEF ≥40% and 23% in HF patients with LVEF <40% ($P = 0.01$).[17] At baseline, 29% of patients who participated in the irbesartan in heart failure with preserved ejection fraction trial (I-PRESERVE; age ≥60 years, LVEF ≥45%) had a history of AF.[19] In the recent European Heart Failure Pilot Survey (ESC-HF Pilot), AF on the ECG at hospital entry for acute HF was diagnosed in 35% of the cases.[30] We found that patients with AF were older, had a longer duration of HF history, more often a history of AF, more often dilated atria, in comparison to patients with SR.

The hemodynamic and clinical impact of atrial fibrillation in HF-REF versus HF-PEF

About half of the patients with acute HF and one third of patients with chronic HF have a normal or relatively preserved LVEF. Although there is considerable controversy about the underlying pathophysiology of HF-PEF, the clinical profile and neurohormonal phenotype, including B-type natriuretic peptides, resembles patients with impaired LVEF.[20,21,31,32] Levels of those peptides in stable HF are lower in the preserved LVEF patients and are related to the severity of diastolic dysfunction.[33] The CHARM Echocardiographic Substudy (CHARMES) investigators demonstrated that moderate and severe diastolic dysfunction were important predictors of adverse clinical outcome in HF patients with preserved systolic function.[34]

Nevertheless, both in patients with a reduced LVEF and in those with a preserved LVEF, B-type natriuretic peptides provide important diagnostic and prognostic information.[35]

Haemodynamic changes associated with AF in HF may further elevate plasma levels of B-type natriuretic peptides in comparison to those HF patients having normal sinus rhythm. However, clinical studies on BNP or NT-proBNP in HF patients with AF are limited and show conflicting results.[36-40] In our previous study in ambulatory patients with advanced HF-REF, we also demonstrated that AF was not independently associated with BNP and/or NT-proBNP.[40] This is confirmed by the results of the present analysis. We found that the presence of AF was not significantly related to the levels of NT-proBNP in HF-REF patients. The enhanced release of B-type natriuretic peptides into the circulation primarily reflects ventricular dysfunction in those patients. Particularly, increased myocardial wall stress induces production and release of these peptides into

the circulation reflecting elevated filling pressure and intracardiac volume overload. In patients with advanced left ventricular systolic dysfunction and concomitant severe diastolic dysfunction with restrictive physiology, the presence or new-onset of AF seems to have only minor hemodynamic consequences. However, in patients with preserved systolic function, the presence of AF with concomitant irregular ventricular rates and the loss of atrial contraction in AF may have more pronounced haemodynamic consequences, reflected by the increased NT-proBNP levels. In our study, the HF-REF patients had more often dilated LA, most likely attributed to higher LV filling pressures, also reflected by higher NT-proBNP levels in comparison to patients with HF-PEF.

Interestingly, we found that the use of β-blockers was independently associated with elevated levels of NT-proBNP in patients with HF-PEF, but not in patients with HF-REF. In the setting of relatively preserved systolic function, other factors like use of β-blockers, may influence to a more significant degree LV-filling pressures as reflected by the levels of NT-proBNP in HF-PEF.

Prognostic value of atrial fibrillation in HF-REF versus HF-PEF

Recently, a meta-analysis on the prognostic significance of AF in chronic HF observed that the presence of AF was associated with an increase of all-cause mortality with an odds ratio (OR) of 1.40 (95% CI 1.32-1.48, $P < 0.0001$) in randomized trials and an OR of 1.14 (95% CI 1.03-1.26, $P < 0.05$) in observational studies.[41] In the largest randomized trial, the CHARM-program, the presence of AF was associated with adverse outcome in patients with stable chronic HF, irrespective of baseline LVEF.[12] Olsson and co-workers reported from this prespecified sub-analysis of the CHARM-program, that AF was associated with a greater relative increased risk of cardiovascular death or hospitalization for worsening HF in patients with HF-PEF than in patients with HF-REF (HR 1.80 (95% CI 1.46-2 .21) and HR 1.38 (95% CI 1.21-1.59)).[12] Seventeen percent of patients in the low EF (≤40%) group and 19% of patients in the preserved EF (>40%) group had AF at baseline. In our study, the prevalence of AF was markedly higher in both HF-REF and HF-PEF, 35% and 40%, respectively, most likely due to the severity of HF of our study patients and the timing of the baseline ECG at hospital discharge after decompensated HF. However, consistent with the findings of the CHARM-program, we also observed a relatively greater prognostic impact of AF in patients with HF-PEF. Several other studies that included patients with HF-PEF had inconsistent results with regard to the prognostic influence of AF, which needs clarification in future outcome studies.[17,18,42]

Study limitations

The present analysis is a post hoc subgroup analysis and can only be considered hypothesis generating. Even large subgroup analyses may be misleading and provide spurious results. The classifying diagnosis of the cardiac rhythm was obtained from the ECG at hospital discharge. Although we were informed on the duration of AF, we could not differentiate between permanent, persistent or paroxysmal AF. In addition, rhythm (atrial fibrillation or sinus rhythm), heart rate and new-onset AF or conversion to sinus rhythm during follow-up were unknown. Furthermore, in the current analysis of our study, we only included medical therapy at hospital discharge. In that way, modifications in the drug treatment and non-pharmacological therapy during follow-up were not accounted for in our analysis. Finally, although we presented data on the individual components of this composite endpoint, the COACH study (1023 randomized HF patients) was powered to detect statistical differences on the primary composite endpoint. It should be addressed that the statistical power of these comparisons is limited. Finally, with respect to subgroups of HF patients, the results from our multivariable analysis should be evaluated in larger clinical studies.

Conclusions

Atrial fibrillation is equally common in patients with HF-PEF and HF-REF. In HF-PEF patients, but not in HF-REF patients, AF was associated with higher NT-proBNP levels and was independently related to death or HF-hospitalization.

Funding

This work was supported by a large program grant from the Netherlands Heart Foundation (grant 2000Z003). Prof. van Veldhuisen and Prof. Voors are Clinical Established Investigators of the Netherlands Heart Foundation (grant D97.017 and grant 2006T037).

Additional unrestricted grants were obtained from Biosite Europe, France (BNP), Roche Diagnostics, The Netherlands (NT-proBNP), and Novartis Pharma BV, The Netherlands.

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Supplementary material (Tables S5 and S6)

Table S5. Outcomes of heart failure patients (LVEF <45% and LVEF ≥45%) with atrial fibrillation vs. sinus rhythm.

	LVEF <45% (n = 701)		LVEF ≥45% (n = 226)	
	Atrial fibrillation (n = 242)	Sinus rhythm (n = 459)	Atrial fibrillation (n = 94)	Sinus rhythm (n = 132)
Death or hospitalization of heart failure	102 (42%)	177 (39%)	44 (47%)	45 (34%)
Hospitalization				
All causes	128 (53%)	256 (56%)	57 (61%)	75 (57%)
Cardiovascular causes	100 (41%)	193 (42%)	44 (47%)	54 (41%)
Heart failure	58 (24%)	123 (27%)	30 (32%)	29 (22%)
Number of hospitalizations				
All causes	282	497	109	184
Cardiovascular causes	187	329	69	108
Heart failure	94	175	34	49
All-cause death	71 (29%)	112 (24%)	27 (29%)	30 (23%)

Table S6. Predictors of outcome (hospitalization for heart failure or death) in heart failure patients with LVEF <45% and LVEF ≥45% (multivariable analysis).

	Univariable HR (95% CI)	P-value	Multivariable HR (95% CI)	P-value
Patients with LVEF <45%				
Atrial fibrillation at baseline	*1.13 (0.87-1.44)*	*0.32*	*1.08 (0.84-1.39)*	*0.55*
NYHA class III vs. II	1.65 (1.29-2.11)	<0.001	1.29 (1.00-1.67)	0.05
NYHA class IV vs. II	2.42 (1.36-4.29)	0.003	2.10 (1.17-3.77)	0.01
Myocardial infarction	1.79 (1.41-2.27)	<0.001	1.56 (1.22-1.99)	<0.001
Duration of HF, years	1.06 (1.04-1.08)	<0.001	1.04 (1.02-1.06)	0.001
eGFR, per 1 ml/min/1.73 m^2	0.98 (0.98-0.99)	<0.001	0.98 (0.98-1.00)	0.001
Hemoglobin, g/dl	0.80 (0.72-0.88)	<0.001	0.80 (0.72-0.89)	<0.001
Valvular dysfunction	1.47 (1.15-1.87)	0.002	1.27 (0.98-1.64)	0.06
Patients with LVEF ≥45%				
Atrial fibrillation at baseline	*1.43 (0.94-2.16)*	*0.09*	*1.56 (1.02-2.38)*	*0.04*
Diastolic blood pressure >70 mm Hg	0.63 (0.41-0.96)	0.03	0.99 (0.98-1.01)	0.049
eGFR, ml/min/1.73 m^2	0.98 (0.97-0.99)	<0.001	0.98 (0.97-0.99)	0.003
Hemoglobin, g/dl	0.75 (0.64-0.87)	<0.001	0.82 (0.69-0.98)	0.02
Valvular dysfunction	2.19 (1.37-3.49)	0.001	1.85 (1.15-2.96)	0.01

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; NYHA = New York Heart Association.

Chapter 7

Urinary NT-proBNP excretion in patients with chronic heart failure

Gerard C.M. Linssen, Kevin Damman, Hans L. Hillege, Gerjan Navis, Dirk J. van Veldhuisen, Adriaan A. Voors

Circulation. 2009;120:35-41

Letter to the Editor by Van Kimmenade et al. Circulation. 2010;121:e242
Response by Linssen et al. Circulation. 2010;121:e243

Abstract

Background

Urinary excretion is currently regarded as the main mechanism of elimination of NT-proBNP. The clinical implications and the value of measurement of urinary NT-proBNP in patients with heart failure are largely unknown.

Methods and Results

We studied 94 patients (age 58±11 years, 79% males) with chronic heart failure (CHF) and 20 age and gender balanced healthy controls. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured as clearance of ^{125}I-iothalamate and ^{131}I-Hippuran, respectively. NT-proBNP levels were determined in both plasma and 24-hour urine collections.

Mean left ventricular ejection fraction (LVEF) of CHF patients was 0.28±0.09. Plasma NT-proBNP levels were higher in CHF patients compared to controls (median 547 versus 41 pg/mL, P<0.001). Urinary NT-proBNP-excretion was however substantially lower in CHF-patients (median 0.13 versus 2.3 mL/min, P<0.001). Urinary NT-proBNP excretion was independent of eGFR. Both in CHF patients and controls, there was a strong and inverse relation between plasma NT-proBNP concentrations and urinary NT-proBNP excretion (r=-0.72 and r=-0.65 respectively, both P<0.001). A decreased renal plasma flow in CHF was significantly associated with a lower excretion of NT-proBNP (P =0.026).

Conclusions

Urinary NT-proBNP excretion is lower in patients with CHF compared to controls, and is inversely related to plasma NT-proBNP. Urinary NT-proBNP is associated with renal plasma flow but not with eGFR. Elevated levels of plasma NT-proBNP in patients with CHF might not only be explained by myocardial stress, but also by a marked decrease in urinary excretion.

Keywords

Heart failure, Kidney, Natriuretic peptides

Introduction

Natriuretic peptides (NPs) have beneficial effects by counteracting the activation of the renin-angiotensin-aldosterone system (RAAS). Elevation of NP levels in heart failure is mainly caused by release from the ventricles in response to increased myocardial stress. Brain-type natriuretic peptide (BNP) and its inactive N-terminal fragment (NT-proBNP) are important markers for the diagnosis and prognosis of patients with suspected or established chronic heart failure (CHF).[1-3]

The exact mechanism of elimination of NT-proBNP is still not well identified neither in health nor in disease states. Besides an increased production, elevated NP levels might also be explained by an altered metabolism and decreased clearance from the circulation. The precise role of the kidney in eliminating NT-proBNP remains however unclear.

It is well known that renal dysfunction is relatively common in patients with heart failure and is an independent risk factor for cardiovascular morbidity and mortality.[4-8] Several studies have been published on the inverse relationship between serum levels of natriuretic peptides and glomerular filtration rate (GFR). These peptides, although with higher optimal cut-off levels, remained to be diagnostic and predictive in all stages of CHF, despite the presence of significant renal dysfunction.[9-18] Recently, the diagnostic and prognostic value of *urinary* concentrations of especially NT-proBNP has been evaluated in several small studies of patients with and without CHF.[19-22]

Our hypothesis was that part of the elevated concentrations of circulating NPs in CHF is related to impaired renal function. The purpose of our present study was to investigate the impact of renal function on the excretion of NT-proBNP in urine of patients with stable CHF.

Methods

Patient population and study design

Details of the study design have been published elsewhere.[23,24] The study was conducted in the outpatient clinic of the department of Cardiology at the University Medical Center Groningen, the Netherlands.

A total of 94 patients were available for this analysis. Briefly, outpatient CHF patients, aged ≥18 years, left ventricular ejection fraction (LVEF) <45%, and clinically stable, were asked to participate. All CHF patients were given sodium-restricted dietary recommendations, according to international and hospital heart failure guidelines. All patients were on angiotensin converting enzyme inhibitors (ACE-I) and/or angiotensin-II receptor blockers (ARB), and all medication had to be stable for at least 1 month. Additionally, 20 age and gender balanced controls were studied for comparison purposes.

Baseline measurements included standard weight, height, systolic and diastolic blood pressure and assessment of NYHA functional class. All CHF patients underwent clearance measurements of renal function. Glomerular filtration rate (GFR) and effective

renal plasma flow (ERPF) were measured by the clearances of ^{125}I-Iothalamate and ^{131}I-Hippuran, respectively.[25, 26] The filtration fraction (FF) was calculated as the ratio of GFR and ERPF and expressed as percentage. Both in CHF patients and in control subjects estimated GFR (eGFR) was calculated using the simplified Modification of Diet in Renal Disease (sMDRD, mL/min per 1.73 m^2) formula: 186.3 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x 0.742 (if patient is female) x 1.212 (if patient is black).[27, 28] Serum creatinine was measured by Jaffé alkaline picrate assay.

NT-proBNP measurements were performed in plasma and in urine on an Elecsys™ 2010 analyser, a commercially available electrochemiluminescent sandwich immunoassay (Elecsys proBNP, Roche Diagnostics, Mannheim, Germany). The intra- and interassay coefficients of variation were 1.2-1.5% and 4.4-5.0% respectively, with an analytical range of 5-35,000 pg/mL.[29] Both investigators and patients were blinded to the NT-proBNP results.

Urine collection and assays

All CHF-patients and control subjects collected 24-hour urine. Urinary creatinine was determined using Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY), an automatic enzymatic method. Urinary NT-proBNP was determined by the same method as plasma NT-proBNP, and expressed as pg/mL. In addition, to account for possible differences in urine concentrations, we also corrected for urinary creatinine concentrations (ng/gram urinary Creatinine or ng/gCr). In order to evaluate the renal handling of NT-proBNP we used different modalities to assess supply, handling and excretion of NT-proBNP. As a measurement of supply, filtered load of plasma NT-proBNP was calculated as eGFR * plasma NT-proBNP levels, which represents the amount of NT-proBNP freely filtered by glomerulus to the tubules. To assess the renal handling of NT-proBNP, we measured the renal excretion (rate) of NT-proBNP (or urinary clearance), which was calculated as follows: (Urinary NT-proBNP concentrations * total urinary volume) / plasma NT-proBNP concentration. As a measurement of total NT-proBNP excretion, we also calculated the total amount of urinary NT-proBNP per day: Urinary concentration of NT-proBNP * total 24 hour urine volume. Finally, to correct for a possible effect of glomerular filtration on NT-proBNP excretion, we also calculated the fractional NT-proBNP excretion as the ratio between NT-proBNP excretion rate and eGFR: NT-proBNP excretion / eGFR * 100%. This reflects the proportion of the filtered load that is actually excreted.

Statistical analyses

Continuous variables with a normal distribution are expressed as means with standard deviation (SD). Levels of NT-proBNP are given as medians with interquartile range (IQR). Nominal variables are expressed as *n* (%). Plasma NT-proBNP levels were correlated with those in urine using Spearman's rank correlation coefficient. Data with a skewed distribution were compared by means of the Mann-Whitney-U tests and categorical

clinical variables were compared with the Fisher's exact test. Kruskal-Wallis one-way analysis of variance test was used to determine differences in fractional NT-proBNP excretion across groups of ERPF.

All reported *P* values are 2-tailed, and $P<0.05$ were considered statistically significant. Analyses were performed using Statistical Package for Social Sciences software (SPSS version 14.0.1 for Windows, SPPS Inc., Chicago, Illinois) and STATA Statistical Software release 10.0 (StataCorp LP, College Station, Texas).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Table 1.Baseline characteristics of the study patients.

Variables	CHF patients (n= 94)	Control subjects (n = 20)
Age, years	58 ± 11	58 ± 4
Male, n (%)	74 (79)	16 (80)
NYHA class I / II / III or IV, %	15 / 49 / 36	NA
Diabetes, n (%)	6 (6)	0
Current smoking, n (%)	15 (16)	0
Ischemic etiology, n (%)	43 (46)	0
Cardio-renal hemodynamic parameters		
LVEF	0.28 ± 0.09	NA
Systolic Blood Pressure, mmHg	121 ± 20	119 ± 11
Diastolic Blood Pressure, mmHg	70 ± 11	71 ± 8
Serum creatinine, mg/dL†	1.26 ± 0.38	0.89 ± 0.15
Blood urea nitrogen, mg/dL	22 ±10	NA
eGFR, mL/min/1.73m^2†	64 ± 17	90 ± 12
$GFR_{IOTH,}$ mL/min/1.73m^2	78 ± 26	NA
ERPF, mL/min/1.73m^2	282 ± 84	NA
FF, %	28 ± 5	NA
UAE, mg/day*†	5.5 (3.4 – 10.7)	1.5 (1.2 – 1.9)
Medication		
ACE-I / ARB, n (% use)	94 (100)	0
ß-blocker, n (% use)	79 (84)	0
Diuretic, n (% use)	64 (68)	0
Spironolactone, n (% use)	30 (32)	0
Calcium antagonist, n (% use)	13 (14)	0
Nitrates, n (% use)	8 (9)	0

NYHA indicates New York heart association functional class; LVEF, left ventricular ejection fraction; $GFR_{IOTH,}$ GFR measured by the clearances of ^{125}I-Iothalamate; FF, filtration fraction; UAE, urinary albumin excretion; ACE-I, angiotensin converting enzyme inhibitors; and ARB, angiotensin II receptor blockers. All continuous variables are presented with mean ± SD.

*Median value with (25^{th} – 75^{th} percentile). †$P<0.001$.

Results

Baseline characteristics

Baseline characteristics of the study patients are presented in *Table 1*. Mean age of the CHF patients was 58 years, and 21% was female. The full range of severity of CHF from NYHA classes I to IV was present. Mean LVEF was 0.28+0.09%. All patients received RAAS-inhibitors, and a large proportion also received ß-blockers (84%) and diuretics (68%). Mean GFR was 78±25 mL/min/1.73 m^2. Patients were classified according to the Kidney Disease Outcome Quality Initiative (K/DOQI).[30] Only 6% of the patients had a GFR <30 mL/min/1.73 m^2, 19% had a GFR between 30 and 60 mL/min/1.73 m^2 and 75% had a GFR >60 mL/min/1.73 m^2. The healthy control subjects were 58±4 years of age, 80% were male, and mean eGFR was 90±12 mL/min.1.73 m^2.

Plasma and urinary NT-proBNP in CHF patients and control subjects

Plasma levels of NT-proBNP of CHF-patients were higher as compared to control subjects (median 547 (IQR 253-1,324) pg/mL) and 41 (IQR 28-69) pg/mL, respectively; *P*<0.001). *Figure 1* demonstrates that urinary NT-proBNP levels were lower in CHF patients than in age and gender matched control individuals. In addition, urinary NT-proBNP excretion was substantially lower in CHF-patients versus control subjects, 0.13 (IQR 0.04-0.32) and 2.3 (IQR 1.1-3.6) mL/min, respectively (*P*<0.001), as presented in *Table 2*.

Table 2.Baseline characteristics: NT-proBNP-related parameters.

Variables*	CHF patients (n= 94)	Controls (n = 20)	P for difference
Plasma NT-proBNP, pg/mL	547 (253 – 1324)	41 (28 – 69)	< 0.001
Urinary NT-proBNP, pg/mL	55 (39 – 72)	84 (57 – 108)	0.001
Urinary NT-proBNP, ng/gCr	73 (57 – 93)	93 (63 – 123)	0.059
NT-proBNP excretion, mL/min	0.13 (0.04 – 0.32)	2.3 (1.1 – 3.6)	< 0.001
Fractional NT-proBNP excretion, %	0.13 (0.06 – 0.40)	2.6 (1.2 – 3.8)	< 0.001
Total urinary NT-proBNP, ng/24h	99 (75 – 138)	154 (85 – 192)	0.036
Filtered load, µg/24h	48 (23 – 106)	6.3 (3.2 – 8.1)	< 0.001

Cr indicates urinary creatinine.

*Median value with (25^{th} – 75^{th} percentiles).

Figure 1. Urinary NT-proBNP concentration in CHF patients vs. control subjects.
Data are presented as medians with IQR and 5 to 95% interval.

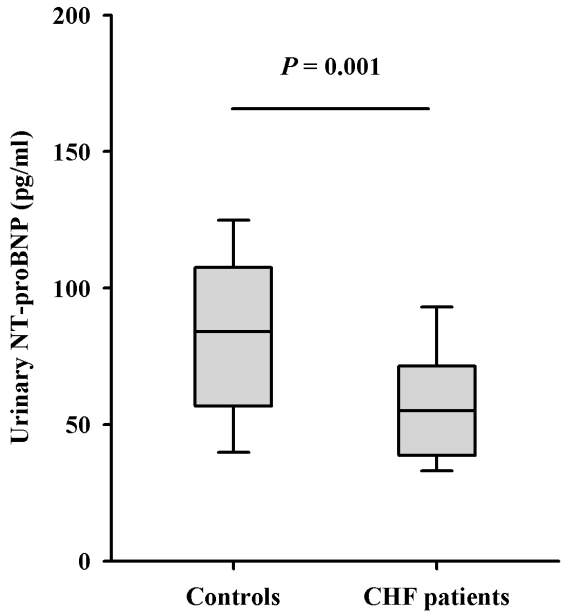


Figure 2. Relationship between NT-proBNP excretion and plasma NT-proBNP concentrations in CHF patients vs. control subjects.

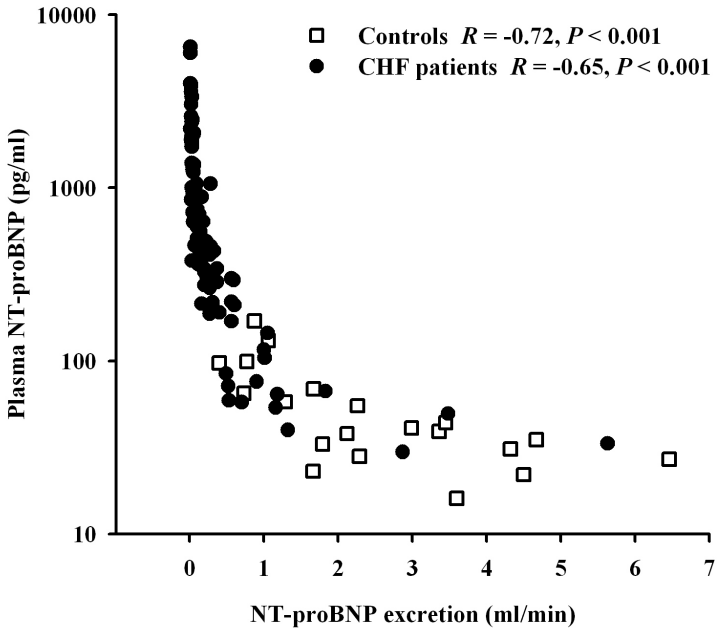
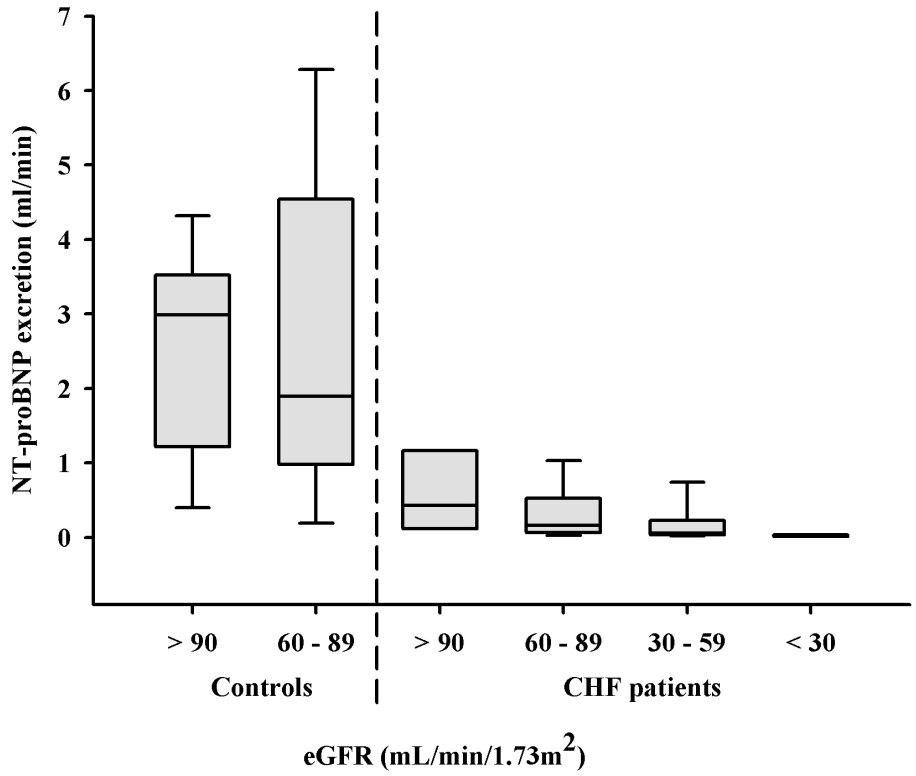


Figure 3. Relationship between estimated GFR stratified according to the Kidney Disease Outcome Quality Initiative guidelines and NT-proBNP excretion in control subjects vs. CHF patients.
Data are presented as medians with IQR and 5 to 95% interval.

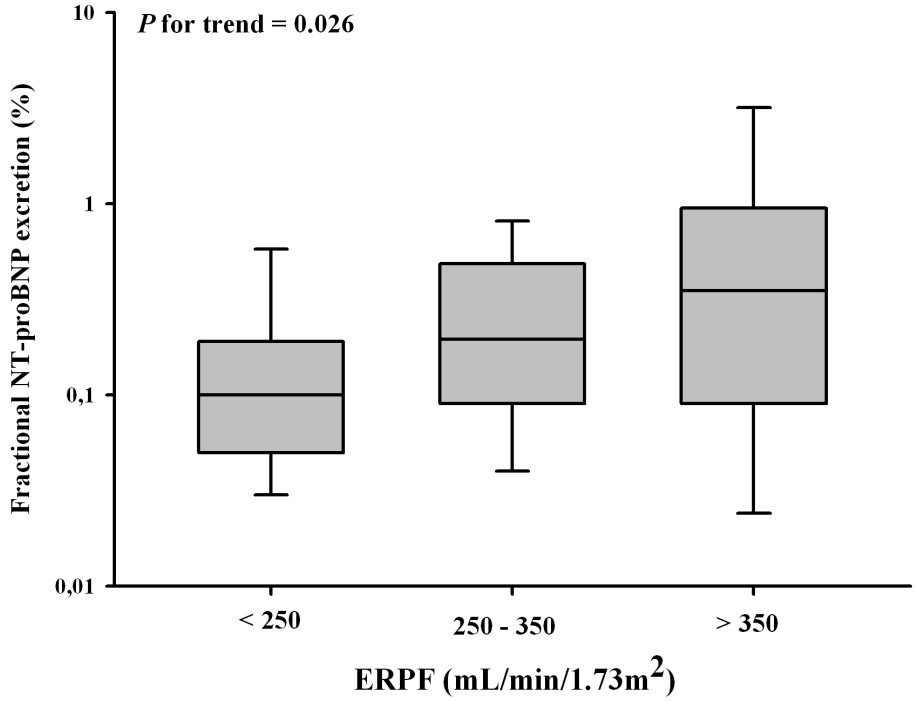


Plasma and urinary NT-proBNP and renal function

Figure 2 shows the inverse and exponential relation between plasma levels and renal excretion of NT-proBNP in CHF patients and in healthy control individuals (r = -0.65, *P*<0.001; and r = -0.72, *P*<0.001, respectively). In *Figure 3* study patients are stratified for the four K/DOQI stages of GFR. In CHF patients with moderately-severe (GFR 30-60 mL/min/1.73 m^2) and severe renal dysfunction (GFR <30 mL/min/1.73 m^2) only slightly lower urinary NT-proBNP excretion was measured in comparison to patients with normal or mildly impaired renal function (GFR 60-90 mL/min/1.73 m^2).

The relation of ERPF and fractional NT-proBNP excretion (*P for trend* = 0.026) in CHF is presented in *Figure 4*, showing that a decreased renal plasma flow in patients with CHF is associated with significantly lower excretion of NT-proBNP.
All patients in the present study were on ACE-I or ARB.

Figure 4. Relationship between effective renal plasma flow (ERPF) and fractional NT-proBNP excretion in CHF patients.
Data are presented as medians with IQR and 5 to 95% interval.



There were no significant differences in either urinary NT-proBNP levels, NT-proBNP excretion or ERPF in patients on ARB therapy compared to patients on ACE-I or a combination of both (all $P>0.05$). Patients on aldosterone antagonists had similar urinary NT-proBNP levels, but tended to have lower NT-proBNP excretion (0.06 (0.03 – 0.27) mL/min versus 0.16 (0.05 – 0.45) mL/min; $P=0.06$). However, it should be noted that plasma NT-proBNP concentrations were significantly higher in patients that used aldosterone antagonists (449 pg/mL versus 1143 pg/mL; $P=0.02$).

Discussion

This is the first study that correlated plasma and urinary NT-proBNP with the exact quantitative assessment of GFR in patients with CHF. Interestingly, in CHF the urinary excretion of NT-proBNP was markedly reduced. In addition, both in CHF patients and controls, we found a strong and inverse relation between plasma NT-proBNP and urinary excretion of NT-proBNP. The reduced urinary NT-proBNP excretion was not related to concomitant impairment of GFR, as apparent from the reduced fractional excretion, although it was associated with impaired renal perfusion. These findings

suggest that reduced NT-proBNP excretion is related to altered tubular handling of NT-proBNP in response to reduced renal perfusion and/or increased plasma NT-proBNP concentrations.

Urinary NT-proBNP and heart failure

There are only few previous studies on the presence and clinical value of urinary NT-proBNP in CHF. Ng and co-workers compared urinary levels of NT-proANP, NT-proBNP and C-type natriuretic peptide (CNP) and plasma levels of NT-proBNP between 34 patients hospitalized for heart failure with 82 age- and gender-matched echocardiographically normal subjects.[19] Urinary NT-proBNP was reported to have a diagnostic accuracy comparable with plasma NT-proBNP for the diagnosis of heart failure. Cortes and colleagues reported similar findings regarding both the diagnostic and the prognostic value of urinary NT-proBNP in 96 CHF patients.[21,31] However, Michielsen and coworkers found a rather poor diagnostic performance of urinary NT-proBNP in 47 patients diagnosed with systolic heart failure (NYHA class III and IV) and in 76 controls.[22] The markedly impaired renal function in their patients with advanced heart failure could have influenced the diagnostic value of urinary NT-proBNP.

In these studies spot morning urine samples were used to determine urinary NT-proBNP concentrations. However, plasma levels have a substantial diurnal variation, which may influence NT-proBNP excretion and consequently urinary concentration. As we measured NT-proBNP in 24-hour urine collections, our study is devoid of such bias.

Clearance of NT-proBNP from the circulation

The exact mechanism of NT-proBNP clearance remains to be elucidated, although renal clearance is currently regarded as its main mechanism.[32] Only few studies explored the renal handling of proBNP-derived peptides. In healthy individuals renal extraction ratios of approximately 0.15-0.20 were reported for both BNP and NT-proBNP.[33-37] Similar values were found in patients with CHF, in patients with liver cirrhosis and in subjects with hypertension. Interestingly, these ratios were not significantly influenced by body mass index, moderate dynamic exercise and diuretic use.[33-35,37] In our cohort of CHF patients we found a reduced GFR, that could theoretically contribute to the reduction in urinary clearance of NT-proBNP. Nevertheless, filtered load was markedly increased, as a result of markedly elevated plasma NT-proBNP levels. Interestingly, despite much higher filtered load of NT-proBNP, the urinary excretion of this peptide was significantly decreased in patients with CHF. This finding indicates altered tubular handling of NT-proBNP in patients with CHF. The exact nature of the altered tubular handling however, cannot be derived from our data, and could involve changes in tubular reabsorption as well as altered local degradation processes. So, changes in both glomerular filtration and tubular handling (reabsorption and/or local degradation processes) may account for the lower renal clearance of NT-proBNP in patients with CHF. The finding that fractional

NT-proBNP excretion was also significantly reduced in patients with CHF, suggests that the contribution of lower glomerular filtration in this process is at best minor, and that accordingly, altered tubular processing must predominantly be involved.

Cardiorenal interactions in heart failure

Both BNP and NT-proBNP (3.5 kDa and 8.5 kDa, respectively) are by definition Small Molecular Weight Proteins (SMWP: 1-50 kDa). These proteins are freely filtered by the glomeruli and catabolized by tubular epithelial cells, without any other renal processing like tubular secretion as for instance in creatinine (0.1 kDa). In hypertensive patients van Kimmenade and coworkers found no significant differences in fractional extraction of BNP and NT-proBNP between subjects with a GFR ≥60 mL/min/1.73 m^2 and subjects with a GFR <60 mL/min/1.73 m^2.[38] They suggest that elevated plasma levels of NP are mainly governed by the rate of production and to a lesser extent by renal clearance. This would imply that plasma levels of NT-proBNP predominantly represent modifications of cardiac function, also in the presence of renal function impairment. The reduction in fractional excretion of NT-proBNP in our study was associated with the reduction in renal blood flow. The reduction in renal blood flow in CHF has long been recognized as reflecting the inadequate tissue perfusion inherent to CHF, associated with an unfavorable shift in renal oxygen supply and hypoxia as indicated by an increase in renal oxygen extraction.[39] Such tubular hypoxia may be involved in altered renal handling of NT-proBNP. It can be hypothesized that heart failure may influence tubular processes in order to maintain plasma natriuretic peptide at high circulating levels as a protective mechanism which counteracts the RAAS by inducing vasodilation, diuresis and natriuresis.

The use of HF medication may have influenced the urinary NT-proBNP excretion as well. All heart failure medication that improves hemodynamics will potentially reduce plasma NT-proBNP, and increase renal perfusion. RAAS-blockers can reduce glomerular filtration rate by lowering intraglomerular pressures, through vasodilatation of the efferent arteriole. However, we found a reduction in fractional excretion of NT-proBNP, which is by definition independent of changes in GFR, so effects on GFR cannot explain our findings. Diuretics will cause afferent vasoconstriction by a tubuloglomerular feedback mechanism, thereby also reducing GFR, but again, since we found a reduction in fractional excretion of NT-proBNP, this is independent of changes in GFR. On the other hand, diuretics will influence sodium absorption in the tubule, but it is unknown whether diuretics influence tubular handling of NT-proBNP. The effects of beta-blockers on renal function in heart failure are not well understood. In patients with hypertension, bisoprolol did not affect renal hemodynamics.[40] The results of our study indicate that the use of aldosterone antagonists was related to a trend towards a lower NT-proBNP excretion, but this might have been related to the higher plasma NT-proBNP levels in patients on aldosterone blockers, probably since they had more severe heart failure.

Although, we cannot rule out a direct effect of aldosterone blockers on renal/tubular function, the present results do not indicate this.

Whether or not the reduced renal excretion of NT-proBNP reflects a protective mechanism at any rate in CHF, the elevation of plasma NT-proBNP levels can not be explained merely by increased cardiac generation, but are also due to reduced renal excretion of NT-proBNP. In addition, our data do not enable quantification of the relative contributions of increased cardiac production and diminished renal clearance to elevated plasma levels of NT-proBNP in patients with CHF. This particularly applies to the tubular fate of reabsorbed NT-proBNP. We cannot establish to what extent the reabsorbed NT-proBNP is shunted back to the circulation (which increases circulating NT-proBNP), and to what extent it is metabolised (which would decrease circulating NT-proBNP). We feel that experimental studies with labelled NT-proBNP and renal extraction studies could further clarify this. These and other unresolved issues on the role of natriuretic peptides and the altered tubular mechanisms in the context of the complex cardio-renal interactions merit further research.

Implications

Urinary NT-proBNP excretion was markedly reduced in CHF. Our data indicate that CHF exerts specific effects on renal handling of NT-proBNP, and reduces NT-proBNP excretion in relation to the reduction in renal blood flow. Sampling of 24-hour urine provided feasible and reliable NT-proBNP concentrations in our study population; however, these collections are not feasible in ambulatory patients compared to plasma samples. Furthermore, ease of spot urine sampling may facilitate community screening.[20] Further research is needed to assess the value of this strategy in accurate risk stratification, monitoring and guiding of therapy in patients with CHF.

Limitations

In this study, all patients were using renin-angiotensin system inhibitors. These drugs are considered essential therapies in patients with CHF. The population consisted only of patients with systolic dysfunction. Renal NT-proBNP handling should also be studied in patients with preserved systolic function. All of our CHF patients were of white ethnicity and formed a representative sample of the Dutch population, but whether our results are the same for CHF patients with black or other ethnicity remains to be established. Patients in the present study were younger, more often male, and had lower mean plasma NT-proBNP levels, compared to a general outpatient CHF population. Although the results could theoretically have been different in patients with more advanced CHF, we demonstrated the strong inverse correlation between plasma and urinary NT-proBNP over a wide range of patients and even in healthy controls, and we did not find any suggestion that the observed relation was different in the more severely diseased heart failure patients.

Although the Modification of Diet Renal Disease formula has been shown to be the most accurate and least biased estimate of GFR in CHF patients, it has not been validated in healthy subjects with higher GFR values.[23] Therefore, the presented results are subject to this bias. However, based on quantitative considerations of the difference in fractional excretion of NT-proBNP between heart failure patients and controls, this would not alter the conclusions regarding the altered NT-proBNP handling to any relevant extent.

Although 25% of our patients had a GFR <60 mL/min/1.73 m^2, there were only 6% with a GFR below 30 mL/min/1.73 m^2. In heart failure with comorbid end-stage renal disease, accumulation of NT-proBNP may be important. Therefore, our conclusions should not be extrapolated to patients with end-stage renal disease or undergoing dialysis.

Conclusions

Renal excretion of NT-proBNP in CHF is significantly lower compared to age and sex balanced control patients, and plasma NT-proBNP concentrations are strongly and inversely related to urine NT-proBNP concentrations. Therefore, elevated levels of plasma NT-proBNP in patients with CHF might not be exclusively explained by myocardial stress, but possibly also by a marked decrease in urinary excretion. The decrease in NT-proBNP excretion was not primarily related to GFR but seems to be related predominantly to altered tubular handling.

Acknowledgments

The authors acknowledge the laboratory assistance of Prof. Muskiet.

Funding Sources

Prof. van Veldhuisen and Dr. Voors are Clinical Established Investigators of the Netherlands Heart Foundation (grant D97.017 and grant 2006T037). Dr. Damman is supported by the Netherlands Heart Foundation (grant 2006B157).

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Letter to the Editor by Roland R.J. van Kimmenade, Harry J.G.M. Crijns, *Department of Cardiology, Maastricht University Medical Centre, Maastricht, The Netherlands* and James L. Januzzi, *Division of Cardiology, Massachusetts General Hospital, Boston (Mass), USA.*

To the Editor:

We would like to compliment Linssen and colleagues on their recent work.[1] We believe, however, that some additional comment is needed regarding the interpretation of their results.

The study by Linssen et al provides unique data; however, as already acknowledged by the authors, the amount of N-terminal prohormone brain natriuretic peptide (NT-proBNP) that is measured in urine depends not only on the filtration (ie, on the level of the glomeruli) but also on the sum of tubular secretion, catabolization at the level of the tubular brush border after secretion, and degradation after release into the urine.

It is well known that small-molecular-weight proteins (defined as peptides with a molecular weight between 1 and 50 kDa) such as NT-proBNP are catabolized in the brush border of the renal tubules after resorption.[2,3] This process of catabolization of small-molecular-weight proteins is usually nearly complete; thus, only a minor amount of NT-proBNP is to be expected to be released into the urine, as can be demonstrated by the authors' own data: the mean renal plasma flow in the heart failure patients in the study by Linssen et al was 314 mL/min,[4] meaning that (314x3600)/1000=1130 L plasma would be expected to be delivered to the kidneys in their study participants during a 24-h period. The median plasma NT-proBNP concentration of the study (547 pg/mL, or $547x10^{-12}$ g/mL=$547x10^{-9}$ g/L) suggests that $547x10^{-9}x1130=618x10^{-6}$ g NT-proBNP would be expected to arrive in the kidney during these 24 hours. Even with a maximum filtration fraction of 28%, this means that $618x10^{-6}x0.28=173x10^{-6}$ g NT-proBNP should be found in a 24-h urine collection. However, the urinary NT-proBNP concentration reported by Linssen and colleagues was only 55 pg/mL ($55x10^{-9}$ g/L). Thus, even in the context of a 24-h urine volume of 5 L, only $5x(55x10^{-9})/173x10^{-6}=0.15\%$ could be found in the urine of these patients.

Inasmuch as we have previously reported that NT-proBNP is stable in urine for more than 24 hours and at several degrees of pH,[5] the data presented by Linssen et al suggest that although NT-proBNP is indeed measurable in urine (and may have diagnostic as well as prognostic meaning when detected), caution should be taken in the interpretation of urinary NT-proBNP concentrations because there seems to be a strong influence of tubular function on concentrations of NT-proBNP that should be taken into account.

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Response by Gerard C.M. Linssen, Kevin Damman, Hans L. Hillege, Gerjan Navis*, Dirk J. van Veldhuisen, Adriaan A. Voors, *Department of Cardiology and *Internal Medicine/Division of Nephrology, University Medical Center Groningen, University of Groningen, the Netherlands.*

We appreciate the valuable comments by Van Kimmenade and colleagues on our recent article.[1] In our study we observed a low urinary excretion of NT-proBNP in patients with chronic heart failure (CHF) as compared to healthy control subjects. We agree that the total amount of this peptide which we measured in 24-hour urine collections of CHF patients is very low.

As Van Kimmenade and colleagues pointed out in their comment, the actual amount of NT-proBNP, a small molecular weight protein (SMWP), that is found in urine, is determined by several circulatory and renal processes, comprising plasma concentration, renal blood flow, glomerular filtration fraction, tubular processes (catabolization, secretion and reabsorption) and degradation in urine. However, the exact contribution of each step in the clearance of NT-proBNP is still unknown. Furthermore, extra-renal clearance contributes substantially to the total body clearance of NT-proBNP.[2] As van Kimmenade and colleagues pointed out, tubular damage seems to play a role in the altered handling of NT-proBNP as well.

Recently, we demonstrated that tubular damage was indeed present in CHF.[3] We indicated that the altered tubular handling of NT-proBNP which related to impaired renal perfusion in heart failure is an important and probably a predominant factor in explaining the net very low excretion of NT-proBNP. Therefore, we fully agree that the diagnostic and prognostic value of urine levels of NT-proBNP in CHF should be interpreted with caution. We expect that the combined information from plasma and urinary levels of NT-proBNP and tubular damage markers, e.g. NGAL may augment prognostication in CHF.

In general the natriuretic peptide system provides a compensatory mechanism to the over-activated renin-angiotensin-aldosterone system in patients with heart failure. The reduced excretion of NT-proBNP in CHF may signal an important step to maintain high circulatory levels as protective mechanism.

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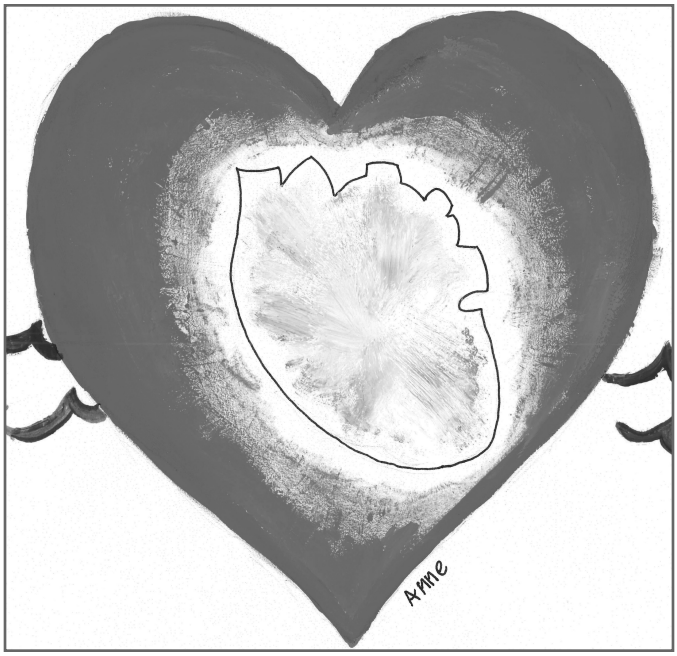
Chapter 8

Summary, conclusions and future perspectives



Summary

Circulating brain type natriuretic peptides (BNP and NT-proBNP) are powerful and established biomarkers in all stages of heart failure (HF). Both BNP and NT-proBNP are integrated in the management of patients with acute and chronic heart failure (HF).[1-6] However, there are several important issues to be addressed with regard to the use in HF management and the value of testing in the general population.

Therefore, the purpose of this thesis was twofold. In **chapters 2 and 3** this work aimed to establish the prognostic value of plasma NT-proBNP in subjects of the general population, and in the subgroup with electrocardiographic left ventricular hypertrophy (LVH). **Chapters 4 to 7** focussed on patients with heart failure. We compared the prognostic performance of BNP and NT-proBNP in HF patients after discharge for decompensated heart failure. In addition, we aimed to study the association of NT-proBNP and the presence of atrial fibrillation (AF), and impact of AF on outcome both in those with reduced versus those with preserved left ventricular ejection fraction (LVEF). In a mechanistic clinical study we aimed to investigate the impact of renal function on the urinary excretion of NT-proBNP in patients with stable chronic HF.

NT-proBNP in the general population

In **Chapter 2** we evaluated the prognostic properties of plasma NT-proBNP in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study. In total 8383 subjects (aged 28-75 years) were prospectively followed for a median period of 7.5 years. Higher levels of plasma NT-proBNP were related to adverse outcome. This study population-based study showed that plasma NT-proBNP was a strong and independent predictor of death and a wide range of CV events.

In **Chapter 3** a subgroup of the PREVEND cohort, comprising 420 individuals with electrocardiographic left ventricular hypertrophy (LVH) at baseline, was investigated. The median follow-up was extended to 10.4 years. The presence of LVH was associated with higher plasma levels of NT-proBNP at baseline. Subjects with LVH had higher cardiac event rates. This study demonstrated that plasma NT-proBNP levels independently predicted CV events in subjects with LVH on the ECG. The presence of LVH on ECG was only predictive for CV events in subjects with elevated NT-proBNP. The combined use of ECG to identify LVH and consecutive measurement of plasma NT-proBNP at baseline may identify increased risk of adverse CV events at 10 years. This strategy might reduce the need for advanced investigations, such as echocardiography.

BNP and NT-proBNP in patients with heart failure

In **chapter 4,** we compared the prognostic values of BNP and NT-proBNP measurements before hospital discharge in 563 stable HF patients who participated in the Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure (COACH). Direct comparison of the prognostic value of BNP and NT-proBNP did not reveal significant

differences. In conclusion, both BNP and NT-proBNP are equally strong and independent predictors of HF hospitalization and all-cause death at hospital discharge.

In **chapter 5** the prognostic value of BNP and NT-proBNP in 615 HF patients from the COACH cohort was reported according to baseline LVEF (divided in 5 groups). In the lower LVEF groups BNP and NT-proBNP levels were higher than in the (relatively) preserved LVEF groups.
However, if similar levels of BNP and NT-proBNP were compared across the whole spectrum of LVEF, and also for reduced (≤40%: HF-REF) and preserved LVEF (>40%: HF-PEF), the associated risk of death or HF hospitalization during 18 months of follow-up was at least as high in HF-PEF patients.

Few data are available regarding the clinical and prognostic relevance of AF in HF-PEF, a common arrhythmia in a broad spectrum of HF patients. Therefore, we studied 927 HF patients of the COACH population, of whom 336 (36%) had AF, as presented in **chapter 6**. This arrhythmia was present at baseline after a HF hospitalization in 215 (35%) patients with HF-REF and in 121 (40%) patients with HF-PEF. Presence of AF was independently associated with elevated NT-proBNP levels in HF-PEF, but not in HF-REF patients. After 18 months of follow-up, AF was an independent predictor of death or HF hospitalization in HF-PEF patients, in contrast to the HF-REF group. So, the presence of AF is equally common in patients with HF-PEF and HF-REF, but has more serious consequences in stabilized patients with HF-PEF. From a pathophysiological point of view, in patients with advanced LV systolic dysfunction, the presence or new-onset of AF have only minor hemodynamic consequences. However, in patients with preserved LV systolic function, the presence of AF with concomitant irregular ventricular rates and the loss of atrial contraction have more pronounced hemodynamic consequences, reflected by the increased NT-proBNP levels and are associated with adverse clinical outcome. From a broader perspective, the prevention of AF by renin-angiotensin system (RAS) inhibition is challenging, particularly in the early, modifiable stages of HF.

In **chapter 7**, new insights on urinary NT-proBNP excretion in patients with chronic heart failure (CHF) were described. This consisted of an analysis of renal parameters in an observational study in 94 patients with stable CHF and in 20 age and gender balanced healthy control subjects. In the CHF patients the renal function (GFR) was measured by the "gold standard" ^{123}I-iothalamate clearance. NT-proBNP levels at baseline were determined both in plasma and in 24-hour urine collections. Plasma NT-proBNP levels were higher in CHF patients compared to controls. Urinary NT-proBNP-excretion was however substantially lower in CHF-patients. Urinary NT-proBNP excretion was independent of renal function (glomerular filtration rate). Both in CHF patients and controls, there was a strong and inverse relation between plasma NT-proBNP concentrations and urinary NT-proBNP excretion. A decreased renal plasma flow in CHF was demonstrated to be significantly associated with a lower excretion of NT-proBNP. So, elevated levels of plasma NT-proBNP in patients with CHF might not only

be explained by myocardial stress, but also by a marked decrease in urinary excretion. Our study results indicate altered tubular handling of NT-proBNP in the kidneys of patients with CHF. So, changes in both glomerular filtration and tubular handling (reabsorption and/or local degradation processes) may account for the lower renal clearance of NT-proBNP in patients with CHF. The reduced renal excretion of NT-proBNP may reflect a protective mechanism which counteracts the renin-angiotensin system by inducing vasodilation, diuresis and natriuresis, in order to restore fluid and salt homeostasis.

Clinical implications

In this thesis we showed the powerful prognostic value of NT-proBNP in the general population and in subjects with LVH. Our findings are valuable for strategies aimed to early and simple identification of subjects at high risk of future CV events or on the other hand to exclude asymptomatic individuals with low CV risk from advanced investigations. In that way, these strategies may prove to be cost-effective. We found that not only subjects without LVH and a low NT-proBNP level, but also subjects with LVH on the ECG and a low NT-proBNP level at baseline had a favorable 10 years CV outcome. Our results can be used in risk stratification protocols including demographic data, traditional risk factors, a readily available ECG and testing of (NT-pro)BNP.
Further analyses of the PREVEND cohort taking incident HF into account as an additional endpoint, may clarify the association of LVH and NT-proBNP and their conjunctive impact on outcome.

A remaining key question to be addressed in future studies concerns the application of NT-proBNP (or BNP) measurements for guidance of preventive and therapeutic interventions in the community and in specific subgroups. In fact, for community screening, there is currently no evidence that the knowledge of a subject's BNP or NT-proBNP in addition to traditional risk factors, should affect clinical management. There may some benefit in subgroups with intermediate risk of CV events, although there is an unmet need for randomized trials. For now, BNP and NT-proBNP are proven particularly useful for diagnostic and prognostic purposes in patients presenting with acute dyspnoea and in those with established cardiovascular disease.

In patients with heart failure (HF) observational clinical studies showed that the presence of atrial fibrillation (AF) and increments of BNP or NT-proBNP had more impact on outcome in HF patients with (relatively) preserved left ventricular systolic function, in which few evidence-based therapies are available, in comparison to HF patients with reduced systolic function. We found in the COACH cohort, that for a given BNP or NT-proBNP level, the rate of adverse outcome in patients with HF-PEF is at least as high as in those with reduced LVEF. Therefore, in HF patients, the presence of AF and elevated plasma levels of (NT-pro)BNP may serve as biological signals of adverse outcome. The clinical implications in daily practice include better identification,

characterization and surveillance, also of HF patients with relatively preserved LVEF. Early detection of elevated filling pressures and congestion by measuring (NT-pro) BNP serially and the occurrence of (incident) AF during follow-up may identify HF patients with increased risk of decompensated or worsening HF. Out-patient disease management programs may provide close monitoring and timely intervention. We speculate that HF-PEF patients benefit at least as much as HF-REF patients from close surveillance in HF management programs.

Many pathophysiological aspects of the cardiorenal interaction in HF and the protective role of B-type natriuretic peptides need to be clarified. Our observational, controlled study provided relevant information on the relationship between the heart failure syndrome and renal hypoperfusion, resulting in lower excretion of natriuretic peptides, as part of a compensatory mechanism. This is important, because the modulation of glomerular and tubular function and its bidirectional influence on the heart failure syndrome in which reduced renal blood flow plays a pivotal role, relevant for the medical treatment with diuretics and blockers of the renin-angiotensin system.[7]

Future perspectives

New research initiatives and more sophisticated clinical applications of natriuretic peptides in cardiovascular disease may provide improved patient management and clinical outcome.

Both plasma and urinary biomarkers can detect maladaptation or early adverse effects of drugs leading to (worsening) heart and renal failure. The first results of studies on the application of several novel biomarkers are promising.[8-11] Exploring how new biomarkers can be linked to specific therapeutic interventions is advocated, in order to translate evidence to clinical practice.

A more integrated and personalized approach for subjects both in the community and in specific CV disease subgroups can profit from advances in the rapidly developing fields of proteonomics and genomics.[12] In addition, a better understanding of which subjects of a population benefit most from further risk stratification and the initiation of randomized trials to test the corresponding hypotheses, may lead to biomarker-guided prevention.[13] In the future, physicians may be able to use a person's genetic-variation profile to determine the optimal therapeutic intervention.[14] From the perspective of the unmet need of individualized strategies, recently, a large European multicenter prospective research program (BIOSTAT-CHF) using a systems biology approach to identify which patient will exerts a poor response to treatment, was initiated.

In recent years BNP and NT-proBNP in conjunction with standard HF care were investigated in clinical studies aimed at improving therapeutic strategies in HF patients. A meta-analysis of 6 randomized controlled trials on so-called biomarker-guided HF therapy showed that titration of medical therapy using serial BNP or NT-proBNP levels was associated with a significant reduction in all-cause mortality compared to usual

care.[15] However, which patients benefit most and what are the instructions for the use of these biomarkers in guidance of HF drug therapy needs to be explored in an adequately powered randomized controlled trial.

The complementary use of biomarkers and cardiovascular imaging techniques holds promise for identifying high-risk patients, and initiation and titration of therapy. Molecular imaging would add to the assessment of biological properties of specific regions of the CV system.[16]

In summary, major pharmacologic and technological advances have been realized in the approach to the management of patients with HF. Blockers of the renin-angiotensin-aldosterone system, beta-blockers, cardiac resynchronization therapy and implantable cardioverter-defibrillators demonstrated favorable effects in HF outcome studies. Nevertheless, morbidity and mortality remain unacceptably high partially due to a treatment gap that exists between HF guidelines and the care of patients with HF. In the 21st century, testing of B-type natriuretic peptides showed to contribute to the identification, risk stratification and monitoring of patients with acute and chronic HF. Therefore, these biomarkers were included in practice guidelines and are widely used. However, consistent implementation and adherence to these evidence-based guidelines should be facilitated even more to deliver optimal care to individual HF patients. The clear benefit of this recommendation was recently demonstrated by The Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE-HF) in the USA, a defined and scalable practice-specific performance improvement intervention, which was associated with substantial improvements in the use of guideline-recommended therapies in outpatient cardiology practices.[17] The results of this registry are quite encouraging and provide stimuli for improving HF patient management. In that way, the merits of evidence-based medicine and consecutive implementation of corresponding practice guidelines will be beneficial for the delivery of patient care, ultimately resulting in improved survival and quality of life.

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Samenvatting

Bepaling van de bloedspiegels van brein-type natriuretische peptiden (BNP en NT-proBNP) is laatste jaren waardevol gebleken bij patiënten met (verdenking op) hartfalen (HF).
Deze laboratoriumonderzoeken zijn geïntegreerd in de dagelijkse praktijk van onderzoek en de behandeling van patiënten met acuut en chronisch hartfalen.

Er zijn echter nog een aantal belangrijke vragen te beantwoorden, zowel op het gebied van HF als over de waarde van het testen in de algemene bevolking.

Globaal was het doel van dit proefschrift daarom tweeledig. Ten eerste werd de voorspellende waarde van plasma NT-proBNP op het ontstaan van atherosclerotische hart- en vaatziekten op lange termijn onderzocht in de algemene bevolking, en in de subgroep met linker ventrikel hypertrofie (LVH), een verdikte linker kamerspier, op het electrocardiogram (ECG). Ten tweede werden aspecten van de prognostische waarde van BNP en NT-proBNP bij HF patiënten na ontslag voor gedecompenseerd hartfalen onderzocht. In dat kader werd eveneens het verband bestudeerd tussen NT-proBNP en de aanwezigheid van boezemfibrilleren (BF) en de betekenis voor de prognose beschreven. Ook werden HF patiënten met een verminderde linker ventrikel ejectiefractie (LVEF) vergeleken met patiënten met een relatief behouden (LVEF).

Tot slot was een pathofysiologische studie bij chronische HF patiënten gericht op het verband tussen nierfunctie en de uitscheiding in de urine van NT-proBNP.

Bepaling van NT-proBNP in de algemene bevolking

In **hoofdstuk 2** werd de prognostische eigenschappen van plasma NT-proBNP in de Groninger Preventie van nier- en vaatschade studie (PREVEND) bestudeerd. In totaal 8383 personen (leeftijd 28-75 jaar) werden gevolgd gedurende een periode van 7,5 jaar. Hogere plasmaspiegels van NT-proBNP waren gerelateerd aan een ongunstige klinische uitkomst. Deze grote studie toont aan, dat plasma NT-proBNP een sterke en onafhankelijke voorspeller is van overlijden en een breed scala aan hart- en vaatziekten op lange termijn.

In **hoofdstuk 3** werd een subgroep van de PREVEND populatie, bestaande uit 420 mensen met linker ventrikel hypertrofie (LVH) op het ECG bij aanvang, onderzocht, gedurende ruim 10 jaar. De aanwezigheid van LVH was geassocieerd met hogere plasmaspiegels van NT-proBNP. Patiënten met LVH had een hogere kans op het ontstaan van een hartziekte, zoals hartinfarct. Deze studie toonde aan dat de plasmaspiegel van NT-proBNP een onafhankelijke voorspeller is van diverse hart- en vaatziekten op lange termijn. Interessant is, dat de aanwezigheid van LVH op ECG alleen in die gevallen voorspellend was voor een ongunstige prognose als zij ook een verhoogde NT-proBNP concentratie hadden. Het gecombineerde gebruik van ECG (LVH) en een opeenvolgende meting van plasma NT-proBNP kan mensen met een verhoogd risico op diverse hart- en vaatziekten op lange termijn identificeren. Deze strategie kan de behoefte aan geavanceerde vervolgonderzoeken, zoals echocardiografie, verminderen, en kan in dat opzicht kostenbesparend zijn.

BNP en NT-proBNP bij patiënten met hartfalen

In **hoofdstuk 4** hebben we de voorspellende waarde van zowel BNP als NT-proBNP metingen bij ontslag uit het ziekenhuis van 563 stabiele HF patiënten beschreven. Deze mensen namen deel aan de landelijke Coördinerende studie ter evaluatie van Resultaten van Advisering en Begeleiding bij hartfalen (COACH). Directe vergelijking van de prognostische waarde van BNP en NT-proBNP leverde geen significante verschillen op. De conclusie was dat BNP en NT-proBNP even sterke en onafhankelijke voorspellers zijn van overlijden en ziekenhuisheropname voor HF binnen anderhalf jaar na ontslag uit het ziekenhuis.

In **hoofdstuk 5** werden de prognostische waarde van BNP en NT-proBNP bij 615 COACH-patiënten, verdeeld in vijf groepen van LVEF onderzocht. In de lagere LVEF groepen waren de bloedspiegels van BNP en NT-proBNP hoger dan in de (relatief) behouden LVEF groepen. Echter, bij een vergelijkbaar niveau van BNP en NT-proBNP was over het hele spectrum van LV functie, het risico van overlijden of ziekenhuisheropname voor HF minstens zo hoog bij hen met een behouden functie.

In het algemeen zijn weinig gegevens beschikbaar over de klinische en prognostische relevantie van BF bij HF met behouden LVEF. BF is een veel vóórkomende hartritmestoornis bij een breed spectrum van HF patiënten. Daarom onderzochten we dit bij 927 COACH-patiënten, van wie er 336 (36%) BF had (**hoofdstuk 6**). Deze ritmestoornis was aanwezig bij aanvang na een ziekenhuisopname voor HF bij 215 (35%) HF patiënten met lage LVEF en bij 121 (40%) patiënten met behouden LVEF. De aanwezigheid van BF was onafhankelijk geassocieerd met verhoogde NT-proBNP niveaus bij hen met een behouden LVEF, maar niet bij hen met een lage LVEF. Na 18 maanden follow-up, bleek BF een onafhankelijke voorspeller van overlijden of ziekenhuisheropname voor HF bij de groep met een behouden LVEF, in tegenstelling tot de groep met een lage LVEF. Dus, de aanwezigheid van BF komt even vaak voor bij HF patiënten onafhankelijk van de LVEF. maar is geassocieerd met een slechtere prognose bij gestabiliseerde HF patiënten met een (relatief) behouden LVEF. Vanuit een pathofysiologisch oogpunt, heeft de aanwezigheid of het opnieuw optreden van BF bij patiënten met een duidelijk verminderde LV systolische functie, slechts geringe, extra hemodynamische gevolgen. Echter, bij patiënten met een behouden LV systolische functie, hebben de aanwezigheid van BF en daarbij onregelmatige kamerfrequenties en het verlies van de boezemcontractie, meer uitgesproken hemodynamische gevolgen. Dat fenomeen weerspiegelt zich in de relatie met NT-proBNP concentraties en is geassocieerd met een ongunstige klinische uitkomst. Vanuit een breder perspectief, is het voorkómen van BF door renine-angiotensine-aldosteron systeem (RAAS) remming een uitdagend concept, vooral in de vroege, beïnvloedbare stadia van HF.

In **hoofdstuk 7**, zijn nieuwe inzichten in de urine NT-proBNP uitscheiding bij patiënten met stabiel hartfalen beschreven. Deze bestond uit een nauwkeurige analyse van de nierparameters in een observationele studie bij 94 patiënten, welke werden

vergeleken een controlegroep van 20 gezonde vrijwilligers. Bij de HF patiënten werd de nierfunctie (GFR) gemeten volgens de gouden standaard, de ^{123}I-iothalamate klaring. NT-proBNP spiegels bij aanvang werden bepaald zowel in plasma als in gedurende 24-uur verzamelde urine. Plasma NT-proBNP was hoger bij de HF patiënten vergeleken met de controlegroep. De uitscheiding van NT-proBNP in de urine was echter aanzienlijk lager in HF groep. Dit bleek onafhankelijk van de nierfunctie. Zowel bij de HF groep als bij de controlegroep, was er een sterke, omgekeerde relatie tussen de plasma NT-proBNP concentraties en urine NT-proBNP excretie. Een verminderde nierdoorbloeding bij hartfalen bleek significant geassocieerd met een lagere uitscheiding van NT-proBNP. Dit betekent, dat verhoogde plasmaconcentraties van NT-proBNP bij patiënten met hartfalen niet alleen verklaard worden door myocard stress, maar ook door een sterke afname van de urine-excretie.

Onze bevindingen wijzen, weliswaar indirect, op een aangepaste functie van de niertubuli bij patiënten met hartfalen. Zo kunnen veranderingen in zowel glomerulaire filtratie als tubulusfunctie (reabsorptie en/of lokale degradatieprocessen) leiden tot een lagere nierklaring van NT-proBNP. De verminderde uitscheiding van NT-proBNP door de nieren kan wijzen op een beschermend mechanisme, dat er voor zorgt dat de invloed van het overgeactiveerde RAAS bij hartfalen, wordt afgeremd. Hierdoor draagt het verhoogde niveau van het biologisch actieve BNP in de circulatie, dat leidt tot vaatverwijding en meer uitscheiding van water en zout, bij aan het herstel van de balans.

Klinische implicaties

In dit proefschrift is de sterke, prognostische waarde van NT-proBNP in de algemene bevolking en bij mensen met LVH aangetoond. Onze bevindingen zijn waardevol voor strategieën gericht op vroegtijdige en eenvoudige identificatie van personen met een hoog risico op diverse hart- en vaatziekten op lange termijn. Tevens kunnen personen met een gunstige prognose uitgesloten worden van ingewikkelde, veelal dure vervolgonderzoeken. Wij vonden, dat personen met een lage NT-proBNP spiegel (met of zonder LVH) een gunstige 10 jaar prognose hebben. Ons concept kan naast traditionele risicofactoren worden gebruikt worden in preventie protocollen.

Verdere analyses van het PREVEND populatie waarbij het ontstaan van hartfalen wordt meegenomen als uitkomstmaat, kunnen de relatie van LVH en NT-proBNP en hun gezamenlijke invloed op de prognose verhelderen.

De centrale vraag in toekomstige studies betreft de toepassing van NT-proBNP (of BNP) metingen bij preventieve en therapeutische interventies in de algemene bevolking en in specifieke subgroepen. Momenteel is er nog onvoldoende bewijs, hoe de kennis van de NT-proBNP of BNP spiegel, van invloed is op de individuele behandeling van personen zonder klachten. Er kan enig voordeel zijn voor het onderzoek van individuen met een intermediair risico op hart- en vaatziekten, hoewel er meer gerandomiseerd onderzoek

nodig is. In de huidige, dagelijkse praktijk, zijn BNP en NT-proBNP vooral nuttig voor diagnostische en prognostische doeleinden bij patiënten die zich presenteren met acute kortademigheid en bij mensen met een bekende hartvaatziekte.

Een groot aantal patiënten met hartfalen heeft tevens boezemfibrilleren. De daarmee gepaard gaande verhoging van (NT-pro)BNP dient als een biologisch signaal voor een slechtere prognose. De kans op overlijden of ziekenhuisheropname voor HF blijkt bij patiënten met een relatief behouden LV systolische functie minstens zo hoog als bij mensen met duidelijk verminderde LV functie.

Daaruit volgt, dat het voor de klinische praktijk belangrijk is om deze patiënten beter te karakteriseren en te vervolgen in zorgprogramma's. Vroege opsporing van verhoogde vullingsdrukken en vochtophoping door het meten van (NT-pro)BNP en het nagaan van boezemfibrilleren in het beloop kan leiden tot een betere herkenning van patiënten met een verhoogd risico op verergering van het HF. De verwachting is, dat deze groep minstens zoveel baat heeft van goede zorgprogramma's als zij die een slechte LV functie hebben.

Veel pathofysiologische aspecten van de cardiorenale interactie bij HF en de beschermende rol van de B-type natriuretische peptiden zijn nog onduidelijk. Onze observationele, gecontroleerde studie leverde relevante informatie op over de relatie tussen het hartfalen syndroom en verminderde nierdoorbloeding, resulterend in een lagere uitscheiding van NT-proBNP, als onderdeel van een compensatiemechanisme. Dit is belangrijk, omdat de verminderde doorbloeding van de nier bij hartfalen een cruciale rol speelt, welke relevant is voor de behandeling met plasmiddelen en blokkers van het renine-angiotensine systeem.

Toekomstperspectieven

Nieuwe onderzoeksinitiatieven en meer geavanceerde toepassingen van natriuretische peptiden bij hart- en vaatziekten kan zorgen voor een betere behandeling van de individuele patiënt en daarmee gepaard gaande betere prognose.

Bepaling van biologische merkstoffen, zowel in het plasma als in de urine, kan verslechtering van hartfalen en het ontstaan van nierschade, evenals nadelige effecten van medicatie tijdig opsporen. De eerste resultaten van onderzoek naar de toepassing van verschillende nieuwe merkstoffen zijn veelbelovend. Daarbij is het essentieel om te onderzoeken, hoe nieuwe "biomarkers" gekoppeld kunnen worden aan specifieke behandelingen. Hierbij kan informatie over het individuele genetische profiel van waarde zijn. In dat kader is onlangs een groot Europees onderzoekprogramma (BIOSTAT-CHF) gestart om na te gaan welke factoren bepalen of een patiënt met hartfalen reageert op noodzakelijk geachte medicijnen.

Ook de waarde van het regelmatig bepalen van (NT-pro)BNP als richtsnoer voor het optimaal instellen van medicatie evenals de geïntegreerde toepassing van beeldvormende technieken dienen nader onderzocht te worden. Veel wordt verwacht

van de toekomstige toepassing van beeldvorming op moleculair niveau om zodoende de biologische eigenschappen van het cardiovasculaire systeem te karakteriseren.

Tot slot, er is de laatste twintig jaar grote vooruitgang geboekt bij de behandeling van hartfalen. Het gebruik van medicijnen die het RAAS blokkeren, bètablokkers, cardiale resynchronisatie therapie (CRT) en implanteerbare cardioverter-defibrillatoren (ICD) is bewezen effectief. Deze therapieën zijn opgenomen in praktijkrichtlijnen, evenals de bepaling van BNP of NT-proBNP. Toch resteert een hoge ziektelast en sterfte, wat deels te wijten is aan een kloof tussen de geadviseerde en de werkelijk uitgevoerde zorg. In dat kader dienen we ons te realiseren, dat het uitvoeren van het onderzoek en de behandeling van hartfalen volgens praktijkrichtlijnen gunstig is zowel voor de overleving als voor de kwaliteit van leven van grote groepen patiënten.

Dankwoord

Promotieonderzoek is teamwerk. Zo ben ook ik omringd door vele waardevolle leiders, coaches, teamspelers en assistenten, professioneel én sociaal, die allen hebben bijgedragen aan dit proefschrift. Hen wil ik hier graag bedanken.

Mijn eerste promotor, prof. dr. D.J. van Veldhuisen, beste Dirk Jan, ik ben jou zeer dankbaar dat jij mij dit promotietraject medio 2006 aanbood en uiterst effectief binnen jouw afdeling in gang wist te zetten. Jouw grote wetenschappelijke inzicht en verdiensten bleken van waarde voor een duidelijke en resultaatgerichte structuur. Zodoende konden de onderzoekresultaten helder voor het voetlicht komen en ontstonden fraaie manuscripten. Daarnaast kon jij mij op geheel eigen wijze persoonlijk adviseren over de meest uiteenlopende zaken in de gezondheidszorg.

Mijn eerste co-promotor en al snel mijn tweede promotor, prof. dr. J.L. Hillege, beste Hans, ik bewonder en waardeer jouw inzet en enthousiasme om ingewikkelde statistische en epidemiologische vraagstukken op te lossen; je hebt een sleutelpositie in de Groninger onderzoekgroep. Op de meest uiteenlopende tijden kon ik een beroep op je doen, om specifieke analyses en figuren rond te krijgen.

Mijn derde promotor (voorheen tweede co-promotor), prof. dr. A.A. Voors, beste Adriaan, jij weet klinische wetenschap en betekenis voor de praktijk van de patiëntenzorg op voortreffelijke en handzame wijze samen te brengen, en daarmee een groot publiek te boeien. Jouw Europese netwerk heeft geleid tot een ambitieus onderzoekproject. Ik voel mij zeer vereerd, dat ik samen met mijn Almelose collegae hieraan mag meewerken. Jij hebt een sterk stimulerende invloed en inbreng gehad op mijn promotietraject, waarvoor veel dank.

Mijn vierde (voorheen derde co-promotor), mw. Prof. dr. T. Jaarsma, beste Tiny: al in Maastricht werkten wij samen ten tijde van jouw promotieonderzoek op de afdeling Cardiologie: een geweldig goed stuk werk! Het vormde de basis voor een voorspoedige start van vele hartfalenpoliklinieken in ons land, onder andere in Almelo in 2000. Met jouw werk voor de Nederlandse Hartstichting en vervolgens het wetenschappelijke megaproject COACH, in 17 Nederlandse ziekenhuizen, heb je de hartfalenzorg en de verplegingswetenschappen, ook ver buiten ons land, een grote dienst bewezen. Dat ik niet alleen lokale onderzoeker in COACH mocht zijn, maar dat hier ook promotieonderzoek uit voort vloeide, heeft mij zeer vereerd. Jouw inzet voor de Europese cardiologie bewonder ik, waarbij je steeds een voorbeeldfunctie en een voortrekkersrol vervult. In je nieuwe hoogleraarfunctie in Zweden zul je ongetwijfeld ook velen inspireren, en studenten, jonge onderzoekers en vele anderen op voortreffelijke wijze begeleiden.

Uit bovenstaande moge blijken, dat de wetenschappelijke loopbanen van mijn gewaarde co-promotoren uiterst succesvol zijn. Een goed promotieteam bleek voor mij de juiste basis.

De leden van de beoordelingscommissie, prof. dr. M.P. van den Berg, prof. dr. W.H. van Gilst en prof. dr. A.W. Hoes, wil ik bedanken voor het doornemen van mijn proefschrift.

Dr. Jochem Hogenhuis, dr. Ivonne Lesman, dr. Martje van der Wal en dr. Marie Louise Luttik, COACH-onderzoekers van het eerste uur, en monitoren in de ziekenhuizen, baanden de weg voor mijn deel van het onderzoek. Minstens zo belangrijk waren jullie enthousiasme, gezelligheid en altijd vriendelijke adviezen van allerlei aard. Zeer bedankt dat jullie mij begeleiden op dit bijzondere pad.

De jongere collegae COACH promovendi: Imke, Maaike, Tialda, Arjen en Maurice bevinden zich in goed gezelschap van deskundige postdocs; ik wens jullie veel succes in onderzoek en loopbaan.

Met dr. Kevin Damman, een wel heel fanatieke en succesvolle, jonge onderzoeker en cardioloog in opleiding, mocht ik samenwerken in het kader van de “cardiorenale” hartfalenstudie: inderdaad, ook hier was succes verzekerd! Kevin zeer bedankt voor jouw uitstekende bijdragen en plezierige teamgeest; ga zo door!

Dr. Michiel Rienstra, een brilliante, jonge, boezemfibrilleren-onderzoeker, leverde grote input aan ons COACH-deelproject. Zelfs tijdens je fellowship in Boston, een topplek, was jij mij van dienst, mijn dank is groot. Ik wens je veel succes in de wetenschap en in je opleiding tot cardioloog.

Prof. Isabelle van Gelder, internationaal expert op het gebied van electrofysiologie, in het bijzonder boezemfibrilleren, bedank ik voor haar waardevolle ideeën en constructieve inbreng. Als onderzoeker in jouw RACE-projecten herken ik steeds opnieuw jouw vooruitstrevende blik op betere zorg.

Prof. Gerjan Navis, een bijzondere samenwerking viel mij ten deel. Onze brainstormsessies op enkele vrijdagmiddagen samen met Adriaan en Kevin, over (experimentele) nierfysiologie in het kader van het hartfalensyndroom, waren een echte belevenis! Ik bedank je voor de opgedane kennis en inzicht, en vooral de geweldige inspiratie, met een gezamenlijk artikel in een toptijdschrift als resultaat!

Enkele leden van het grote PREVEND team, dr. Stephan Bakker, dr. Ron Gansevoort (een van mijn oud-assistenten in Almelo, en ook nu uitmuntend), prof. Paul de Jong, prof. Rijk Gans, prof. Dick de Zeeuw, wil ik in het bijzonder bedanken voor het meedenken en kritisch beoordelen van onderzoekplannen en manuscripten.

Marco Assman van het Trial Coordination Center in Groningen bedank ik voor de ondersteuning van de COACH-database.

Met collegae, jonge onderzoekers, post-docs en stafleden, beleefden we vele plezierige ”Groninger avonden” tijdens buitenlandse congressen. Ik voelde me opgenomen in de Groninger clan, heel leuk!

Secretaressen van de staf Cardiologie, UMCG, Alma en Audrey, dank ik voor de praktische adviezen en steun, altijd vriendelijk, behulpzaam en meelevend.

Mijn Maastrichtse opleider Cardiologie destijds, prof. dr. H.J.J. Wellens, beste Hein: al decennia ben jij een kennis- en inspiratiebron voor mij en vele andere collegae wereldwijd. Jij ging ons voor in het streven naar deskundige en toegewijde zorg aan de hartpatiënt; mijn waardering is groot.

Mijn collega cardiologen van de Ziekenhuisgroep Twente in Almelo, dank ik in het bijzonder voor de gelegenheid om mijn breed gedragen ambities voor onderzoek en opleiding te realiseren. Jullie vonden het als vanzelfsprekend en zinvol, dat ik het motto “Time dedicated to research” introduceerde en handhaafde, ook in drukke tijden; voila, het is gelukt!

De Almelose hartfalenverpleegkundigen, Elly (tevens nurse-practitioner), Bernarda, Joke, Marijke, en voorheen Mini, Liesbeth en Wendy, brengen goede patiëntenzorg, deskundig, vriendelijk, meelevend en zeer toegankelijk in de praktijk. Zij vervullen al meer dan tien jaar een spilfunctie in ons multidisciplinaire team. Als groep werkten zij op voortreffelijke wijze mee aan het COACH-onderzoek en momenteel aan het COACH-2 project.

De researchverpleegkundigen van Cardioresearch Almelo, Anke Pieterse en Lucy Kuipers, en klinisch-chemisch laborant Jelle Sanderman, ben ik dankbaar voor de deskundige en plezierige samenwerking, al vele jaren, bij cardiovasculaire onderzoeken in ons ziekenhuis en hulp bij COACH.

Bestuur en staf van de vereniging WCN te Utrecht, waarmee ik al vanaf 1996 zeer aangenaam en productief samenwerk, vormen een dankbare stimulans en landelijk netwerk in coöperatie met (inter)nationale wetenschappelijke partijen.

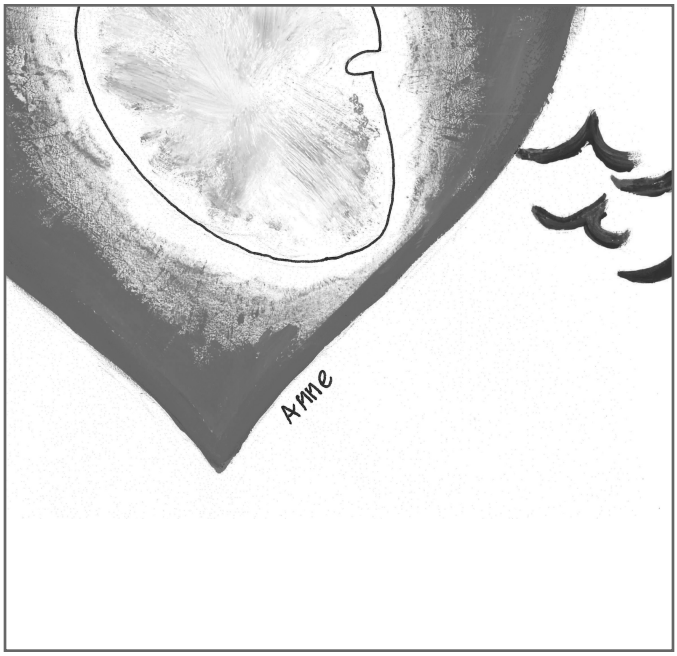
Mijn paranimfen, Ivonne en Susanne, dank ik voor de aangename, vriendelijke, en zeer toegewijde vervulling van een speciale rol bij de voorbereiding van mijn promotiedag, de openbare plechtigheid en de feestelijkheden.

De vele patiënten en hun partners die deelnamen aan hét Nederlandse onderzoek naar het effect van extra voorlichting en begeleiding bij hartfalen; en ook de vele Groningers die al gedurende vele jaren deelnemen aan het PREVEND bevolkingsonderzoek wil ik oprecht bedanken voor hun bereidwillige medewerking. Zij vormen de basis en de doelgroep in brede zin, van ons werk!

En tot slot, mijn kleinste, maar dierbaarste netwerk, mijn echtgenote en maatje Marian, en onze kinderen Raoul, Martijn en Anne; dank voor jullie onvoorwaardelijke steun, begrip en vooral liefde, die ik als onmisbaar ervaar en met diep respect waardeer.

Gerard

Dankwoord
COACH betrokkenen



Dankwoord NHS-COACH betrokkenen

De NHS-COACH studie is uitgevoerd in 17 ziekenhuizen in Nederland. Zonder de grote inzet van vele medewerkers aldaar was de COACH-studie niet tot stand gekomen en had dit proefschrift er niet gelegen. Ik wil een ieder die in de centra heeft mee gewerkt; hartfalenverpleegkundigen, cardiologen en interviewers maar ook de mensen van de laboratoria en alle deelnemers van het multidisciplinair overleg, langs deze weg hartelijk bedanken:

Universitair Medisch Centrum Groningen
Cardiologen: Prof. dr. D. J. van Veldhuisen, Dr. A.A. Voors
Hartfalenverpleegkundigen: Drs. A. Koops, Mevr. A. Klungel, Mevr. K van Dijk, Dhr. G. Westra.
Dataverzamelaars: Mevr. G. Feringa, Mevr. A. Schwencke, Mevr. L. Grevink, Mevr. K. Bruggink

Academisch Medisch Centrum, Amsterdam
Cardiologen/artsen Prof. dr. J.G.P. Tijssen, Dr. W. Kok, Drs. L.M. Konst, Dr. J. van der Sloot.
Hartfalenverpleegkundigen: Mevr. T. Veelenturf, Dhr. R. Zwart, Mevr. S. de Vries
Dataverzamelaars: Mevr. L. IJzerman, Dhr. R. Zuidervaart, Mevr. E. Spoelstra, Mevr. S. Stultiëns

Universitair Medisch Centrum St. Radboud, Nijmegen
Cardiologen: Prof. dr. F. Verheugt, Drs. L. Bellersen
Hartfalenverpleegkundigen: Dhr. L. Knubben, Mevr. L. Baltussen
Dataverzamelaars: Mevr. J. de Natris, Drs. L. Hogenhuis

Medisch Centrum Leeuwarden
Cardiologen: Drs. C.J. de Vries, Drs. R. Breedveld
Hartfalenverpleegkundigen: Mevr. A. Obbema, Mevr. A. Rijenga, Mevr. D. van der Woude, Mevr. J. de Bruin
Dataverzamelaars: Mevr. A. Jonkman, Mevr. C. Wassenaar

Twenteborg Ziekenhuis, Almelo
Cardioloog: Drs. G.C.M Linssen
Hartfalenverpleegkundigen: Mevr. E. Rodijk, Mevr. M. Samsen, Mevr. B. Beverdam, Mevr. L. Bogemann
Dataverzamelaars: Mevr. H. Hondebrink, Mevr. A. Disberg, Mevr. M. Slaghekke

Atrium Medisch Centrum, Heerlen
Cardioloog: Dr. J.A. Kragten
Hartfalenverpleegkundigen: Dhr. T. Thuis, Mevr. I. Kremer, Mevr. V. Post, Mevr. S. Jongen
Dataverzamelaars: Drs. S. Hogenhuis, Drs. E. Gaasbeek, Drs. C. Beumer, Mevr. B. Hoen

Jeroen Bosch Ziekenhuis, Den Bosch
Cardioloog: Dr. M.C.G. Daniëls
Hartfalenverpleegkundigen: Dhr. D. Jaftoran, Dhr. V. van Zonsbeek, Mevr. A. Berkhout
Dataverzamelaars: Mevr. I. Samshuizen, Mevr. D. Oosterkerk

Rijnstate Ziekenhuis, Arnhem
Cardioloog: Dr. F.F. Willems
Hartfalen verpleegkundigen: Drs. M. Rolfes, Mevr. P. Nienaber
Dataverzamelaars: Mevr. J. de Natris, Mevr. M. Hubertus, Drs. L. Hogenhuis, Mevr. E. Eleveld

Streekziekenhuis Midden Twente, Hengelo
Cardioloog: Drs. A. Derks
Hartfalen verpleegkundigen: Mevr. L. Odink, Mevr. P. ter Horst, Mevr. W. Wolters, Mevr. L. Navis
Dataverzamelaars: Mevr. J. Bijen, Mevr. I. Horstman, Mevr. A. Ottenhof, Mevr. W. Bakker, Mevr. B. Nijhuis

Refaja Ziekenhuis, Stadskanaal
Cardioloog: Dr. L. van Wijk, Drs. K. de Vries
Hartfalen verpleegkundigen: Mevr. D. Thoma, Mevr. R. Niewold, Mevr. M. Wijbenga
Dataverzamelaars: Mevr. S. Vennik, Drs. E. Prins

Tweesteden Ziekenhuis, Tilburg
Cardioloog: Dr. J. Widdershoven
Hartfalen verpleegkundigen: Dhr. E. Hendriks, Dhr. H. Broers
Dataverzamelaars: Dhr. K. Jansen, Mevr. B. de Kruijf, Mevr. K. de Beer

Amphia Ziekenhuis, Breda
Cardioloog: Dr. P.H.J.M. Dunselman
Hartfalenverpleegkundigen: Mevr. N. Creemer, Mevr. I. de Regt
Dataverzamelaars: Mevr. J. Hendriks, Mevr. A. Lotstra, Dhr. K. Terlaak

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Cardioloog: Drs. D.J.A. Lok
Hartfalenverpleegkundigen: Dhr. J. Burger, Mevr. D. Pruijsers
Dataverzamelaars: Mevr. L. Schoterman, Mevr. M. van Buijsen, Mevr. M. Scholten, Dhr. H. Verheij

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Hartfalenverpleegkundigen: Mevr. A. Bakker, Dhr. W. Veenstra, Dhr J.W. van Brakel
Dataverzamelaars: Mevr. J. Kruimink, Mevr. J. Pool, Mevr. R. de Heus

Medisch Spectrum Twente, Enschede
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Hartfalenverpleegkundigen: Mevr. J. Roukema, Mevr. H. Glazenburg, Mevr. J. Grooters
Dataverzamelaars: Mevr. T. Meijer, Mevr. H. Vroom, Mevr. J. Poggenklas

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Dr. J.H. Cornel
Dr. R..W.M.M. Jansen
Dr. F.H. Rutten
Dr. F. van den Berg

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Curriculum Vitae

Curriculum vitae

De auteur van dit proefschrift werd geboren op 17 augustus 1961 te Maasbracht. In 1979 behaalde hij het V.W.O. diploma aan het Bisschoppelijk College te Echt. Van 1979 tot 1982 studeerde hij Scheikunde aan de Katholieke Universiteit Nijmegen en behaalde het kandidaatsexamen in 1982. Aansluitend startte hij met de studie Geneeskunde aan de Rijksuniversiteit Limburg te Maastricht. Gedurende deze studie was hij enkele jaren werkzaam als student-assistent in het klinisch-electrofysiologisch laboratorium (dr. P. Brugada en Prof. dr. H.J.J. Wellens). In 1987 volgde hij een wetenschapstage van drie maanden op het gebied van hartfalen en kamerritmestoornissen aan de Universiteit van Californië in Los Angeles (Dr. L. Warner Stevenson en Dr. W.G. Stevenson). Eind 1988 werd het artsexamen behaald, waarna werd aangevangen met de B-opleiding Interne Geneeskunde in het Maaslandziekenhuis te Sittard (nu Orbis Medisch Centrum Sittard/Geleen) onder leiding van Dr. Th.W.M. van der Wiel, internist/nefroloog. Van 1991 tot 1994 volgde hij de opleiding Cardiologie in het Academisch Ziekenhuis Maastricht (nu Maastricht Universitair Medisch Centrum) onder leiding van Prof. dr. H.J.J. Wellens. Op 1 januari 1995 werd hij geregistreerd als cardioloog. Tot 1 juli 1996 was hij in Maastricht werkzaam als klinisch cardioloog. Nadien was hij, in zijn huidige functie, als algemeen cardioloog verbonden aan de Ziekenhuisgroep Twente (ZGT, voorheen Twenteborg Ziekenhuis in Almelo en Streekziekenhuis Midden-Twente in Hengelo). Hij vervulde in dit ziekenhuis vele staffuncties, onder andere als (waarnemend) vakgroepvertegenwoordiger, coördinator klinische cardiologie, lid van de werkgroep Cardiovasculaire beeldvorming, voorzitter van de stafcommissie Kwaliteit en van de commissie Orgaan- en Weefseldonatie. Al vele jaren is hij stagebegeleider Cardiologie in het kader van de (voor)opleiding Interne Geneeskunde en is lid van de Centrale Opleidingscommissie van de ZGT. Vanuit de vakgroep Cardiologie richtte hij de Hartfalenpolikliniek en de afdeling Cardioresearch op. In de regio Twente en Oost-Achterhoek heeft hij zitting in de Adviesraad van de Stichting Hartcentrum Twente. Van 2002 tot 2005 was hij lid respectievelijk voorzitter van de Commissie Indeling Centra en van 2006 tot 2012 lid (secretaris) van het dagelijkse bestuur van de vereniging Werkgroep Cardiologische centra Nederland (WCN) te Utrecht. Als onderzoeker is hij betrokken bij vele cardiovasculaire studies naar nieuwe geneesmiddelen, behandelstrategieën en zorgmodellen.

Sinds 2006 is hij “Fellow of the European Society of Cardiology” (FESC).

Het in dit proefschrift beschreven onderzoek werd vanaf oktober 2006 in deeltijd uitgevoerd bij de afdeling Cardiologie van het Thoraxcentrum van het Universitair Medisch Centrum Groningen.

Gerard Linssen is gehuwd met Marian Canters en zij hebben drie kinderen, Raoul, Martijn en Anne.

Curriculum vitae

The author of this thesis was born on August 17, 1961 in Maasbracht, the Netherlands. In 1979 he graduated from the Bishop College in Echt (Atheneum Beta). From 1979 to 1982 he studied Chemistry at the University of Nijmegen and obtained a bachelor's degree in 1982. Afterwards he started to study medicine at the University of Limburg in Maastricht. During this study he worked for several years as a student assistant in the clinical electrophysiology laboratory (Dr. P. Brugada and Prof. H.J.J. Wellens). In 1987 he attended for three months a scientific internship in the field of heart failure and ventricular arrhythmias at the University of California at Los Angeles (Dr. W.G. Stevenson and Dr. L. Warner Stevenson). Late 1988, he obtained his medical degree, then was started the Internal Medicine training at the Maasland Hospital in Sittard (now Orbis Medical Center Sittard / Geleen) led by Dr. Th.W.M. van der Wiel, internist / nephrologist. From 1991 to 1994 he was trained in cardiology at the University Hospital Maastricht (Maastricht University Medical Center now) led by Prof. H.J.J. Wellens. On January 1, 1995 he was registered as a cardiologist. Until July 1, 1996 in Maastricht, he worked as a clinical cardiologist. Afterwards he was in his current position, as a general cardiologist affiliated with the Hospital Group Twente (ZGT in Almelo and Hengelo). He served many staff positions, including as (acting) department representative, coordinator of clinical cardiology, member of the cardiovascular imaging working group, chair of the Medical Quality Committee and staff of the Committee organ and tissue donation. Since many years he is supervisor of Cardiology in the context of training Internal Medicine and is a member of the Central Education Committee of the ZGT. From the department of Cardiology, he founded the Heart Failure Clinic and the department of Cardiovascular Research. In the region of Twente he sits on the Advisory Board of the Foundation's Heart Centre Twente. From 2002 to 2005 he served as member and chairman of the Committee on Selection of centers and subsequently from 2006 to 2012 member (secretary) of the board of the Working on Cardiovascular research the Netherlands (WCN) in Utrecht. As a researcher and study-director of WCN he participated in numerous cardiovascular studies of new drugs, treatment strategies and models of care. In 2006 he became a "Fellow of the European Society of Cardiology" (FESC).

This thesis was conducted at the department of Cardiology of the Thoraxcenter at the University Medical Center Groningen (UMCG), the Netherlands.

Gerard Linssen is married to Marian Canters and they have three children, Raoul, Martijn and Anne.