# BNP and NT-proBNP in heart failure

## Benefits and limitations for clinical practice; data from COACH and other studies

Jochem Hogenhuis

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# Chapter 1

# General introduction and aims of the thesis

# Introduction

Heart failure (HF) is a complex syndrome which is defined by symptoms of HF, typically breathlessness or fatigue either at rest or during exertion or ankle swelling, in combination with objective evidence of cardiac dysfunction at rest.[1] The most common cause of HF is coronary artery disease, but other well known aetiologies are hypertension, valvular disease, cardiomyopathy and myocarditis. Most patients with HF suffer from a variety of signs and symptoms that influence their health status, quality of life and prognosis. The syndrome of HF is a large problem in Western societies, especially since its prevalence will probably increase further in the near future due to aging of the population and more successful treatment of acute cardiac disease.[2,3] Additionally, HF puts a substantial burden on health care facilities and costs.[4]

For the diagnosis of HF a variety of diagnostic tests is available including assessment of clinical signs and symptoms of HF, laboratory blood tests, radiological examinations, electrocardiography and echocardiography.[1] In 1988 a new cardiac natriuretic peptide, B-type Natriuretic Peptide (BNP) was discovered,[5] which in the following years was shown to have prognostic properties[6] and later also appeared to have diagnostic properties in the emergency department[7] and out-patient settings.[8] In addition, one study also reported improved prognosis when patients' medication was guided by NT-proBNP compared to 'clinical view' guided treatment. Therefore, cardiologists, primary care physicians, and other clinicians became enthusiastic about the role of natriuretic peptides in diagnosis, prognosis and guidance of medical treatment of HF patients. The use of natriuretic peptides in the diagnosis of HF was included in recent guidelines, including the European Society of Cardiology[1] and Dutch primary care guidelines.

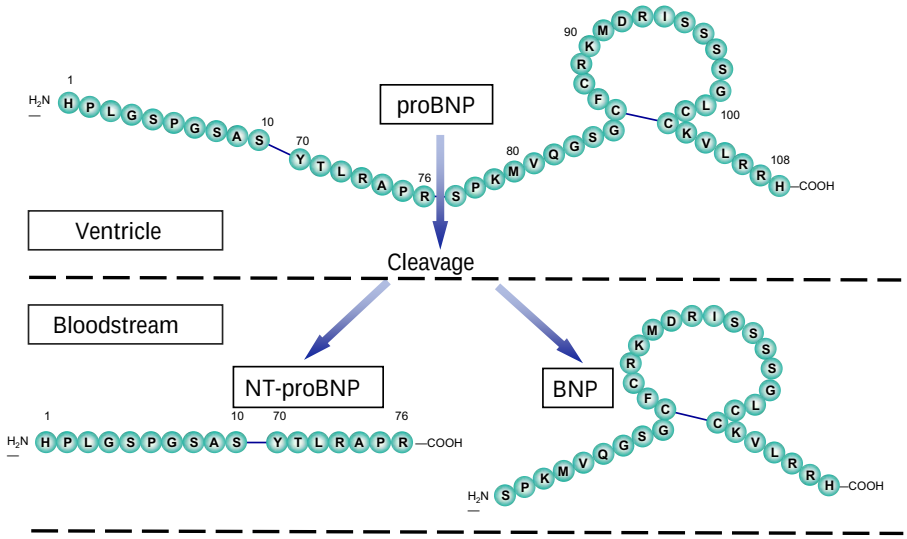
Before explaining the potential benefits and limitations of BNP and NT-proBNP in clinical practice, and before outlining the aims of this thesis, an introduction to the mechanism of action of BNP and NT-proBNP will be given.

# Differences between BNP and NT-proBNP: physiology

BNP is a hormonally active natriuretic peptide that is mainly released from the cardiomyocytes in the left ventricular wall. In reaction to stretch and tension of the myocardial wall the pro hormone proBNP splits into BNP and the hormonally inactive remnant N-terminal proBNP (NT-proBNP) by proteolytic cleavage (figure 1).[9] This process occurs under influence of integrins, structures at the Z-disc of sarcomeres, that measure stretch of these sarcomeres[10,11] after which both peptides will be secreted in equimolar amounts into the circulation.

Circulating BNP acts as an antagonist of the renin angiotensine aldosterone system, and protects the body from plasma overload by inducing diuresis, natriuresis, vascular dilatation and inhibition of the sympathetic nerves system.[5] The half life of BNP is around 20 minutes and the half life of NT-proBNP is around 120 minutes. BNP is known to be cleared from the blood by natriuretic peptide clearance receptors, by neuro endopeptidases and by the kidneys. Little is known on the exact clearance mechanism of NT-proBNP, although it has been suggested that the kidneys play a major role in this clearance.[12] Absolute values

**Figure 1**: Secretion of BNP and NT-proBNP (Courtesy from Roche Diagnostics)




of BNP are significantly lower than values of NT-proBNP, despite equimolar secretion. The reference ranges for BNP and NT-proBNP vary depending on the assay that is used and the nature of the control population. In general, the suggested normal range for circulating BNP is 0.5 – 30 pg/ml and for circulating NT-proBNP the suggested normal range is 68 – 112 pg/ml.[13] These natriuretic peptides may be beneficial in clinical practice since plasma levels of BNP and NT-proBNP are elevated in patients with HF and are related to the severity of the disease.[14]

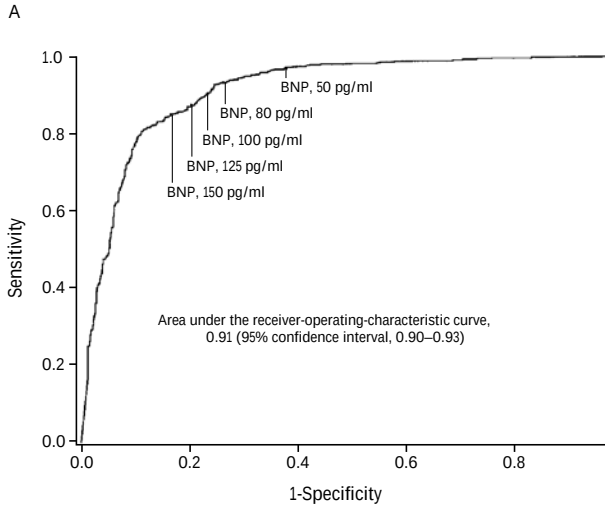
## BNP and NT-proBNP in clinical practice: promises

BNP and NT-proBNP plasma levels are promising tools in the daily management of suspected or established HF. Most studies on the use of BNP and NT-proBNP in clinical practice addressed their diagnostic properties. However, an increasingly amount of evidence is available on the prognostic value of BNP and NT-proBNP and a single study provided hopeful results for the benefits of NT-proBNP guided medical treatment.

### Diagnosis

Recent trials provided strong evidence that BNP and NT-proBNP are powerful diagnostic tools in exclusion and diagnosis of HF. The Breathing Not Properly study showed, by means of receiver operating characteristics analyses, that a BNP value of 100 pg/ml was the optimal value to differentiate patients with dyspnoea caused by HF from patients with dyspnoea due to pulmonary pathology at the emergency department (figure 2a).[15]

**Figure 2:** ROC curves for BNP (A) and NT-proBNP (B) in the diagnosis of heart failure at the emergency department.

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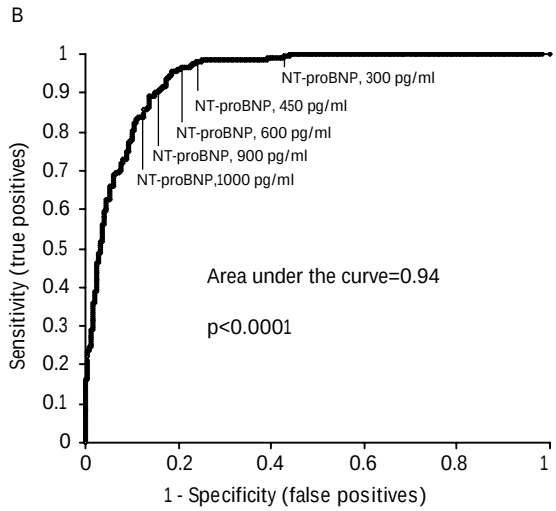


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This value of 100 pg/ml also discriminated non-systolic HF (LVEF <45%) from non-HF patients at the emergency department.[16] It has also been suggested that BNP could be used to discriminate systolic from diastolic HF. Although non-systolic HF patients had significantly lower BNP plasma levels than systolic HF patients (LVEF >45%), BNP only had modest added value in differentiating non systolic from systolic HF. In another study, a BNP value of 100 pg/ml added significant value to the diagnosis of HF on top of clinical judgement.[17] An international pooled analysis of 1256 patients provided cut off values for NT-proBNP in an emergency department setting. An age independent cut point of 300

pg/ml had a negative predictive value of 98%. Additionally, an optimal strategy to identify acute HF was to use age stratified cut off points of 450, 900 and 1800 pg/ml for ages <50, 50-75, and >75 respectively which yielded 90% sensitivity and 84% specificity for acute HF (figure 2b).[18,19]Furthermore, BNP and NT-proBNP seem useful as diagnostic tools in primary care (where most patients with suspected HF are encountered and where only limited diagnostic tools are available) and as such are recommended in recent guidelines.[1] The *added* value of these natriuretic peptides on top of established diagnostic tools, including symptoms and signs, has not been properly studied, in particular in relevant subgroups, and currently large studies are underway addressing this issue.

Discharge diagnoses have been instrumental in providing estimates and time trends in prevalence and incidence of HF. However, previous studies in the Netherlands, Sweden and in the United States showed that respectively 20%, 18% and 33% of the patients that were given the discharge diagnosis 'HF' at close examination did not have HF at all.[20-22] Evidence is lacking on potential independent predictors of the discharge diagnosis HF, including BNP and/ or NT-proBNP and an easy applicable scoring rule could be helpful in this setting. Moreover, it is unknown whether the established BNP cut off value of 100 pg/ml can also be used at discharge after admission for HF.

### Prognosis

The prognostic value of BNP and NT-proBNP is well established in several groups of patients. An early study on 85 patients with chronic HF revealed that BNP is a strong independent predictor of mortality.[6] Another study confirmed these results in a larger research population of 452 systolic HF patients (LVEF <35%). In this study BNP was found to be a strong independent predictor of sudden death during a follow up period of 3 years.[23] Furthermore, NT-proBNP was a predictor of sudden death in this study population. A substudy of the COPERNICUS trial (n=1011) revealed that NT-proBNP was consistently associated with an increased risk for all-cause mortality and hospitalisation for HF in patients with severe HF (LVEF <25%).[24] Another study by Gardner et al. on 142 patients with advanced HF also reported that NT-proBNP was an independent predictor of all cause mortality.[25]

### Guidance of treatment

BNP and NT-proBNP are influenced by drugs that are prescribed to HF patients like diuretics,[26] beta blockers,[27] ACE inhibitors or angiotensine II receptor blockers [28] and therefore these natriuretic peptides could possibly be used to guide medical treatment. A small study by the Australia-New Zealand Heart Failure Group including 69 patients with symptomatic HF provided evidence of the possible benefit of a NT-proBNP guided approach to therapy. Half of the patients received therapy guided by plasma NT-proBNP, therapy in the remaining patients was guided by clinical monitoring at the same frequency, but with the physician blinded to the NT-proBNP result. Clinical monitoring was based on scores assigned to 10 symptoms or signs of HF used in the Framingham criteria for HF. The study found significantly lower mortality, fewer hospitalisations and episodes of decompensated HF in the NT-proBNP-guided therapy group (target 1680 pg/ml).[29]

Larger studies are underway that are about to provide firmer evidence as to whether or not BNP and NT-proBNP can be used as a marker in the monitoring of treatment of HF patients.[13]

### Assay considerations

Recently, the US Food and Drug Administration (FDA) approved two rapid and fully automated assays for natriuretic peptide measurement assessing diagnosis and prognosis in cardiac abnormalities. These assays, the Triage® BNP meter (Biosite Incorporated, San Diego, CA) and the Elecsys NT-proBNP assay (Roche diagnostics, Mannheim Germany), are used to determine BNP and NT-proBNP levels in this thesis. BNP is stable in EDTA plasma without addition of aprotinin at room temperature for at least 24 hours [30] and NT-proBNP is stable for at least one year when stored at -80°C in several different serum and plasma conditions amongst which EDTA plasma.[31] Both assays have been validated repeatedly,[32-34] but the Elecsys NT-proBNP assay showed an approximately 2 – 3 fold better precision compared to the Triage BNP assay.[35,36] Although there are pre-analytical and analytical differences between the Triage BNP assay and the Elecsys NT-proBNP assay, they do not seem to translate into clinically significant differences in their diagnostic and prognostic application.[36]

Before the two assays that are used for most determinations in the present study became available, another commercially available assay, the Shionoria BNP assay and in house developed radioimmunoassay kits for NT-proBNP were used. These systems show good performance.[37]

Altogether, BNP and NT-proBNP are promising tools for the management of suspected and established HF in clinical practice, but it is time for an critical evaluation of their limitations to their usefulness in daily care, especially in the typical older patient with relevant co-morbidity.

## Variables influencing BNP and NT-proBNP levels: potential limitations?

Although natriuretic peptide levels are of value in the diagnosis and prognosis of HF patients, several clinical conditions other than HF influence BNP and NT-proBNP plasma levels as well. These influences may be a disadvantage for the use of BNP and NT-proBNP in clinical practice of HF since it may lead to biased interpretations of the test results.

### Cardiac variables

BNP and NT-proBNP are also elevated in patients with acute coronary syndrome. After acute myocardial infarction, levels of BNP rise rapidly during the first 24 hours and then tend to stabilize,[38] and in patients with a Q-wave infarction, a peak in NT-proBNP levels was found after 12 – 48 hours.[39] In patients with unstable angina pectoris, BNP levels were found to be four times higher compared to patients with stable angina pectoris.[40] Moreover, atrial fibrillation resulted in increased BNP levels in patients without, but not in patients with HF.[41] Right ventricular failure due to acute pulmonary embolism can also be determined by BNP.[42] Furthermore, hypertensive patients have higher BNP and NT-proBNP levels compared to non-hypertensive subjects.[43]

### Non-cardiac variables

A few studies in relatively small study populations without HF showed that anaemia causes elevated BNP levels[44-46] and in a study on a small group of HF patients anaemia was also

related to increased NT-proBNP levels.[47] However, besides that these studies were limited in sample size, they only investigated one of the two peptides and only the effect of anaemia on NT-proBNP was investigated in HF patients. Furthermore, anaemia is often caused by renal dysfunction, but this co-morbidity has not been investigated in detail in these studies. Since both BNP and NT-proBNP are known to be elevated in case of renal dysfunction,[48] and because renal function and HF are interrelated, a study investigating the effect of anaemia and renal function on both BNP and NT-proBNP in HF patients is needed.

An additional variable that is related to both BNP and NT-proBNP is obesity. In several large studies lower natriuretic peptide levels were associated with higher body mass indexes.[49-52] As far as diabetes is concerned, results are conflicting between BNP and NT-proBNP; BNP levels did not differ between patients with or without diabetes,[53] but NT-proBNP levels seem to be higher in diabetic patients compared to non diabetics.[54]

Furthermore, ascitic cirrhosis, hyperaldosteronismus, hypercortisolismus, carcinoma, subarachnoid hemorrhage,[9] lung cancer, tuberculosis and pulmonary embolism[7] are clinical conditions with reported elevated natriuretic peptide levels.

### Patient related variables

Recent studies showed that both BNP and NT-proBNP levels are influenced by biological variation, with the biological variation of BNP being higher compared to NT-proBNP (up to 44% and up to 35% respectively).[55,56]

Both BNP and NT-proBNP increase with advancing age and are higher in females compared to males in healthy subjects.[57] Nevertheless it is unknown whether there are differences in the age and gender dependency between the two peptides and only limited data are available on the age dependency of BNP and NT-proBNP in HF patients. Furthermore, before BNP and NT-proBNP were discovered, Atrial Natriuretic Peptide (ANP) and N-terminal ANP (NT-ANP), natriuretic peptides that are mainly produced in the atria and with properties comparable to BNP and NT-proBNP, were studied. Although evidence is available on the superiority of BNP over ANP in the diagnosis of HF and of BNP/ NT-proBNP over ANP/ NT-ANP in the prognosis after myocardial infarction, it is unknown which peptide is influenced most by age and gender.

Previous research shows that BNP is related to maximal exercise performance.[58] Moreover, the influence of moderate physical activity (75% of the maximum) on BNP levels was investigated in 10 healthy subjects, 10 HF patients with NYHA class I-II and in 10 HF patients with NYHA class III-IV. A significant increase in BNP levels was observed directly after exercise.[59] However, it is not known whether B-type natriuretic peptide levels also reflect sub-maximal functional capacity during daily activities and whether they are related to quality of life.

## Aims of this thesis

Further research is needed to study the influence of age on BNP and NT-proBNP in patients with HF since until now this relation has only been properly investigated in healthy subjects. Furthermore, renal dysfunction and anaemia are known to be closely related to cardiac dysfunction and by respectively decreased clearance and increased blood volume,

these conditions may influence both BNP and NT-proBNP levels. However, these relations have not been investigated in a large group of HF patients. These conditions potentially influence (the interpretation of) BNP and NT-proBNP levels when measurement of HF severity is the main goal. Insight in the relations between BNP and NT-proBNP levels and sub maximal functional capacity and physical dimensions of quality of life is needed as these measures reflect aspects that are important for HF patients in their daily life. For clinical practice it is useful to know whether single BNP and NT-proBNP cut off values should be used or whether these cut off values should be stratified according to variables that influence BNP and NT-proBNP plasma levels.

Previous research showed that patients are often discharged with the wrong diagnosis.[20-22] Since diagnosis and medical treatment are related, it is important that patients are properly diagnosed before discharge in order to start the right medical treatment. As stated before, BNP and NT-proBNP have strong diagnostic properties in an emergency department setting in the differentiation between cardiac and pulmonary cause of dyspnoea, but it is unknown whether BNP and NT-proBNP can be used in the discharge diagnosis of patients admitted with suspected HF.

Furthermore, it is unknown whether the promising cut off value for BNP that was determined in an emergency department setting, is also valuable at discharge after hospital admission for suspected HF.

We therefore aimed:

1. To assess the role of age, renal dysfunction, anaemia, functional capacity and quality of life on (the interpretation of) BNP and NT-proBNP plasma levels. This is addressed in the chapters 3, 4 and 5.
2. To identify which of the readily available diagnostic tools are independent predictors of the discharge diagnosis HF, and to develop an easy applicable scoring rule using these independent predictors and BNP and/or NT-proBNP levels. This is studied in chapter 6.
3. To investigate the value of the currently available cut off value of BNP levels for exclusion of HF in a setting of discharge from the hospital after admission for HF. This is addressed in chapter 7.

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Chapter 2

# Design and methodology of the COACH study: a multicenter randomized coordinating study evaluating outcomes of advising and counselling in heart failure

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*Eur J Heart Fail* 2004;6:227-33.

## Abstract

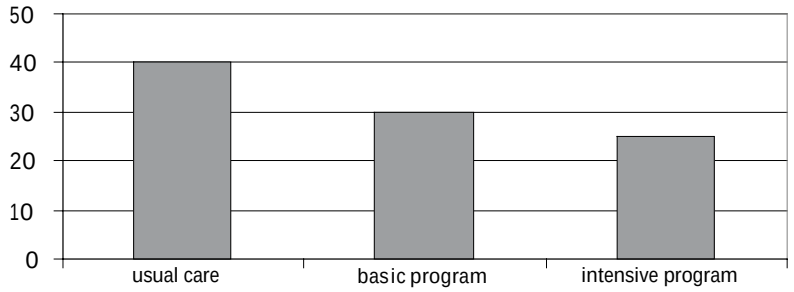
**Background:** While there are data to support the use of comprehensive non-pharmacological intervention programs in patients with heart failure (HF), other studies have not confirmed these positive findings. Substantial differences in the type and intensity of disease management programs make it impossible to draw definitive conclusions about the effectiveness, optimal timing and frequency of interventions.
**Aims:** 1. To determine the effectiveness of two interventions (basic support vs. intensive support) compared to 'care as usual' in HF patients, on time to first major event (HF readmission or death), quality of life and costs. 2. To investigate the role of underlying mechanisms (knowledge, beliefs, self-care behaviour, compliance) on the effectiveness of the two interventions.
**Methods:** This is a randomised controlled trial in which 1050 patients with heart failure will be randomised into three treatment arms: care as usual, basic education and support or intensive education and support. Outcomes of this study are; time to first major event (HF hospitalisation or death), quality of life (Minnesota Living with HF Questionnaire, RAND36 and Ladder of Life) and costs. Data will be collected during initial admission and then 1, 6, 12, and 18 months after discharge. In addition, data on knowledge, beliefs, self-care behaviour and compliance will be collected.
**Results:** The study started in January 2002 and results are expected at the end of 2005.
**Conclusions:** This study will help health care providers in future to make rational and informed choices about which components of a HF management program should be expanded and which components can possibly be deleted.


## Background

In contrast to favourable trends for most cardiovascular diseases in recent years, the number of patients with chronic heart failure (CHF) is still growing. CHF presents a significant and growing public health problem in industrialised countries and is sometimes referred to as an epidemic.[1] Because the incidence of CHF rises with age, its prevalence will markedly increase as our population ages.[2,3] CHF places a significant economic burden on society, consuming about 1-2% of the health care budget, and a large proportion (approximately 70%) of this is spent on hospitalisations.[3] There is growing evidence that many of these hospitalisations can be prevented by improved patient care.[5,6] Additionally, CHF is a significant burden to patients themselves. CHF has a high mortality rate and patients experience many adverse effects both from the disease and its treatment. Indeed, symptoms such as breathlessness, fatigue and oedema are frequently present, which can substantially affect quality of life.[7]

To improve patient outcomes, a number of heart failure management programs have been developed and tested over the past twenty years.[8,9] In these programs, several organisational models have been used. Examples of these models are a heart failure clinic, a home based intervention and a hospital outreach program. Key components of all of these models are education and counselling by a heart failure nurse, accessibility of a health care provider in

**Figure 1:** Expected event rates if a basic program provides most of the beneficial effect




case of problems (mostly a nurse), optimization of medication and increased support after discharge.

To address the effectiveness of heart failure management programs, a number of randomised controlled studies have been conducted, some of which have reported decreased readmission rates, increased time to first major event, decreased costs and an improvement in quality of life.[10-16] Moreover, a higher survival rate was recently reported in a randomised, controlled trial of a home-based management program in Australia.[17] However, several other studies have failed to support these positive findings, either by reporting negative or inconclusive results.[18,21]

Substantial differences in the type and intensity of disease management programs make it impossible to draw definitive conclusions about the effectiveness, optimal timing and frequency of interventions.

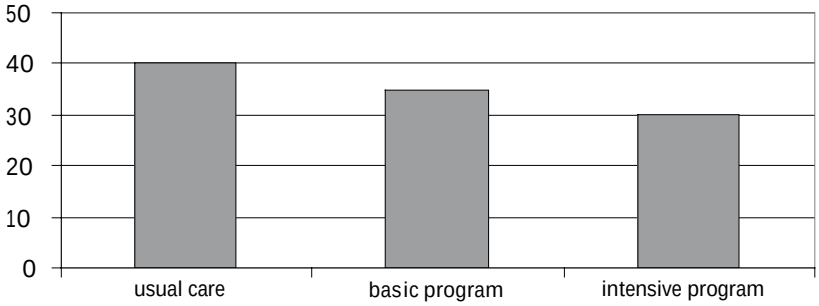
In addition, differences in national health care systems raise questions about the suitability and comparability of heart failure management programs in different countries. To illustrate this, we have previously reported that an educational intervention with one home visit was not enough to significantly reduce re-hospitalization in a group of Dutch CHF patients.[20] In contrast, Stewart and co-workers have reported a lower readmission rate in a CHF population as a result of a single home visit by a cardiac nurse.[11,17]

It is therefore a major challenge to identify, which program is most effective and the level of intensity required. There are currently no studies that compare the relative effectiveness of different programs.[22]

This background was the rationale for designing the Coordinating study evaluating Outcomes of Advising and Counselling in Heart Failure (COACH). In this multicenter randomised study, advising and counselling at two different intensity levels will be compared to "care as usual" in order to evaluate the level of advising and counselling required. The rationale behind COACH is that if a basic program provides most of the beneficial effect (Figure 1), a much more intensive program is unnecessary, and too costly. In contrast, if the effect can *only* be gained by intensive advising and counselling (Figure 2) a basic support program may fail to provide that effect. This may indeed explain some of the "negative" studies, which may not have provided *enough* advising and counselling.

In addition to the discussion on the effectiveness and intensity of interventions, it is vital to identify the mechanisms of action. Some authors state that education, follow up and

**Figure 2:** Expected event rates if a significant effect can only be gained by intensive advising and counselling




availability of a health care provider in case of problems are the most important components of interventions. Others emphasize the importance of compliance to treatment and the early detection and treatment of clinical deterioration, suggesting that these were the key elements in the success of these interventions. Improved knowledge or self-care behaviour of patients are also considered as part of the underlying mechanism for better outcomes.[11,13,14,17]

# Methods

### Study hypothesis

The hypothesis of the COACH study is that advising and counselling will be beneficial to CHF patients, as compared to "care as usual", in terms of prevention of CHF related mortality and morbidity, as well as quality of life and health care costs.

### Primary objective

To determine the effectiveness of two interventions (*basic* support vs. *intensive* support) compared to "care as usual" in CHF patients, on time to first major event (heart failure readmission or death).

### Secondary objectives

- To determine the effectiveness of two interventions (*basic* support vs. *intensive* support) compared to "care as usual" in CHF patients, on quality of life and costs.
- To investigate the role of underlying mechanisms (knowledge, beliefs, self-care behaviour, compliance) in the effectiveness of the 2 interventions.

### Study design

A multicenter, randomised, controlled design will be used. The aim is to recruit 1050 patients with heart failure, randomised into one control group 'care as usual' and two experimental groups' basic support or intensive support.

The study has been approved by the central Ethics Committee.

**Table 1:** Questionnaires used in the COACH-study

| | Assessment at | Questionnaire |
|---|---|---|
| Quality of life | Baseline, 1, 6, 12, 18 months | RAND36 |
| | | Ladder of Life |
| | | Minnesota Living with Heart Failure Questionnaire |
| Knowledge | Baseline, 1, 6, 12, 18 months | Dutch Heart Failure Knowledge Questionnaire |
| Beliefs | Baseline, 1, 6, 12, 18 months | Beliefs about Compliance Scales |
| Compliance | Baseline, 1, 6, 12, 18 months | Compliance questionnaire |
| | | Medication Monitoring system (MEMS®) |
| | | Food diary |
| Self-care behaviour | Baseline, 1, 6, 12, 18 months | European Heart Failure self-care behaviour scale |
| Depression | Baseline | CES-D |
| Type-D | Baseline | Type-D |
| Reason for readmission | During the study | Reasons for readmission interview |

## Study population

All patients will be required to have a hospital admission for CHF (NYHA II-IV). In addition, patients must be at least 18 years of age, with evidence of structural underlying heart disease. Reasons for exclusion from the study are: concurrent inclusion in a study requiring additional visits to research health care personnel; restrictions that make the patient unable to fill in the data collection forms; invasive intervention within the last 6 months (PTCA, CABG, HTX, valve replacement) or planned during the following 3 months; ongoing evaluation for Heart Transplantation; inability or unwillingness to give informed consent.

After confirmation of eligibility according to the above mentioned criteria, patients will be randomised to one of the three intervention strategies, i.e. "care as usual", basic support, or intensive support.

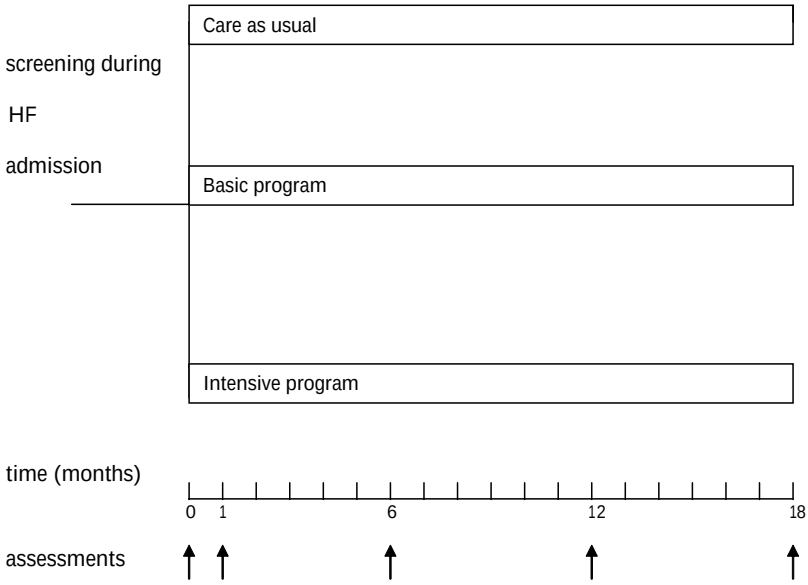
## Primary endpoint

The primary endpoint is the time to first event (readmission for CHF or death). A hospitalisation for CHF is defined as an unplanned overnight stay in a hospital (different dates for admission and discharge) due to progression of CHF or directly related to CHF.

Secondly, the proportion of 'unfavourable days' during the study will be analysed. A day is considered as 'unfavourable' if the patient is hospitalised or dead.

In addition, data will be collected on the number of readmission days, number of readmissions per patient and hospitalisations for CHF. Data will be collected by chart reviews, use of databases and interviews.

**Figure 3:** Trial design




### Secondary endpoints

The secondary endpoints are quality of life, health care costs, compliance, knowledge, beliefs and self-care behaviour.

## Assessment, randomisation and intervention protocol

### Assessment and randomisation

Following confirmation of suitability and informed consent, patients' baseline characteristics will be assessed from the medical chart, patient interview and patient questionnaires (Table 1). After the baseline assessment, patients will be randomised by a central randomisation service on a 1:1:1 basis, to either "care-as-usual", basic support or intensive support (Figure 3).

Follow-up assessments will take place 1, 6, 12 and 18 months after discharge. Data will be collected at the patients' home by an independent data collector using a structured interview. Additional data will be collected from the medical chart.

### Treatment and care

Two different types of interventions will be tested and compared to a control group as described below (Table 2). The content of the interventions is derived from interventions used in other countries, from interventions that are relevant and realistic in the Netherlands and according to the Dutch Heart Failure Guidelines.

**Table 2:** Treatment and care for patients in the 'care as usual' group (control), and intervention groups

| | Care as usual | Basic program | Intensive program* |
|---|---|---|---|
| Hospital | | Visits by HF Nurse | Visits by HF Nurse Multi-disciplinary Advice |
| 1 week | | | Advising☏<br>Home visit by HF nurse |
| 2 week | | Advising☏ | Advising☏ |
| 3 week | | | Advising☏ |
| 4 week | | Visit to HF nurse | Visit to HF nurse |
| 8 week | Visit to cardiologist | Visit to cardiologist<br>Visit to HF nurse | Visit to cardiologist<br>Visit to HF nurse |
| 3 months | | Visit to HF nurse | Visit to HF nurse |
| 4 months | | | ☏<br>Multidisciplinary Advice |
| 5 months | | | Visit to HF nurse |
| 6 months | Visit to cardiologist | Visit to cardiologist<br>Visit to HF nurse | Visit to cardiologist<br>Visit to HF nurse |
| 7 months | | | ☏ |
| 8 months | | | Visit to HF nurse |
| 9 months | | Visit to HF nurse | Visit to HF nurse |
| 10 months | | | ☏ |
| 11 months | | | Home visit by HF nurse |
| 12 months | Visit to cardiologist | Visit to cardiologist<br>Visit to HF nurse | Visit to cardiologist<br>Visit to HF nurse<br>Multidisciplinary Advice |
| 13 months | | | ☏ |
| 14 months | | | Visit to HF nurse |
| 15 months | | Visit to HF nurse | Visit to HF nurse |
| 16 months | | | ☏ |
| 17 months | | | Visit to HF nurse |
| 18 months | Visit to cardiologist | Visit to cardiologist<br>Visit to HF nurse | Visit to cardiologist<br>Visit to HF nurse |

* if needed additional visits or phone calls will be made.

Care-as-usual: Patients in the control group will receive usual treatment and care. After hospital discharge patients assigned to the control group will continue to receive routine management by the cardiologist and, subsequently, by their general practitioner. No extra follow-up by a heart failure nurse or a multidisciplinary team will be provided. Since counselling and advising by a heart failure nurse is not the usual care in the Netherlands, this control situation is (still) ethically feasible. Patients will visit the cardiologist at the outpatient clinic according to a defined schedule. This schedule consists of visits to the outpatient clinic 8 weeks after discharge, 6 months, 12 months, and every 6 months thereafter. Patients will be treated using current guidelines, receiving optimal doses of standard medication.

Intervention group 1: basic support: These patients will receive care from the cardiologist as described above. In addition, the following support will be provided:

- Patient (and family) education according to guidelines and protocol in hospital and during visits to the outpatient clinic. Behavioural strategies will be used to improve compliance.
- A telephone contact will be made within 2 weeks of discharge.
- During their regular visits to the cardiologist at the outpatient clinic patients will also visit the heart failure nurse. In addition, there will be visits to the heart failure nurse after 4 weeks and then 3, 9 and 15 months after discharge.
- Telephone access to a heart failure nurse. Patients and their family/carers will be encouraged to contact the nurse if there is a change in the patients' condition or if there are any problems or questions. The nurse can be contacted Monday to Friday 0900-1700.

Intervention group 2: intensive support: In this group, the most intensive level of advising and counselling will be provided. This means that patients in this group will receive education and counselling similar to that in intervention group 1.

The following extra support is provided:

- A home visit will be made within 10 days after discharge from the hospital. The home visit will allow the nurse to assess how the patient is coping in the home environment, the patients' CHF status, the patients' general health status, available medical support, health care and social support and future health care needs based upon this. An additional home visit will be made 11 months after discharge.
- Patients in this group will be contacted each month during the course of the study by the heart failure nurse (and by their cardiologist during usual visits). If needed, additional visits or telephone calls will be made.
- In the first month telephone calls will be made weekly.
- Telephone availability of a heart failure nurse during office hours and 24-hour coverage by a back up system.
- The nurse will consult a multidisciplinary team at least once during hospital admission and once at follow-up to optimise her advice for each patient.
  This multidisciplinary team will consist of a physiotherapist, dietician and social worker. Other health care professionals will be consulted, as required.

In both intervention groups the heart failure nurses will use a computer program to guide patient education and counselling. This program consists of an assessment form and patient education topics, which are specified for each patient visit (incl. home visit). Additionally patient progress is reported and the number of patient contacts that are initiated either by the health care provider or by the patients, are registered.

In the training of the HF nurses, the importance of counselling strategies is stressed and explained. In addition to providing information to patients, HF nurses are trained to increase self-efficacy of patients. Material used in the intervention include a patient diary, brochures and samples of sodium restricted seasoning/spices

# Statistical issues

### Analysis

All analyses will be conducting according the intention-to-treat principle. To meet the primary objective in the study, the primary variable 'time to the first hospitalisation for heart failure or death' will be evaluated using Kaplan-Meier survival analysis. Log-rank testing will be done to compare the different treatment strategies. In addition, a Cox proportional hazard model will be fitted for a multivariate analysis. A p-value below 0.05 will be considered as statistically significant and the incidence curves will be considered to be confirmed different.

Secondly, the proportion of 'unfavourable days' during the study will be analysed. A day is considered as 'unfavourable' if the patient was hospitalised or dead.

### Power calculation

The number of 1050 patients in the COACH study is based on the primary endpoint of time to major event. In previous international studies, event rates (hospital admission and/or death) ranging from 30-54% are reported. It should be noted that several studies only include patients with a low ejection fraction and patients in NYHA III-IV. In patients with NYHA II, a lower event rate can be expected. In a Dutch intervention study, a readmission rate of 50% (control) versus 37% (experimental) within 9 months has been reported.[21] The effect-size of nursing interventions vary from a reduction in readmission rates of 27%, 42% or 44%.[11-13] In the current study with an 18 months follow-up period, the event rate (readmission or mortality) of control patients is estimated at 40% within 1 year. A 25% reduction of the major events in the basic follow up intervention ($A+C_b$) group is considered both realistic and clinically relevant.

It was calculated that 698 subjects (349 in each group) will be needed to detect a 25% reduction in events (power of 90%, alpha of 0.05) in the basic intervention group ($A+C_b$). For the additional intervention group, another 349 patients will be included.

Moreover, with 349 patients per group, the study has a 90% power to show that the number of 'unfavourable days' reduces by 50% by the intervention - from 60 days to 30 days (sd 120) during the study period of 18 months.

# Study organisation

### Study centres

In order to include the 1050 patients in 18 months, 17 hospitals in the Netherlands are participating in this study.

### Steering Committee

Prof. dr. DJ van Veldhuisen, Chairman and Principal Investigator, dr. T. Jaarsma, Principal Investigator, DJA Lok (on behalf of the Working Group on Heart Failure of the NVVC), Prof. dr. KI Lie, Prof. dr. R Sanderman, Prof. dr. JGP Tijssen, dr. PHJM Dunselman, Prof. dr. WH van Gilst, dr. HJ Hillege, Prof. dr. AW Hoes, dr. JE Speksnijder and dr. MCM. Senten (both on behalf of the NHF)

### Endpoint Committee

A panel of 2 cardiologists and an internist/geriatrician will judge whether a reported hospitalisation of a study participant is related to heart failure (primary endpoint), cardiovascular death or cardiovascular events. The panel will be blind as to whether the patient was in the control group or one of the intervention groups.

### Support and monitoring

The study will be supported and monitored by the Trial Coordination Centre (dr HJ Hillege MD PhD, N Veeger MSc) a contract research organization for clinical trials. Both the quality of the research data and of the intervention will be structurally monitored. To address the quality of the intervention the data from the computer program -which is used for the education and counselling- is monitored and discussed monthly with the HF nurses by an on site visit of a research fellow.

### Financial support

The Netherlands Heart Foundation (NHF) financially supports the study as one of their top down research programs (2000Z003).

### Conclusion

To obtain an insight into the optimisation of education and counselling of HF patients, this multi-centre randomised trial, aims to include 1050 HF patients. Results from this trial, which recently started recruitment, will help health care providers in future to make rational and informed choices about which components of a HF management program should be expanded and which components can possibly be deleted.

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Chapter 3

# Influence of age on Natriuretic Peptides in patients with chronic heart failure: a comparison between ANP/ NT-ANP and BNP/ NT-proBNP

Jochem Hogenhuis, Adriaan A. Voors, Tiny Jaarsma, Hans L. Hillege, Frans Boomsma, Dirk J. van Veldhuisen.

*Eur J Heart Fail* 2005;7:81-7.

# Abstract

**Background:** Natriuretic peptides are currently used in the diagnosis and follow-up of patients with Chronic Heart Failure (CHF). However, it is unknown whether there are different influences of age on atrial natriuretic peptide (ANP)/N-terminal-ANP (NT-ANP) or B-type natriuretic peptide (BNP)/N-terminal-proBNP (NT-proBNP).
**Aims:** To compare the influence of age and gender on plasma levels of ANP/NT-ANP and BNP/NT-proBNP in CHF patients.
**Methods and Results:** Natriuretic peptides were measured in 311 CHF patients (68 ± 8 years, 76% males, left ventricular ejection fraction (LVEF) 0.23 ± 0.08). All natriuretic peptides were significantly related to age ($p<0.05$) on multivariate regression analysis, with partial correlation coefficients of 0.18, 0.29, 0.28 and 0.25 for ANP, NT-ANP, BNP and NT-proBNP respectively. The relative increase of both BNP/NT-proBNP were more pronounced than of ANP/NT-ANP ($p<0.01$). Furthermore, the relative increase of BNP with age was markedly larger than of NT-proBNP ($p<0.01$). Levels of all natriuretic peptides were also significantly related to cardiothoracic ratio, renal function and LVEF.
**Conclusion:** In patients with CHF, BNP/NT-proBNP were more related to age than ANP/NT-ANP, and BNP was more related to age than NT-proBNP. However, in these CHF patients the influence of age on the levels of all natriuretic peptides was modest, and comparable to several other factors.


# Introduction

Plasma natriuretic peptides have been shown to be of additional value in the diagnosis[1-4] and prognosis[5] of Chronic Heart Failure (CHF) patients. Research initially focussed on the Atrial Natriuretic Peptides (ANP) and N-terminal ANP [NT-ANP]), which are primarily secreted in the atria. In recent years, peptides secreted in the ventricles (B-type Natriuretic Peptide [BNP], and N-terminal proBNP [NT-proBNP]) have been increasingly studied. In a comparative study, the diagnostic value of BNP appeared to be superior to ANP, especially with regard to the positive predictive value (BNP 70%, ANP 55%).[6] Furthermore BNP and NT-proBNP are better predictors of prognosis after myocardial infarction than ANP and NT-ANP.[7] However, plasma levels of natriuretic peptides are influenced by age and gender in healthy subjects.[8-10] Although natriuretic peptides are largely used in CHF patients, only limited data about the influence of age[11,12] and gender[13] on natriuretic peptides in CHF patients are available. Despite the prognostic and diagnostic superiority of BNP, direct comparative studies on the influence of age on BNP/NT-proBNP and ANP/NT-ANP in CHF patients are lacking. We therefore compared the effects of age and gender on ANP/NT-ANP and BNP/NT-proBNP in a large group of CHF patients.

# Methods

## Study sample

The present analyses used the baseline data of patients included in the Netherlands in the Prime-II study. Prime-II was designed to examine the effect of oral ibopamine against pla-

cebo, on all cause mortality in patients with moderate to severe CHF.[14] Systolic dysfunction was an inclusion criterion of the Prime-II study (left ventricular ejection fraction < 35%). The design, and more inclusion and exclusion criteria of Prime-II were described in detail by Hampton et al. (1997).[14]

A predefined neurohormonal substudy consisted of 372 patients, with 311 patients having complete datasets. The study was approved by each local Ethical Committee, and prior to the announcement of the investigation all patients provided informed written consent. The investigation conforms with the principles outlined in the declaration of Helsinki.

## Natriuretic peptide measurement

At baseline of the Prime-II study, before the study drug ibopamine was started, blood was collected between 9:00 and 10:00 AM after patients had rested in supine position for >30 minutes. An intravenous canula was used to pour blood into chilled 10 ml tubes containing EDTA (19 mg) and aprotinin (1000 kIU). The tubes were centrifuged within 30 minutes (4° C, 10 minutes, 2000 x g) and plasma was separated and stored in polyethylene tubes at -70°C. The plasma natriuretic peptide samples were transported (on dry ice) to the Core Laboratory at the University Hospital Dijkzigt, Rotterdam, the Netherlands, where all measurements were executed. Measurement of ANP (normal value:15-35 pmol.l-1) was performed after SepPak extraction, with commercially available radioimmunoassay kits from the Nichols Institute, Wijchen, The Netherlands, as previously described.[15-17] Plasma NT-ANP (normal value: 150-500 pmol.l-1) was determined using a commercially available radioimmunoassay kit (Biotop, Oulu, Finland).[18] NT-proBNP was measured using a radioimmunoassay kit with reagents including antibody, standards, and radiolabel. The assay uses 50 µl of unextracted plasma and has a standard range of 60- 1000 pmol.l-1. All samples giving results of >900 pmol.l-1 were re-analysed in appropriate dilutions with physiological salt. In 12 consecutive assays, variability was 14, 11, 4 and 4 % at concentrations of 131, 199, 293 and 901 pmol.l-1, respectively. BNP was determined by a commercially available immunoradiometric assay (Shionoria, Osaka, Japan).

## Statistical analyses

To investigate the relation between natriuretic peptides and other patient characteristics Pearson and Spearman correlation coefficients were calculated, when appropriate. For all natriuretic peptides, the following predictor variables were used in univariate analyses: age, gender, NYHA class, the existence of coronary artery disease, dilated cardiomyopathy or hypertension, systolic and diastolic blood pressure, heart rate, left ventricular ejection fraction, cardio-thoracic ratio, sinus rhythm or atrial fibrillation, renal function and the medication that was taken by the patient (β-blockers, ACE inhibitors, diuretics, digoxin and anti-arrhythmics). A multivariate regression analyses was performed to study the relation between natriuretic peptides on the one hand and age and gender on the other. Because the plasma natriuretic peptides had a skewed distribution, the natural logarithm was used to get an optimal residual analysis. A p-value < 0.15 was required to enter a variable into the multivariate model, and a p-value > 0.05 was needed to remove a variable from the model. Partial correlation coefficients of the plasma level of ANP/NT-ANP and BNP/NT-proBNP were calculated with correction for the predictors that were entered in the multivariate regression model.

**Table 1:** Characteristics of study population divided in age quartiles.

| | Total (n=311) | Q1: 38-62 (n=76) | Q2: 63-69 (n=77) | Q3: 70-73 (n=67) | Q4: 74-80 (n=91) |
|---|---|---|---|---|---|
| Age (years) | 68 ± 8 | 57 ± 5 | 66 ± 2 | 71 ± 1 | 76 ± 2 |
| Gender (%men) | 76% | 83% | 78% | 73% | 71% |
| NYHA | | | | | |
| III | 68% | 78% | 68% | 72% | 63% |
| III/IV | 29% | 21% | 29% | 28% | 33% |
| IV | 3% | 1% | 3% | 0% | 4% |
| Aetiology | | | | | |
| Coronary artery disease | 76% | 68% | 83% | 72% | 78% |
| Dilated cardiomyopathy | 17% | 25% | 12% | 18% | 14% |
| Hypertension | 5% | 3% | 4% | 3% | 8% |
| Other | 3% | 4% | 1% | 7% | 0% |
| Heart rate (beats . min-1) | 81 ± 15 | 81 ± 17 | 81 ± 15 | 81 ± 15 | 81 ± 14 |
| Blood pressure | | | | | |
| Systolic (mmHg) | 125 ± 18 | 125 ± 18 | 123 ± 17 | 123 ± 19 | 126 ± 18 |
| Diastolic (mmHg) | 76 ± 10 | 73 ± 8 | 75 ± 9 | 75 ± 10 | 76 ± 9 |
| Serum sodium (mmol . l-1) | 139 ± 3 | 139 ± 3 | 139 ± 3 | 139 ± 4 | 139 ± 3 |
| Evidence of heart disease | | | | | |
| LVEF | 0.23 ± 0.08 | 0.24 ± 0.08 | 0.23 ± 0.09 | 0.25 ± 0.06 | 0.23 ± 0.08 |
| CT Ratio | 0.56 ± 0.07 | 0.55 ± 0.05 | 0.55 ± 0.06 | 0.56 ± 0.07 | 0.57 ± 0.07 |
| Rhythm | | | | | |
| Sinus rhythm | 74% | 87% | 79% | 72% | 75% |
| Atrial fibrillation/ flutter | 26% | 13% | 21% | 28% | 25% |
| Renal function | | | | | |
| Creatinine (μmol/L) | 118 ± 39 | 107 ± 31 | 114 ± 33 | 120 ± 32 | 130 ± 50 |
| Concomitant medication | | | | | |
| ACE inhibitors | 94% | 96% | 96% | 97% | 92% |
| Diuretics | 99% | 96% | 100% | 99% | 99% |
| Digoxin | 59% | 50% | 68% | 63% | 58% |
| Anti- arrhythmics | 18% | 20% | 21% | 13% | 18% |
| Beta blockers | 9% | 12% | 8% | 15% | 8% |

CT-ratio = Cardio-thoracic ratio, LVEF = Left Ventricular Ejection Fraction, NYHA = New York Heart Association functional class, Q = quartile.

Age was divided into quartiles, using the first quartile as the reference group. In all quartiles the relative differences between lnANP and lnBNP, lnNT-ANP and lnNT-proBNP, lnANP and lnNT-ANP and lnBNP and lnNT-proBNP were investigated with paired samples t-tests.

Outcomes were considered significant when $p < 0.05$. Results were presented as means ± standard deviations except when stated otherwise.

**Table 2:** Natriuretic peptide plasma levels in age quartiles (median [minimum-maximum]).

| | Total (n=311) | Q1: 38-62 (n=76) | Q2: 63-69 (n=77) | Q3: 70-73 (n=67) | Q4: 74-80 (n=91) |
|---|---|---|---|---|---|
| ANP (pmol.l$^{-1}$) | 103 (12-815) | 88 (12-597) | 103 (19-508) | 115 (18-720) | 105 (28-815) |
| NT-ANP (pmol.l$^{-1}$) | 1078 (129-4280) | 689 (129-3414) | 1066 (256-3081) | 1151 (239-4210) | 1148 (344-3760) |
| BNP (pmol.l$^{-1}$) | 60 (0.6-502) | 33 (0.6-352) | 47 (3-322) | 79 (1.4-502) | 65 (7.6-373) |
| NT-proBNP (pmol.l$^{-1}$) | 610 (2-5295) | 372 (3-2928) | 527 (5-3380) | 711 (3-5295) | 715 (14-4820) |

ANP = Atrial Natriuretic Peptide, BNP = B-type Natriuretic Peptide, NT-ANP = N-terminal Atrial Natriuretic Peptide, NT-proBNP = N-terminal pro B-type Natriuretic Peptide, Q = quartile.

**Table 3:** Partial correlation coefficients for natriuretic peptides in relation with age and gender (corrected for CT-ratio, LVEF, plasma Creatinine, use of diuretics, SBP, CAD).

| | ANP | NT-ANP | BNP | NT-proBNP |
|---|---|---|---|---|
| Age | 0.18* | 0.29* | 0.28* | 0.25* |
| Gender# | -0.14† | -0.18* | -0.09 (NS) | -0.05 (NS) |

* = $p < 0.01$, † = $p < 0.05$, # coding: 1 = male, 2 = female, ANP = Atrial Natriuretic Peptide, BNP = B-type Natriuretic Peptide, CAD = Coronary Artery Disease, CT-ratio = Cardio-thoracic ratio, LVEF = Left Ventricular Ejection Fraction, NT-ANP = N-terminal Atrial Natriuretic Peptide, NT-proBNP = N-terminal pro B-type Natriuretic Peptide, SBP = Systolic Blood Pressure.

# Results

Demographic and clinical characteristics of the 311 patients are presented in table 1. On average patients were 68 ± 8 years of age, the majority (76%) of patients of this study was male. A significant age difference between males and females was found (p-value < 0.05). The median and ranges of ANP, NT-ANP, BNP and NT-proBNP in the patient population were 103 (12-815) pmol.l-1, 1078 (129-4280) pmol.l-1, 60 (0.6-502) pmol.l-1 and 610 (2-5295) pmol.l-1 respectively (table 2).

Plasma levels of ANP/NT-ANP and BNP/NT-proBNP showed significant positive correlations with age on univariate regression analyses (p-values < 0.05). Furthermore, ANP and NT-ANP plasma levels were significantly higher in patients with atrial fibrillation compared to patients with sinus rhythm (p-values < 0.05). Although a similar difference was indeed present, it was not statistically significant for BNP and NT-proBNP.

## Multivariate predictors of natriuretic peptide plasma levels

Left ventricular ejection fraction, cardio-thoracic ratio and renal function added significant value to the multivariate regression model (p-values < 0.05) for all tested natriuretic peptides. Gender was significantly related to ANP and NT-ANP in the multivariate model, while this was not the case for BNP and NT-proBNP (table 3). Use of diuretics was only related to ANP, and systolic blood pressure was only related to NT-ANP and NT-proBNP. The existence of coronary artery disease was only related to NT-proBNP. The multivariate partial

correlation coefficients in relation to age were 0.18, 0.29, 0.28 and 0.25 for ANP, NT-ANP, BNP and NT-proBNP respectively (table 3). The interaction term between age and gender did not add significant value to the multivariate regression model of all tested natriuretic peptides.

### Direct comparisons

To directly compare the age dependency between ANP/NT-ANP and BNP/NT-proBNP, we divided our population in quartiles. The relative increase in lnBNP was significantly larger than the relative increase in lnANP, and the relative increase in lnNT-proBNP was significantly larger than the relative increase in lnNT-ANP (figure 1). In addition, we directly compared lnANP to lnNT-ANP and lnBNP to lnNT-proBNP. The relative increase of lnANP and lnNT-ANP with age was similar (figure 1). However, the relative increase of lnBNP with age was significantly larger than the relative increase of lnNT-proBNP with age (figure 1).

## Discussion

Plasma natriuretic peptides are of added value both in the diagnosis[1-4] and prognosis[5] of CHF. Direct comparative studies indicated both diagnostic[6] and prognostic [7] superiority of BNP/NT-proBNP over ANP/NT-ANP. Although age-dependency of plasma levels of both ANP/NT-ANP and BNP/NT-proBNP has been demonstrated, direct comparative studies on age-dependency between ANP/NT-ANP and BNP/NT-proBNP in CHF patients were not available. In a large group of CHF patients, we demonstrated that BNP/NT-proBNP were influenced by age to a larger extend than ANP/NT-ANP. We also demonstrated that the relative increase of BNP with age was significantly larger than NT-proBNP.

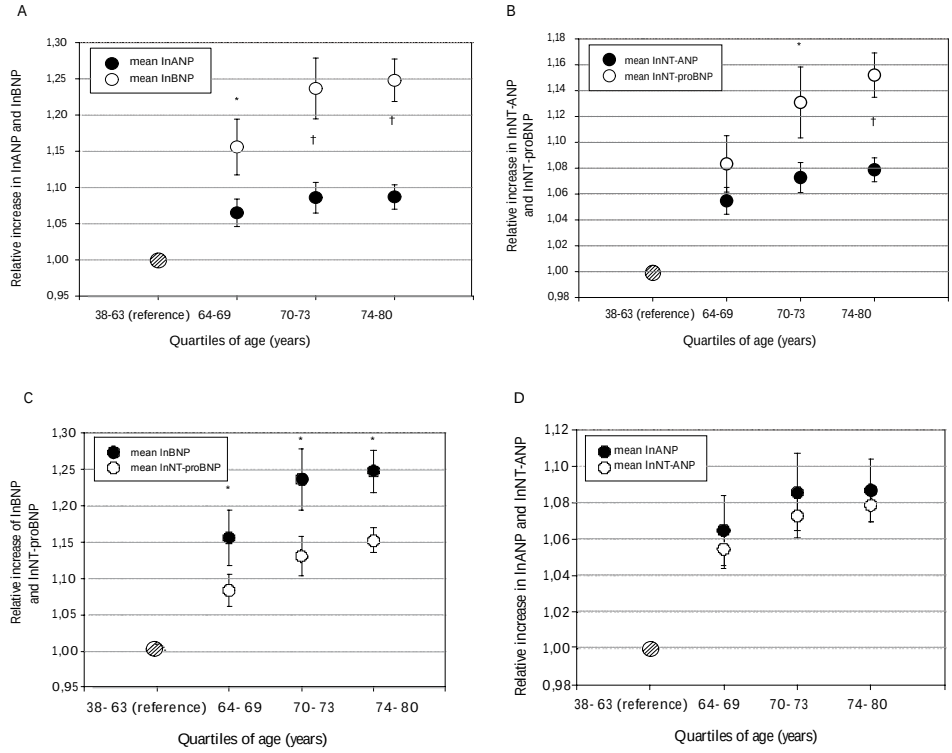
### Relation ANP/NT-ANP, BNP/NT-proBNP and age in healthy adults

The relation between age and levels of natriuretic peptides is well described in healthy subjects.[9,19] In a large group of healthy adults (n=911), Wang and co-workers calculated multivariate correlations between ANP/NT-ANP, BNP and age. After multivariate adjustment, a 10 year increase in age was associated with a 1.4 fold increase in BNP levels and a 1.2 fold increase in NT-ANP.[10] Another large study in healthy subjects (n=216) showed a weak, but significant relationship between age and both ANP and BNP.[8] Raymond et al. analysed a healthy sub group (n=130) of a large sample of the general population, and found a strong positive relationship between NT-proBNP and age.[20]

### Relation ANP/NT-ANP, BNP/NT-proBNP and age in CHF patients

In contrast to healthy subjects, the relation between age and natriuretic peptides is less well described in CHF patients. This seems contradictory, since natriuretic peptides are generally used in CHF patients. Interestingly, Dutka et al. demonstrated that although ANP levels increased with age in healthy subjects, in CHF patients, ANP levels appeared to decrease with age.[11] In contrast, an increase of NT-ANP with age was demonstrated in a large sample of CHF patients.[12] Although the multivariate correlation was only modest, NT-ANP increased approximately 3 fold from the age of 40- 80 years.[12] Differences between these studies might be related to differences between ANP and NT-ANP, although in the current study,

**Figure 1:** Comparison of lnANP vs lnBNP (A), lnNT-ANP vs lnNT-proBNP (B), lnBNP vs lnNT-proBNP (C) and lnANP vs lnNT-ANP (D) in their relative increase in age quartiles related to reference group (38-62 years).
* = p < 0.01, † = p < 0.001




both ANP and NT-ANP increased with age, and we did not find a difference between the relative increase of either ANP or NT-ANP with age. To our knowledge, only one small study has demonstrated an age-dependency of BNP and NT-proBNP in CHF patients (n=92).[21] In this study of Masson et al., the increase in plasma levels of BNP and NT-proBNP with age was similar.[21] We confirmed this age dependency of both BNP and NT-proBNP in a large group of patients classified in NYHA functional class III/IV. However, we demonstrated that the relative increase of BNP with age was significantly larger than the relative increase of NT-proBNP with age. The difference between our study and the results by Masson et al. might be related to the severity of CHF (NYHA III-IV and mainly NYHA II, respectively), and the difference in age (68 vs. 57 years respectively), although these explanations remain highly speculative.

## Direct comparisons between ANP/NT-ANP and BNP/NT-proBNP

Clerico et al. described the age dependency of ANP and BNP of healthy adults in the same paper. Although they found significant correlations with age for both peptides (ANP:

r=0.350; BNP: r=0.254), no direct comparisons were performed.[8] Another study reported on the age dependency of both BNP and NT-ANP. Again, significant increases with age were described in healthy subjects (BNP: 1.4 fold and NT-ANP: 1.2 fold increase per age decade), but no statistical comparisons between the natriuretic peptides were shown.[10]

So, although age-dependency of both ANP/NT-ANP and BNP/NT-proBNP has been well described, to our knowledge this is the first direct comparative study. Since age dependency may be a disadvantage, natriuretic peptides without age dependency will favour the ones with age dependency. We found significant differences between natriuretic peptides in favour of ANP/NT-ANP over BNP/NT-proBNP and also of NT-proBNP over BNP, although differences appeared to be generally small.

### Relation ANP/NT-ANP, BNP/NT-proBNP and gender

In healthy adults, gender differences in plasma levels of natriuretic peptides are found, with females having higher plasma levels.[9,10,13] However, we only found a gender difference for ANP/NT-ANP and not for BNP/NT-proBNP. This might reflect the age difference between men and women; because BNP/NT-proBNP were shown to be more affected by ageing compared to ANP/NT-ANP, this age difference could be more powerful in BNP/NT-proBNP.

### Interpretation of the findings

Age dependency of natriuretic peptides has been clearly shown in a healthy population.[8-10,19,20] We demonstrated that the influence of age on natriuretic peptides in CHF patients was modest, and comparable to several other factors, such as cardio-thoracic ratio, renal function and left ventricular ejection fraction. Therefore, indexing natriuretic peptides for age seems reasonable in case of diagnosis of CHF. However, when natriuretic peptides are used for prognosis or to guide medical treatment in patients already diagnosed with CHF, we do not recommend to routinely indexing natriuretic peptides for age.

### Limitations

First, the current study was relatively small. The majority of the patient population was male (76%), and in some age quartiles less than 20 females were present. Therefore, power was too small to draw definite conclusions regarding gender differences between ANP/NT-ANP and BNP/NT-proBNP.

Second, several other factors appeared to be related to the levels of some natriuretic peptides, but not to others. This is in contrast to the age-dependency, which was demonstrated with all natriuretic peptides. Since we cannot clearly explain these findings, we think that these might have been due to chance finding.

Third, measurements of plasma levels of NT-proBNP were performed using a non-commercially available assay developed by Prof. O. Vuolteenaho (Oulu, Finland). The disadvantage of using this assay is that no solid validation information is available. Because different assays have different outcomes, current results are only valid for the natriuretic peptide plasma levels determined with the same assays.

### Conclusions

The present analysis confirmed the positive relation between ANP/NT- ANP, BNP/NT-proBNP and age in a large group of CHF patients. In addition, the influence of age appeared to be more pronounced on levels of BNP/NT-proBNP than on ANP/NT-ANP. Also, the relative increase of BNP with age was significantly larger than of NT-proBNP. Nevertheless, many other factors were also related to plasma levels of both ANP/NT-ANP and BNP/NT-proBNP, and partial correlation coefficients were relatively low.

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Chapter 4

# Anaemia and renal dysfunction are independently associated with B-type Natriuretic Peptide and N-terminal pro B-type Natriuretic Peptide in patients with heart failure

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*Submitted*

# Abstract

**Aims:** Anaemia (by increasing plasma volume) and renal dysfunction (by decreasing clearance) may affect B-type Natriuretic Peptide (BNP) and N-terminal proBNP (NT-proBNP) levels, although this has not been well described in heart failure (HF) patients. We therefore aimed to study the influence of anaemia and renal function on BNP and NT-proBNP levels in hospitalised HF patients.

**Methods and Results:** We studied 541 patients hospitalised for HF, and BNP and NT-proBNP levels were measured before discharge. Of these patients (71 ± 11 years of age, 62% males, left ventricular ejection fraction 0.33 ± 0.14), 30% (n=159) was anaemic (Hb<7.5 mmol/L for women and Hb<8.1 mmol/L for men). Of the 159 anaemic patients, 73% had renal dysfunction (eGFR <60 ml/min/1.73m$^2$) and of the non-anaemic patients, 57% had renal dysfunction. Multivariable analysis demonstrated that both plasma haemoglobin and eGFR were independently related to the level of both BNP and NT-proBNP (standardized beta's of -0.20, -0.13 [BNP] and -0.26, -0.28 [NT-proBNP] respectively, P-values <0.01).

**Conclusion:** Anaemia and renal dysfunction are related to increased BNP and NT-proBNP levels, independent of the severity of HF. Thus, false positive values of elevated BNP and NT-proBNP levels can be anticipated in HF patients with anaemia and/or renal dysfunction.


# Introduction

The diagnostic accuracy of B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) in patients who are presented at the emergency department for acute dyspnoea is well described.[1,2] However, even with optimal cut-off values determined by receiver operating characteristic curves, approximately 10% of the patients have false negative outcomes, and 16%-24% of the patients have false positive outcomes.[1,2] To further increase the diagnostic accuracy of these natriuretic peptides, it is important to identify other factors, beside the severity of HF, that influence BNP levels and NT-proBNP levels. We and others have previously described that, in addition to its correlation with severity of HF,[3] both BNP and NT-proBNP levels are influenced by several other factors such as age, gender, obesity and renal function.[4-11]

Another factor that might influence NT-proBNP levels and that is frequently found in patients with heart failure is anaemia. Since anaemia causes increased plasma volume independent of severity of HF,[12] and because natriuretic peptides are released in reaction to ventricular plasma overload[13] it is conceivable that natriuretic peptides are higher in anaemic HF patients compared to non-anaemic HF patients. In 209 patients without HF or renal disease Willis et al. recently demonstrated that NT-proBNP concentrations were significantly higher in patients with anaemia compared to patients without anaemia.[14] In contrast, in a subgroup analysis of the Breathing Not Properly trial, no correlation was found between BNP levels and haemoglobin in 200 patients with systolic HF, and only a weak correlation was found between BNP levels and diastolic HF.[15] In that study patients with renal failure were excluded. To our knowledge, the independent influence of anaemia on NT-proBNP levels has never been investigated in a HF population without exclusion of patients with renal failure. Moreover, we are not aware of any study investigating the influence of anaemia

and renal dysfunction on levels of BNP and NT-proBNP. Since renal dysfunction is a well known cause of anaemia[16] and because it may influence both BNP levels and NT-proBNP levels by decreasing clearance,[17] renal dysfunction should be taken into account when studying the effect of anaemia on BNP levels and NT-proBNP levels. Hence, the aim of the present study was to investigate the relationship between anaemia and renal function with BNP levels and NT-proBNP levels in HF patients.

# Methods

## Study population

The present study complies with the Declaration of Helsinki, the local ethics committee has approved the research protocol and informed written consent has been obtained from the subjects. All patients in the present study were recently admitted for decompensated HF (NYHA II-IV), when they were included in a multicenter HF trial conducted in the Netherlands (COACH).[18] All participating sites (n = 17) were experienced HF centre's. Patients were at least 18 years of age with evidence of structural underlying heart disease. Detailed information on the study design has been published before.[18] In short, COACH is a randomised controlled trial investigating the effect of education and counselling on readmission for HF and mortality. Of the 1049 patients included in the COACH study, 543 patients had NT-proBNP levels available at baseline, 601 patients had BNP levels available at baseline, and 541 patients had both BNP and NT-proBNP levels available at baseline. Main reasons for missing BNP data were: no Triage® BNP meter available and the absence of a possibility to store plasma samples at - 80°C (n = 177), unplanned hospital discharge (n = 75) or death during admission (n = 20). Main reasons for missing NT-proBNP data were: the start of the NT-proBNP sub study after already 272 patients were included in COACH, the absence of a possibility to store plasma samples at - 80°C (in 1 out of 17 clinics; n = 71), unplanned hospital discharge or logistical problems (n = 155) and death during admission (n = 9).

## Measurement of BNP and NT-proBNP levels

Blood was collected shortly before discharge between 8:00 AM and 4:00 PM, after patients had been clinically stabilised and were recovered well enough to go home. 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 -70°C to -80°C. The plasma samples were transported (on dry ice) to the Core Laboratory at the University Medical Centre Groningen, the Netherlands.

*BNP measurement:* In 364 out of the 541 patients, BNP levels were determined on site in whole blood within 4 hours after blood collection. In 177 out of the 541 patients BNP levels were determined in plasma at the Core Laboratory. 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 validated before.[19] The measurable range of the BNP assays was 5.0- 5000.0 pg/ml.

*NT-proBNP measurement:* All measurements of NT-proBNP levels were performed in plasma at the Core laboratory on an Elecsys™ 2010 analyser, a commercially available electrochemiluminescent sandwich immunoassay (Elecsys proBNP, Roche Diagnostics, Mannheim, Germany). The intra-assay precision (coefficient of variation) is 1.2 – 1.5%, and the inter-assay precision (coefficient of variation) is 4.4 – 5.0%, with an analytical range of 5 – 35000 pg/ml.[20,21]

### Anaemia

The definition of anaemia according to the World Health Organisation was used; Hb <7.5 mmol/l (12 g/dl) for women and Hb < 8.1 for men (13 g/dl).[22]

### Renal function

Serum creatinine was determined from a blood draw shortly before discharge, in the local laboratory at each centre. Estimated Glomerular Filtration Rates (eGFR's) were calculated using the Levey – modified Modification of Diet in Renal Disease formula:[23]

$eGFR\ (ml/min/1.73m^2) = 186 \times SCr^{-1.154} \times age^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$

### Boston score

For 501 out of the 541 patients with BNP and NT-proBNP levels available, the Boston score, a quantification related to severity of HF, was calculated.[24] This score was used in combination with left ventricular ejection fraction (LVEF) to adjust possible determinants of BNP levels and NT-proBNP levels for severity of HF in the multivariable regression analysis. In short, the score consists of a medical history sub score, a physical examination sub score and a chest radiography sub score. For each sub score, a maximum of 4 points is allowed. The diagnosis HF is classified definite for a total score of 8 – 12 points, possible for a total score of 5 – 7 points and unlikely for a total score of 4 points or less. The Boston score was missing in 13 cases, since no chest radiography data were available of these patients.

### Statistical analyses

In order to study the independent relationship between anaemia haemoglobin (Hb) and renal function (as expressed in the eGFR) with BNP and NT-proBNP levels, univariable and multivariable linear regression analyses were performed in the patient population with both BNP and NT-proBNP levels available (n=541). Because the BNP and NT-proBNP levels had a skewed distribution the natural logarithm was used to get an optimal residual analysis. To study potential confounding factors, the following variables were used in univariable analyses (Pearson and Spearman correlation coefficients when appropriate) with BNP and NT-proBNP as the dependent variables: age, gender, LVEF, the Boston score, New York Heart Association (NYHA) functional class, HF aetiology, duration of HF symptoms, pulmonal congestion, rales, heart rate, systolic and diastolic blood pressure, presence of atrial fibrillation/ flutter, presence of pacemaker, hematocrit, renal disease, body mass index (BMI), hypertension, pulmonary embolism, chronic obstructive pulmonary disease or asthma, diabetes mellitus (type 1 and 2), HF II medication at admission and at discharge (diuretics, ACE inhibitors/ angiotensin receptor blocker, beta-blockers, spironolactone). In the multivariable linear regression analysis, a stepwise approach was used. Besides Hb and eGFR, a univariable P-value < 0.15 was required to enter a variable into the multivariable model, and if the P-value was > 0.05 a variable was removed from the model. NT-proBNP or BNP

levels were presented in bar charts stratified by quintiles of Hb. To get more insight in the distribution of NT-proBNP and BNP across the ranges of Hb, ANOVA trend analyses were performed for NT-proBNP or BNP after these were divided by quintiles of Hb. The associations of the anaemia and renal function with NT-proBNP and BNP were presented in bar charts. Outcomes were considered significant when $P<0.05$. Values are presented as means ± SD except when stated otherwise. All analyses were performed with SPSS version 11.

# Results

### Study populations

Demographic and clinical characteristics of the 541 patients with both BNP and NT-proBNP available are presented in table 1. Mean age of these 541 patients was 71 (± 11) years, and more than half of the population was male (62%) and had a non-ischemic aetiology for HF (59%). On average, LVEF was 0.33 (±0.14), Hb was 8.4 (±1.2) mmol/l, eGFR was 54 (±20) ml/min/1.73m$^2$ and BMI was 26 (±5) kg/m$^2$. At discharge, patients were classified as NYHA functional class II (52%), III (46%) or IV (2%), and were on medical therapy including diuretics (88%), ACE inhibitors/ angiotensin II receptor blockers (71%), beta-blockers (61%) (table 1). Characteristics were not significant different between patients with available BNP/NT-proBNP levels (n=541) and the total patient group included in COACH (n=1049).

### BNP and NT-proBNP levels

The median BNP value in the 541 patients with BNP and NT-proBNP available was 448 pg/ml, the interquartile range 209 – 916 pg/ml, the minimum value 14 pg/ml and the maximum value 5000 pg/ml. The median NT-proBNP value was 2599 pg/ml, the interquartile range 1314 – 5885 pg/ml, the minimum value 39 pg/ml and the maximum value 75361 pg/ml (table 1).

### Anaemia

Hb levels were available in 528 of the 541 patients. BNP and NT-proBNP levels divided by quintiles of haemoglobin are presented in figure 1. Anaemia was present in 30% (n=159) of the 541 patients in which BNP and NT-proBNP levels were available. Of these 159 anaemic patients 114 (73%) also had renal dysfunction (eGFR < 60 ml/min/1.73m$^2$) and of the 369 non-anaemic patients 209 (57%) had renal dysfunction (figure 2).

### Univariable determinants of BNP levels

Hb ($P<0.001$) and eGFR ($P<0.01$) were univariably related to the natural logarithm of BNP. Additionally, the following variables were potential confounders to these relationships ($P<0.15$): age ($P=0.11$), LVEF ($P<0.001$), NYHA functional class ($P=0.01$), Boston score ($P=0.14$), ischemic/ non-ischemic aetiology of HF ($P=0.04$), pulmonary congestion ($P=0.05$), myocardial infarction before admission ($P=0.12$), systolic ($P<0.01$) and diastolic blood pressure ($P<0.01$), atrial fibrillation/ flutter ($P=0.11$), hematocrit ($P<0.001$), BMI ($P<0.001$), prescribed diuretics at admission ($P=0.06$) .

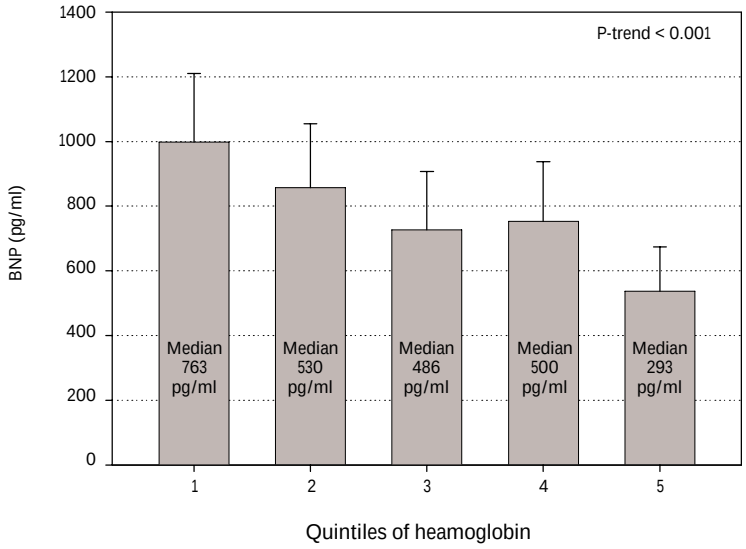
**Table 1:** Patient characteristics (n=541)

| | |
|---|---|
| Demographics | |
| Age (yrs) | 71 ± 11 |
| Gender (m) | 62% |
| Heart failure/ physical examinations | |
| BNP (median [IQR], pg/ml) | 448 (209 – 916) |
| NT-proBNP (median [IQR], pg/ml) | 2599 (1314 – 5885) |
| LVEF | 0.33 ± 0.14 |
| NYHA at discharge (II, III, IV) | 48%, 49%, 3% |
| Ischemic/ non-ischemic HF | 41% / 59% |
| Duration HF symptoms (yrs) | 2.7 ± 4.5 |
| Pulmonal congestion (X-ray) | 65% |
| Rales during admission | 89% |
| Heart rate (bpm) | 74 ± 13 |
| Systolic BP (mm/Hg) | 118 ± 21 |
| Diastolic BP (mm/Hg) | 69 ± 12 |
| Sinus rhythm | 55% |
| Atrial fibrillation/ flutter | 38% |
| Medical History/ Co-morbidities | |
| Myocardial infarction | 41% |
| Hypertension | 43% |
| COPD/ Asthma | 31% |
| Diabetes (type1 or 2) | 29% |
| Renal diseases | 8% |
| eGFR (ml/min/1.73m$^2$) | 54 ± 20 |
| Haemoglobin (mmol/l) | 8.4 ± 1.2 |
| Hematocrit (1/l) | 0.41 ± 0.06 |
| Body Mass Index (kg/m$^2$) | 26 ± 5 |
| Medication at admission | |
| Diuretics | 65% |
| ACE/ARB | 45% |
| Beta-blockers | 40% |
| Medication at discharge | |
| Diuretics | 88% |
| ACE/ARB | 71% |
| Beta-blockers | 61% |

ACE/ARB = ACE inhibitor or Angiotensin Receptor Blocker, BNP= B-type Natriuretic Peptide, BP = Blood Pressure, COPD= Chronic Obstructive Pulmonary Disease, eGFR= estimated Glomerular Filtration Rate, HF= Heart Failure, LVEF= Left Ventricular Ejection Fraction, NT-proBNP = N-terminal pro B-type Natriuretic Peptide, NYHA= New York Heart Association functional class.

**Figure 1:** BNP (A) and NT-proBNP (B) (95% CI) divided by quintiles of Haemoglobin.

A




B

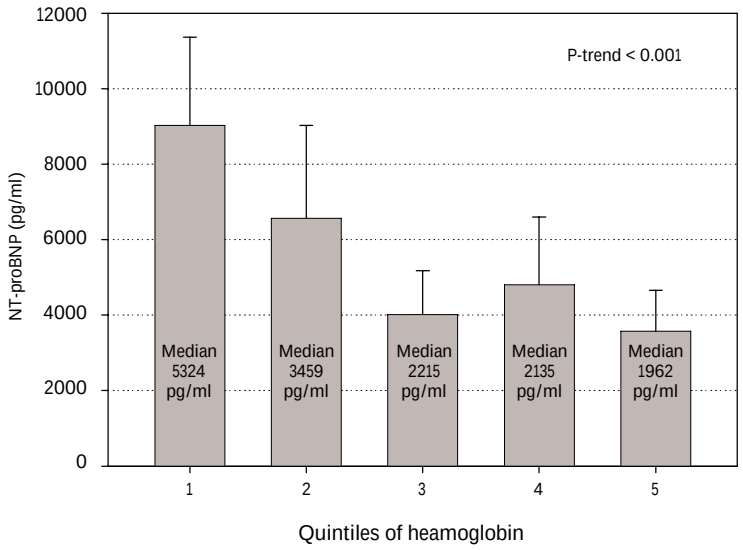


**Table 2:** Multivariable linear regression analyses for the relationships of anaemia and renal function with lnNT-proBNP and lnBNP

| | lnNT-proBNP $R^2 = 0.35$ | | lnBNP $R^2 = 0.21$ | |
|---|---|---|---|---|
| Multivariable related | St. Beta | P-value | St. Beta | P-value |
| eGFR* | -0.28 | <0.001 | -0.13 | 0.001 |
| Haemoglobin* | -0.26 | <0.001 | -0.20 | <0.001 |

* Corrected for body mass index, left ventricular ejection fraction and the Boston score.
eGFR = Estimated Glomerular Filtration Rate, LnBNP = natural logarithm of B-type natriuretic Peptide plasma levels, LnNT-proBNP = natural logarithm of N-terminal proB-type natriuretic Peptide plasma levels, St. = standardised. The interaction term between Boston score and LVEF added significant value to the multivariable model of lnNT-proBNP (Standardized Beta 0.11, P=0.02) and the interaction term between eGFR and LVEF added significant value to the multivariable model of lnBNP (Standardized Beta 0.11, P=0.03).

### Multivariable determinants of BNP levels

Hb and eGFR were independently related to the natural logarithm of BNP, and these relationships were confounded by BMI, LVEF and the Boston score (P-values ≤ 0.02). The interaction term of LVEF*eGFR added significant value to the multivariate regression model (standardised Beta = 0.11, P = 0.03). The R-square of the multivariable model was 0.21 (table 2).

### Univariable determinants of NT-proBNP levels

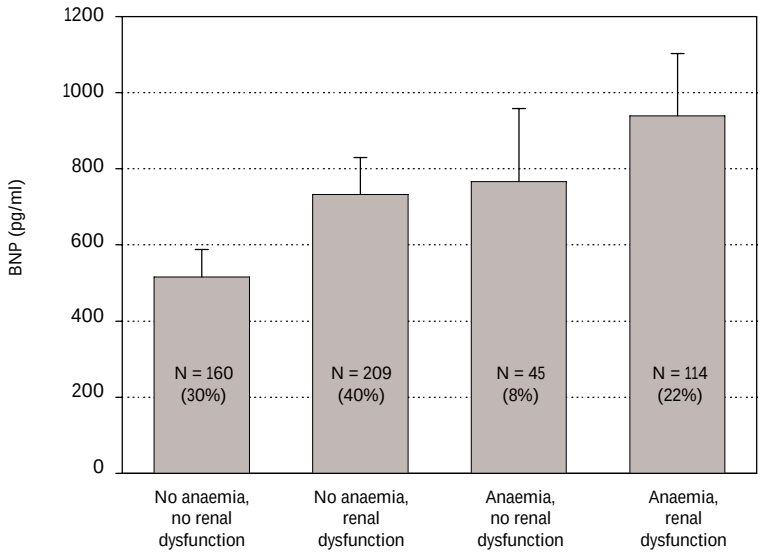
Hb (P<0.001) and eGFR (P<0.001) were univariably related to the natural logarithm of NT-proBNP. Additionally, the following variables were potential confounders to these relations (P<0.15): age (P<0.01), LVEF (P<0.001), NYHA functional class (P<0.01), Boston score (P=0.10), pulmonary congestion (P=0.01), systolic (P=0.03) and diastolic blood pressure (P=0.01), hematocrit (P<0.001), BMI (P<0.001), hypertension (P=0.14), prescribed diuretics at admission (P<0.01) and prescribed diuretics at discharge (P=0.13).

### Multivariable determinants of NT-proBNP levels

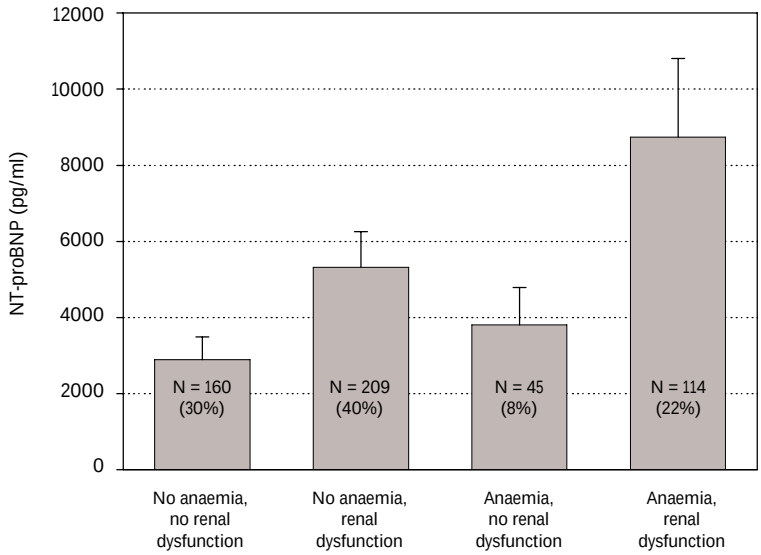
Hb and eGFR were independently related to the natural logarithm of NT-proBNP levels, and these relations were confounded by BMI, LVEF and the Boston score (P-values ≤ 0.01). The interaction term of Boston score*LVEF added significant value to the multivariate regression model (standardised Beta = 0.11, P = 0.02). The R-square of the multivariable model was 0.35 (table 2).

**Figure 2:** BNP levels (A) and NT-proBNP levels (B) (95% CI) divided by anaemia status and renal function

A




B




Anaemia was defined as Hb < 7.5 for women and Hb < 8.1 for men. Renal dysfunction was defined as eGFR < 60 ml/min/1.73m$^2$.

# Discussion

The major finding of the present study is that both BNP levels and NT-proBNP levels are associated with anaemia and renal dysfunction, independent of the severity of heart failure.

## Anaemia and BNP/ NT-proBNP levels

Anaemia is a common phenomenon in HF, and is related to the severity of disease.[25] Although BNP and NT-proBNP are also related to severity of HF, the negative association between both BNP and NT-proBNP and Hb, as found in the present study, cannot only be explained by the severity of HF. Hb was related to BNP and NT-proBNP levels independent of severity of HF as measured by both LVEF and the Boston score. The present findings are in agreement with the results of Willis et al. on 209 patients without HF or renal failure.[14] They found that Hb added significant value to the multivariable linear regression model of NT-proBNP determinants. Another study in patients with suspected coronary artery disease (n=234) also showed an independent association between Hb and BNP levels.[26] However, Wu et al. found no correlation between BNP levels and Hb in 200 patients with systolic HF, and only a small correlation was found between BNP and diastolic HF (n=121; r=0.047; $p<0.05$).[15] The differences compared to our results might be explained by the exclusion of patients with renal dysfunction in this study by Wu et al.[15] Since anaemia is often caused by renal insufficiency, a subgroup of HF patients without renal insufficiency does not fully represent HF patients in clinical practice and one might argue whether such a subgroup is the best to investigate the effect of anaemia on BNP levels.

The most obvious explanation for the independent associations of anaemia with BNP/ NT-proBNP levels is that anaemia results in elevated plasma volume independent of severity of HF.[12] Since BNP and NT-proBNP are released in reaction to ventricular plasma overload,[13] it is conceivable that BNP and NT-proBNP levels are higher in anaemic HF patients compared to non-anaemic HF patients. Additionally, patients with anaemia and renal dysfunction showed higher BNP and NT-proBNP levels, compared to anaemic patients without renal dysfunction (figure 1, 2). This finding can be explained by previous findings, where renal dysfunction was found to be a major cause of anaemia in HF patients, mediated by a erythropoietin production deficiency in the kidneys.[16]

## Renal function and BNP/ NT-proBNP levels

Elevated levels of BNP were also independently related to renal dysfunction and, although not directly compared, this relation seemed less powerful than the relation between renal dysfunction and NT-proBNP (-0.13 vs. -0.28 respectively). This difference may be explained by differences in clearance. NT-proBNP is probably mainly cleared from the blood by the kidneys,[17] while BNP is most likely mainly cleared by neutral endopeptidases and natriuretic peptide clearance receptors.[27,28] This implies that the influence of renal dysfunction should be more pronounced on NT-proBNP levels compared to BNP levels.

## Implications for clinical practice

Our data indicate that haemoglobin and renal function should be taken into account when interpreting elevated levels of BNP and NT-proBNP. Although elevated levels naturally

could be related to worsening of heart failure, they can also be caused by anaemia or renal dysfunction, while the severity of heart failure remains unchanged.

### Conclusions

In this large group of hospitalised heart failure patients, lower haemoglobin levels and worse renal function were independently associated with elevated BNP levels and elevated NT-proBNP levels. These results indicate that in HF diagnosis BNP levels but especially NT-proBNP levels might be overestimated in patients with renal dysfunction and/or anaemia.

## Ackowledgments

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# Chapter 5

# BNP, functional status and quality of life in heart failure patients

§ 5.1

# Correlates of B-type Natriuretic Peptide and 6-minute Walk in Heart Failure Patients

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# Abstract

**Background:** B-type Natriuretic Peptide (BNP) and 6-minute walk test (6MWT) are both related to severity and prognosis in chronic heart failure (CHF), but may reflect different aspects of CHF. We related BNP and 6MWT to left ventricular ejection fraction (LVEF), New York Heart Association functional class (NYHA), and 2 indices of quality of life (physical subscales): the Minnesota Living with Heart Failure Questionnaire (MLwHFQph) and the RAND-36ph.

**Methods:** Plasma BNP and 6MWT were measured at discharge in 229 patients who had been admitted for CHF. LVEF and NYHA were determined, and patients completed the MLwHFQ and RAND-36 questionnaire.

**Results:** BNP was weakly correlated to LVEF ($r=-0.29$, $P<0.01$), and NYHA ($r=0.20$, $P<0.01$), but not to MLwHFQph and RAND-36ph. On the other hand, 6MWT is related to the MLwHFQph ($r=-0.23$, $P<0.01$), the RAND-36ph ($r=0.52$, $P<0.01$) and to the NYHA ($r=-0.46$, $P<0.01$), but not to LVEF ($r=-0.15$, $P=0.05$). There is also no correlation between BNP and 6MWT ($r=-0.01$, $P=0.87$).

**Conclusions:** The present data show, that BNP and 6MWT represent different aspects of the clinical syndrome of CHF. The outcomes of this study suggest that BNP plasma levels are more related to cardiac function, while 6MWT reflects functional capacity and quality of life.


# Introduction

B-type Natriuretic Peptide (BNP) plasma levels and 6 minute walk test (6MWT) are related to severity[1-3] and prognosis[4,5] in chronic heart failure (CHF). BNP plasma levels reflect stretch and tension of the myocardial wall[6,7] and 6MWT is used to measure submaximal functional capacity of CHF patients.[3]

Older studies have suggested a very weak relationship between (peak) exercise functional capacity and parameters of cardiac function, such as left ventricular ejection fraction (LVEF) in CHF patients.[8-11] Dracup et al. also found no correlation between LVEF and 6MWT, which is generally considered a measure of submaximal exercise capacity.[10] Other investigators showed that exercise intolerance in CHF patients was more related to peripheral abnormalities than to central cardiac function.[12,13] Despite this, two recent relatively small studies, performed in an outpatient clinic setting, showed a significant and positive correlation between BNP and 6MWT in patients with CHF.[14,15]

Quality of life is one of the hallmarks of the CHF syndrome, and is increasingly being recognized as an important target for treatment.[16] The 6MWT is related to the physical dimensions of quality of life measured using the Heart Failure Functional Status Inventory questionnaire[10] and to daily activities.[17,18] BNP has become an important tool in the clinical assessment of CHF patients, but its relation with indices of quality of life is less well examined.

Accordingly, we determined BNP and 6MWT at discharge after a hospital admission for CHF, and related these parameters to cardiac function (LVEF) and symptoms (NYHA functional class), as well as to 2 indices of quality of life (physical subscales): the Minnesota Living with Heart Failure Questionnaire (MLwHFQph) and the RAND-36ph.

# Materials and methods

## Study population

All patients in the present study were part of a multicenter CHF trial conducted in the Netherlands. The design, inclusion and exclusion criteria have been described elsewhere.[9] All patients were admitted for symptomatic CHF (NYHA II- IV), and none of them had a cardiogenic shock. Patients were at least 18 years of age with evidence of structural underlying heart disease. Two hundred and twenty nine CHF patients, with complete datasets of BNP and 6MWT, were included in the analysis. The study was approved by a central Ethical Committee, and all patients provided informed written consent. The study protocol conforms with the ethical guidelines of the 1975 Declaration of Helsinki.

## BNP measurement

At the day of hospital discharge or the day before hospital discharge, between 8:00 AM and 16:00 PM, 5 ml of whole blood was taken from an antecubital vein and collected into tubes containing potassium ethylenediaminetetraacetic acid (EDTA) (1 mg/ml blood). Within 4 hours after blood collection BNP plasma levels were determined using a fluorescence immunoassay kit (Triage®, Biosite diagnostics Inc. San Diego CA). Precision, analytic sensitivity and stability characteristics of the system have previously been described.[21] The measurable range of the BNP assays was 5.0- 5000.0 pg/ml.

## Functional capacity

At the day of blood collection, patients performed a 6MWT on a predefined course in a hospital corridor. Patients were instructed to walk as many meters as they could within 6 minutes. At standardized moments the instructor told the patients the amount of time remaining and patients were allowed to stop or slow down if necessary. The 6MWT is a reliable and well validated test in CHF patients.[22]

## Physical dimension of quality of life

Physical functioning was measured by two different questionnaires. Perceived physical functioning was measured by one out of eight dimensions of the RAND-36 Health Survey: RAND-36 physical functioning (RAND-36ph). The range of the RAND-36ph was 0-100 with higher scores mean better perceived physical functioning. Physical functioning related to CHF was measured by the Minnesota Living with Heart Failure questionnaire subscale of physical functioning (MLwHFQph). The range of the MLwHFQph was 0 to 40 with higher scores mean worse quality of life. These two questionnaires are reliable and well validated.[23,24] Patients completed the questionnaires during their hospital admission.

Additional demographic and clinical data were collected by chart review.

## Statistical analysis

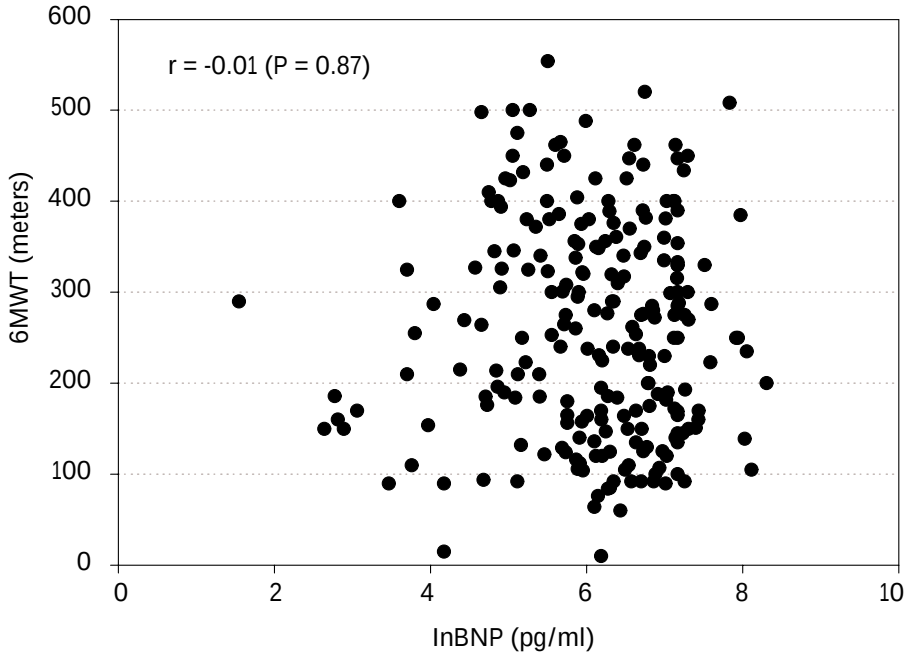
Because the plasma BNP had a skewed distribution the natural logarithm was used to get an optimal residual analysis. Pearson or Spearman correlation coefficients were calculated between lnBNP, 6MWT, New York Heart Association functional class (NYHA), LVEF, MLwHFQph and RAND36ph, when appropriate. Outcomes were considered significant when $P<0.05$. Values are presented as means $\pm$ SD except when stated otherwise.

**Table 1:** Characteristics of study population (n=229).

| | |
|---|---|
| Demographics | |
| Age (years) | 70 ± 12 |
| Gender (men) | 63% |
| Clinical parameters | |
| NYHA II, III, IV | 58, 40, 2% |
| LVEF | 35 ± 14% |
| HR (beats . min-1) | 74 ± 13 |
| Blood pressure (mmHg) | |
| Systolic | 119 ± 21 |
| Diastolic | 69 ± 11 |
| Body mass index (kg/m$^2$) | 27 ± 15 |
| Pulmonary congestion | 73% |
| Heart failure cause | |
| Ischemic | 41% |
| Non-ischemic | 59% |
| Medical history | |
| Previous myocardial infarction | 41% |
| Atrial fibrillation | 39% |
| Hypertension | 33% |
| COPD | 23% |
| Type II diabetes mellitus | 23% |
| Peripheral vascular disease | 16% |
| Renal disease | 5% |
| Duration hospitalization (days) | 12 ± 9 |
| Medical treatment at discharge | |
| Diuretics | 94% |
| ACE inhibitors and/or ARB | 84% |
| Beta blockers | 59% |
| Spironolacton | 32% |
| Study variables | |
| Median, 25$^{th}$ and 75$^{th}$ percentile of BNP (pg/ml) | 530, 245, 1050 |
| 6MWT distance (meter) | 259 ± 119 |
| MLwHFQph (range: 0-40) | 23 ± 10 |
| RAND36ph (range: 0-100) | 36 ± 27 |

NYHA= New York Heart Association functional class, LVEF= Left Ventricular Ejection Fraction, HR= Heart rate, COPD= Chronic Obstructive Pulmonary Disease, ARB= A-II receptor antagonist, BNP= B-type natriuretic peptide, 6MWT= 6 Minute Walk Test, MLwHFQph= physical subscale of Minnesota Living with Heart Failure Questionnaire, RAND36ph = RAND 36-item Health Survey physical functioning subscale.

**Figure 1:** Correlation between InBNP and BMWT distance (n=229)




# Results

## Study population

Demographic and clinical characteristics of the 229 patients are presented in table 1. On average patients were 70 ± 12 years of age and the majority (63%) of patients was male. More than half of the patients had a non-ischemic primary reason for CHF, and most of them were in NYHA functional class II or III (58%, 40% respectively), and were on medical therapy including diuretics, ACE inhibitors and Beta blockers (table 1).

## Study variables

The median and 25th, 75th percentile of BNP in the sample was 530, 245, 1050 pg/ml. On average patients walked 259 ± 119 meters in 6 minutes. The average score on the MLwHFQph was 23 ± 10 and on the RAND36ph 36 ± 27 (table 1).

## Correlations

lnBNP showed a weak correlation to LVEF (r= -0.29, P<0.01) and NYHA (r=0.20, P<.01), but not to the indices of quality of life (table 2). In contrast, 6MWT was significantly related to both MLwHFQph (r= -0.23, P<0.01) and the RAND36ph (r=0.52, P<0.01) and also to NYHA class (r= -0.46, P<0.01); there was no significant correlation to LVEF (table 2). Additionally, lnBNP was not associated to 6MWT (r= -0.01, P=0.87) (figure 1).

**Table 2**: Correlation matrix (n=229).

| | lnBNP r | P-value | 6MWT r | P-value |
|---|---|---|---|---|
| LVEF | -0.29 | <0.01 | -0.15 | 0.05 |
| NYHA | 0.20 | <0.01 | -0.46 | <0.01 |
| MLwHFQph | 0.03 | 0.67 | -0.23 | <0.01 |
| RAND36ph | -0.002 | 0.97 | 0.52 | <0.01 |

lnBNP = lnB-type Natriuretic Peptide, 6MWT = 6 Minute Walk Test, LVEF = Left Ventricular Ejection Fraction, NYHA = New York Heart Association functional class, MLHFQph = Minnesota Living with Heart Failure Questionnaire physical subscale, RAND36ph = RAND 36-item Health Survey physical functioning subscale.

# Discussion

The main finding of the present study is that BNP plasma levels are related to LVEF, but not to parameters which reflect quality of life, in particular those that are related to physical discomfort. In contrast to BNP, the 6MWT shows a significant relation to these parameters (MLwHFQph and RAND36ph), but not to LVEF. Furthermore, in agreement with other studies,[1-3] we found a correlation between BNP and symptoms of CHF (NYHA functional class) and also between 6MWT and NYHA functional class. Although correlation coefficients are relatively weak, the present results show that reduced cardiac function is not necessarily associated with decreased submaximal functional capacity in CHF.

BNP secretion rises in the case of decreased left ventricular function, due to stretch and tension of the ventricular wall.[25] Indeed, BNP may thus be a good reflection of cardiac function. However, BNP plasma levels can vary in a short period of time due to biological variation,[26] physical activity[27] and change in medication.[28,29] Accordingly, Kazanegra et al. showed that BNP plasma levels decreased significantly within 24 hours, simultaneous to peak capillary wedge pressure, after treatment was given with diuretics, vasodilators and inotropic drug agents.[30]

On the other hand, the 6MWT is a measure of physical dimensions of quality of life and submaximal functional capacity. It probably reflects more gradual changes and thus may be a more global reflection of severity of disease.[22,31] During the progression of CHF, skeletal muscle properties change; strength reduces and fatigue appears sooner. As a result patients have limited functional capacity.[11]

In 78 stable CHF patients, Tjeerdsma et al. showed a significant correlation between BNP and maximal exercise tolerance (peak VO2; $r = -0.52$, $P < 0.001$).[21] It cannot be excluded that a correlation between BNP and peak VO2 might have existed in our study population as well. However, no sufficient data on peak VO2 were available (n=12).

In contrast, in the present study population there was no correlation between BNP and 6MWT at hospital discharge after admission for CHF. This finding is in contrast to two other outpatient studies.[13,14] The patients in these two studies, however, were in different stages of their disease, and not all of them were clinically stable. Our present population consisted

of patients who had been recently hospitalized for symptomatic CHF which most probably influenced the measurements of BNP and 6MWT. At the time of discharge, however, these patients were clinically stable. It is conceivable that by that time, BNP levels had significantly dropped or even normalized, as compared to possibly high levels at admission to the hospital.[28,29] The improvement in 6MWT probably takes much longer than the normalization of BNP plasma levels, which might explain the dissociation between these parameters in the setting of discharge after admission for CHF.

### Limitations

In the current study population many patients (23%) had COPD as co-morbidity, which might have influenced the study results. However, when patients with COPD were excluded from the analysis, the correlation coefficient between lnBNP and 6MWT only changed slightly ($r = -0.11$, P-value $= 0.15$). Furthermore, in clinical practice a significant proportion of CHF patients also has COPD. Hence, our study population reflects the CHF population of the clinical practice.

### Conclusion

These results suggest that BNP is more related to cardiac function, while 6MWT reflects functional capacity and quality of life. Therefore, BNP plasma levels and functional capacity as measured by the 6MWT reflect different aspects of CHF although both are important parameters, and have been shown to be related to clinical outcome.

## Ackowledgments

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§ 5.2

# BNP and functional status in heart failure

Jochem Hogenhuis, Tiny Jaarsma, Adriaan A. Voors, Dirk J. van Veldhuisen.

*Cardiovasc Drugs Ther* 2004;18:507 (*letter*).

# Editor,

In the current era of growing incidence and prevalence of chronic heart failure (CHF), the functional status assessment of CHF patients is increasingly needed, as it is one of the tools to investigate severity of CHF. B-type natriuretic peptide (BNP) is gradually more used in the diagnosis, prognosis and management of CHF patients. Since BNP is an easy, cheap and readily available test, an investigation that evaluates the value of BNP in functional status assessment is important.

In their recent paper in *Cardiovascular Drugs and Therapy* Abdulla et al. evaluate the potential of BNP as a surrogate marker for traditional methods of assessing functional status of patients with left ventricular systolic dysfunction.[1] The authors describe a meta-analysis of four articles that all reported the correlation between BNP and functional status as assessed by either peak VO2 or 6-minute walk test. Because the meta analysis showed only a moderate correlation (r=-0,59), the authors carefully concluded that the traditional methods should still be considered as standard methods in assessing functional capacity. We agree with this conclusion, but we would like to add some strength to it and support the notion that BNP is not a good marker for measuring functional capacity. Also we would like to make few comments.

First, we noticed that two relevant papers were not included in the meta analysis. These studies by Brunner-La Rocca et al.[2] and Kinugawa et al.[3] also described the correlation between BNP and peak VO2 in a tertiary care centre and an outpatient clinic setting respectively. Both studies reported a very low correlation coefficient between BNP and peak VO2 ($r \leq -0.33$), and adding these studies would have further weakened the moderate correlation as found in the meta analysis by Abdulla et al.

Second, the authors do not mention the clinical setting of the studies they reviewed. The studies were all performed in an outpatient clinic setting, making the results difficult to generalize to the total CHF population.

We recently studied a group of 120 CHF patients at time of discharge after admission for CHF (age 70 ± 12 years, 58% males, left ventricular ejection fraction 34 ± 14%, 41% ischemic aetiology of CHF). BNP was assessed and 6-minute walk test was performed on the day before discharge from the hospital. No correlation between BNP and functional status (6 minute walk test) was found ($r=0.005$, $P=0.95$).[4] Therefore we argue that the clinical setting should be taken into account when conclusions are drawn about the correlation between BNP and functional status.

As stated by the authors, BNP is a very valuable marker in the management of CHF, but its plasma levels can change due to several variables like age, gender, renal function, use of medication, body weight. We want to stress the importance of the clinical setting, especially when evaluating the relationship between BNP and functional status.

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# BNP and functional status in heart failure (response)

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We would thank Hogenhuis et al. for their worthy commentary letter on our article.[1] We agree with the authors that the two studies they mentioned[2,3] should also be included in the meta-analysis. Therefore we have reanalysed the data including these two studies, the result showed a weaker correlation (Table 1). When we also combined the result of the recently published study by the authors (Hogenhuis et al.) on 120 patients before hospital discharge[4] the correlation was even weaker $R = -0.41$. Our aim was to demonstrate in general that brain natriuretic peptide (BNP) levels are poorly correlated to the functional status and BNP measurement seems not to be a reliable surrogate in this setting; however, we agree with the authors that the clinical setting of patients with heart failure is also important.

**Table 1.** The studies that evaluated the correlation between resting brain natriuretic peptide (BNP) levels and functional status in patients with left ventricular systolic dysfunction (LVSD) in outpatient clinic.

| No. | Author of the study and publication year | Population and aetiology of LVSD | Methods used to assess functional status and its correlation to plasma BNP level expressed as R and p-values |
|---|---|---|---|
| 1 | Brunner-La Rocca 1999 [2] | N=48 IHD 58%, Non-IHD 42% | Symptoms R= –0.48, p = 0.001 Treadmill test measuring PVO2 R= –0.31, p < 0.05 |
| 2 | Krüger 2002 [5] | N = 70 IHD 40%, Non-IHD 60% | Bicycle ergometer measuring PVO2 R= –0.56, p < 0.001 |
| 3 | Tjeerdsma 2002 [6] | N = 78 Aetiology unavailable | NYHA R= 0.83, p < 0.0001 Treadmill test measuring PVO2 R= –0.52, p < 0.001 |
| 4 | Jourdain 2002 [7] | N = 151 IHD 63%, Non-IHD 37% | NYHA p < 0.0016-MWT (distance) R= –0.69, p < 0.001 |
| 5 | Kinugawa 2003 [3] | N = 84 IHD=17%, Non-IHD 83% | Bicycle ergometer measuring PVO2 R= –0.33, p=NS |
| 6 | Wieczorek 2003 [8] | N = 44 IHD = 57%, Non-IHD 43% | 6-MWT (distance) R= –0.47, p = 0.001 |
| Combined meta-analytic result | | N = 475 IHD = 47%, Non-IHD = 53% | Correlation of all exercise variables to BNP (PVO2 and 6-MWT) R= –0.52 |

N = number, NYHA = New York Heart Association, IHD = Ischaemic heart disease, PVO2 = Peak oxygen uptake, 6-MWT = 6 minutes walk test, NS = not significant, R = correlation coefficient.

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# Chapter 6

# Establishing the discharge diagnosis of patients admitted for suspected heart failure: development of a simple score including BNP or NT-proBNP

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Hans L. Hillege, Dirk J. van Veldhuisen

# Abstract

**Background:** Previous studies showed that 18% -33% of patients admitted for suspected heart failure (HF) receive a false-positive discharge diagnosis of heart failure. We aimed to identify the most important independent predictors of a (false) HF discharge diagnosis to construct a score to improve the discharge diagnosis of HF.

**Methods:** Using univariable and multivariable logistic regression and Receiver Operating Characteristics (ROC) analysis, the value of potentially important diagnostic determinants including B-type Natriuretic Peptide (BNP) and N-terminal proBNP (NT-proBNP) was assessed and combined in a scoring rule.

**Results:** In the present study population (n = 540, 71 ± 11 years of age, 62% male), an outcome panel identified 6% with a discharge diagnosis other than HF. Univariable predictors of the discharge diagnosis HF were dyspnoea at rest, absence of COPD/ asthma, absence of anaemia, renal dysfunction, BNP > 100 pg/ml and NT-proBNP > 300 pg/ml. In multivariable logistic analyses, all of these, except BNP > 100 pg/ml, remained independent predictors of a HF discharge diagnosis. The ROC area of a model combining these predictors was 0.78.

**Conclusion:** In our population, a discharge diagnosis other than HF occurred in only 6% of the patients. Four readily available patient characteristics together with NT-proBNP are independent predictors of a discharge diagnosis of patients admitted for suspected HF, and these were combined in a scoring rule to optimize the discharge diagnosis of these patients. This score should be validated in other populations before its use in clinical practice can be recommended.


# Introduction

Discharge diagnoses have been instrumental in providing estimates of and time trends in the incidence of heart failure (HF). However, studies in the Netherlands, the United States and in Sweden showed that respectively 20%, 33% and 18% of the patients hospitalized for HF receive a false-positive discharge diagnosis of HF,[1-3] which may suggest that up to one third of the patients in these studies may be discharged without optimal medical treatment, which may lead to inappropriate care and unnecessary high expenses.

Although B-type Natriuretic Peptide (BNP)[4] and N-terminal pro BNP (NT-proBNP)[5] are known to be useful in the emergency diagnosis of HF, little evidence is available on their diagnostic value in establishing the discharge diagnosis in patients admitted for suspected HF. When BNP or NT-proBNP is an independent predictor of a HF discharge diagnosis in these patients, it could be combined with routinely available patient characteristics to develop a scoring rule to be applied in clinical practice. Therefore, we aimed to: 1) investigate whether NT-proBNP, BNP and routinely available patient characteristics, including comorbidity, are independent predictors of the discharge diagnosis of HF in patient admitted with suspected HF and 2) develop a score combining the most important predictors of a HF discharge diagnosis.

# Methods

## Study population

All 540 patients in this study were recently admitted for suspected HF (NYHA II-IV), and were included in a multicenter HF trial conducted in the Netherlands (COACH).[6] Data for the present study were collected before randomization. All participating sites (n = 17) were centres with vast experience in HF care. Patients were at least 18 years of age and admitted with a clear suspicion of heart failure. The design, inclusion and exclusion criteria of the trial have been described in detail elsewhere.[6] In short, COACH is a randomized controlled trial investigating the effect of education and counselling on readmission for HF and mortality.

## Availability and measurement of BNP and NT-proBNP levels

Of the 1049 patients included in the COACH, 541 patients had both BNP and NT-proBNP plasma levels available. Temporary, usually in the starting phase of the study, unavailability of the necessary laboratory facilities was the main reason for missing BNP and NT-proBNP data. Blood was collected shortly before discharge between 8:00 AM and 4:00 PM, after patients had been clinically stabilised and recovered enough to go home. 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 -70°C to -80°C.

*BNP measurement:* In 364 out of the 541 patients, BNP levels were determined on site in whole blood within 4 hours after blood collection. In 177 out of the 541 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.[7] The measurable range of the BNP assays was 5.0- 5000.0 pg/ml.

*NT-proBNP measurement:* All measurements of NT-proBNP levels were performed in plasma at the Core laboratory on an Elecsys™ 2010 analyser, a commercially available electrochemiluminescent sandwich immunoassay (Elecsys proBNP, Roche Diagnostics, Mannheim, Germany). The intra-assay precision (coefficient of variation) is 1.2 – 1.5%, and the inter-assay precision (coefficient of variation) is 4.4 – 5.0%, with an analytical range of 5 – 35000 pg/ml.[8,9]

## Renal function

Serum creatinine was determined from the blood drawn shortly before discharge, in the local laboratory at each centre. Estimated Glomerular Filtration Rates (eGFR's) were calculated using the Levey – modified Modification of Diet in Renal Disease formula:[10]

$eGFR\ (ml/min/1.73m^2) = 186 \times SCr^{-1.154} \times age^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$

Renal dysfunction was defined as an eGFR < 60 ml/min/1.73m$^2$.

### Anaemia

The definition of anaemia according to the World Health Organisation was used; haemoglobin levels < 7.5 mmol/l (12 g/dl) for women and < 8.1 for men (13 g/dl).[11]

### Determination of discharge diagnosis i.e. reference (or 'gold') standard

Two cardiologists that were blinded to BNP and NT-proBNP plasma levels reviewed the discharge reports of the 540 patients that were admitted for suspected HF. These reports included information on physical examination, medical history and the results of ECG, radiological examinations, laboratory blood tests, echocardiography and effects of treatment. To determine the actual discharge diagnoses of these patients, the cardiologists independently classified the discharge diagnosis as 'HF' or 'other discharge diagnosis'. In case of disagreement about the discharge diagnosis between the two cardiologists, they discussed the discharge diagnosis until agreement was reached. The cardiologists could not draw any conclusion about the discharge diagnosis of one patient because the discharge report did not contain sufficient information. This patient was excluded from the analysis.

### Statistical analyses

To prevent chance findings we a priori decided to study a limited number of potential diagnostic determinants. Selection of the 11 variables was based on the literature and availability in every day practice. Univariable logistic analyses were performed to identify which variables were associated with the discharge diagnosis HF. Because BNP and NT-proBNP levels had a skewed distribution, the levels were dichotomized (BNP below or above or equal to 100 pg/ml[4] and NT-proBNP below or above or equal to 300 pg/ml[5] was used. A p-value <0.15 was required to enter a variable into the multivariable logistic analyses. Either BNP or NT-proBNP was included in the multivariable regression analysis (and not both of these) because of the danger of multicollinearity and, first and foremost, because in clinical practice usually only one of the two is available. A Lemeshow and Hosmer goodness of fit statistic was calculated to evaluate the fit of the multivariable logistic regression model. The diagnostic performance of the combination of independent predictors (p-value < 0.05 in the multivariable analysis) was quantified by calculating the area under the receiver operating characteristic (ROC) curve. An ROC area of 0.5 signifies no discriminatory value (like a flip of a coin), while an area of 1.0 means perfect discrimination between those with and without a HF discharge diagnosis.

Since any model is too optimistic when the model is used on the dataset from which it was developed (over fitting), we used bootstrapping techniques in order to internally validate the final multivariate model and to adjust the estimated ROC area under the curve and regression coefficients. The performance of a model after bootstrapping is more in concordance with the performance that can be expected in future patients.[12,13]

Eighteen patients had 27 missing values. Since missing values usually do not occur at random, deletion of subjects with a missing value may lead to biased results and loss of power. Hence, we imputed any missing values by using a regression method with the addition of a random error term (SPSS version 11.0). The imputation was based on the correlations between each variable with missing values and all other variables from the 522 (97%) complete datasets.

In order to create an easy applicable diagnostic rule or score, we transformed the original

**Table 1:** Association between patients characteristics and the discharge diagnosis in patients admitted with suspected heart failure. Results from the univariable analysis.

| | Heart Failure as discharge diagnosis (n=506) | Other discharge diagnosis (n=34) | Odds ratio (95% CI) | P-value |
|---|---|---|---|---|
| Age (y) | 71 ± 11 | 69 ± 11 | 1.01 (0.98 – 1.04) | 0.45 |
| Gender (m) | 62% | 62% | 0.98 (0.48 – 2.00) | 0.95 |
| NYHA (II-III / IV) | 60% / 40% | 83% / 17% | 3.15 (1.28 – 7.75) | 0.01 |
| Cardiovascular history* | 73% | 68% | 1.15 (0.56 – 2.35) | 0.70 |
| Previous HF hospitalizations > 1 | 35% | 32% | 1.11 (0.53 – 2.34) | 0.77 |
| AF/flutter | 39% | 29% | 1.52 (0.71 – 3.24) | 0.28 |
| Hb (mmol/l) | 8.5 ± 1.2 | 8.0 ± 1.5 | 1.32 (1.00 – 1.76) | 0.05 |
| eGFR (ml/min/1.73m$^2$) | 53 ± 20 | 60 ± 22 | 0.98 (0.97 – 1.00) | 0.05 |
| COPD/ asthma | 29% | 50% | 0.41 (0.20 – 0.82) | 0.01 |
| BNP > 100 pg/ml | 91% | 79% | 2.7 (1.12 – 6.58) | 0.03 |
| NT-proBNP > 300 pg/ml | 97% | 82% | 6.56 (2.38 – 18.06) | <0.01 |

AF= atrial fibrillation, BNP= B-type natriuretic peptide, COPD= chronic obstructive pulmonary disease, eGFR= estimated Glomerular Filtration Rate, Hb= haemoglobin, HF= heart failure, NYHA= New York Heart Association functional class at admission. * = previous MI, CVA, TIA, CABG or PTCA, DM 1 or 2 and BMI > 30.

regression coefficients (after adjustment for over fitting) of the variables in the final model to points according to their relative contribution to the estimation of the discharge diagnosis. We calculated the score for each patient and estimated the absolute percentages of correctly diagnosed patients across score categories. To allow the construction of a diagnostic points score haemoglobin and eGFR were dichotomised into presence of anaemia (according to WHO definition) and renal dysfunction (< 60 ml/min/1.73m$^2$) respectively.

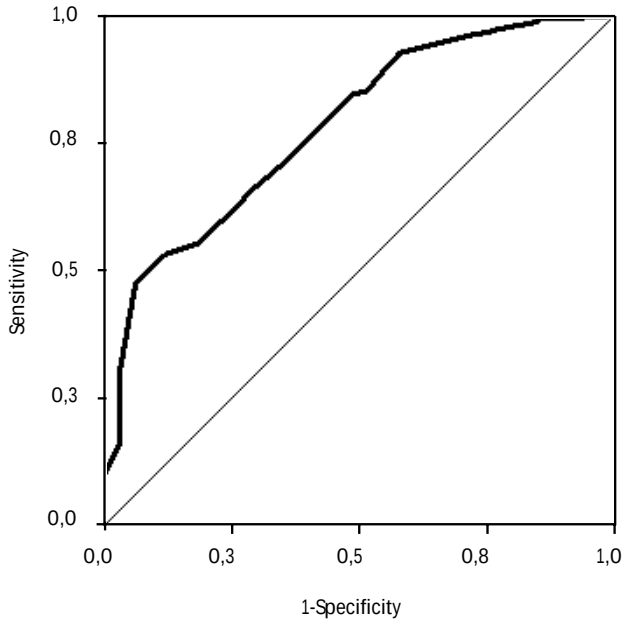
The analyses were performed with S-Plus version 6.1 except for the imputation procedure, as stated above.

# Results

Demographic and clinical characteristics of the 540 patients are presented in table 1. Mean age of the 540 patients was 71 (± 11) years, and more than half of the population was male (62%). The characteristics were not significantly different between patients with available BNP/NT-proBNP levels (n=540) and the total patient group included in COACH (n=1049).

The consensus panel classified 506 patients (94%) with a discharge diagnosis of heart failure, and in 34 patients (6%) another discharge diagnosis was established. These included: acute myocardial infarction, unstable angina pectoris, atrial fibrillation, chronic obstructive pulmonary disease (COPD)/asthma and pulmonary embolism.

**Figure 1:** Receiver Operating Characteristics curve for discharge diagnosis HF.
Area under curve: 0.78 (0.70 – 0.86)




The median BNP value of the patients with HF as discharge diagnosis was 459 pg/ml (interquartile range 212 – 938 pg/ml), and the median BNP value of the patients with another discharge diagnosis was 297 pg/ml (interquartile range 135 – 632 pg/ml). The proportion of patients with BNP > 100 pg/ml differed between the two groups (91% vs. 79%; P=0.03). The median NT-proBNP value of the patients with a HF discharge diagnosis was 2718 pg/ml (interquartile range 1379 – 6168 pg/ml), while the value in patients with another discharge diagnosis was 1501 pg/ml (interquartile range 739 – 4920 pg/ml). The proportion of patients with NT-proBNP > 300 pg/ml was 97% and 82%, respectively ($p<0.01$) (table 1).

The following variables were associated with the discharge diagnosis 'HF' ($p<0.15$) in the univariable analysis: BNP > 100 pg/ml, NT-proBNP > 300 pg/ml, dyspnoea at rest (NYHA class IV) at hospital admission, absence of COPD / asthma, higher haemoglobin and lower eGFR (table 1). After bootstrapping, exactly the same variables showed p-values < 0.15, although the individual odds ratios slightly changed.

All of these, except BNP, were independent predictors of the discharge diagnosis HF the multivariable analyses, and the Lemeshow and Hosmer goodness of fit statistic of the model was 5.0 ($p=0.76$). The ROC area of the combination of these 5 items was 0.78 (95% confidence interval 0.70-0.86; figure 1). Internal validation of the multivariable model by means of bootstrapping techniques yielded an ROC area of 0.67. Regression coefficients were rounded tot whole points according to their relative contribution to the discharge diagnosis (table 2). The score ranged from 0 to 14 point. For each score category, sensitivity, specificity and predictive values were calculated (table 3).

**Table 2:** Independent predictors (and their points assigned in the score) of a discharge diagnosis of heart failure in patients admitted with suspected heart failure. Results from multivariable logistic regression analyses.

| Variables | OR (95% CI) | P-value | Points for rule |
|---|---|---|---|
| Absence of anaemia | 2.10 (0.97 – 4.54) | 0.02 | 2 |
| NYHA class IV | 2.51 (0.98 – 6.43) | 0.01 | 3 |
| Absence of COPD/ Asthma | 2.01 (0.96 – 4.19) | 0.01 | 2 |
| Renal dysfunction (eGFR<60ml/min/1.73m$^2$) | 2.07 (0.97 – 4.40) | <0.01 | 2 |
| NT-proBNP>300pg/ml | 4.95 (1.62 –15.15) | <0.001 | 5 |

**Table 3:** Sensitivity, specificity and predictive values of different categories of the score.

| Risk category of simplified model (points) | Heart failure as discharge diagnosis (n=506) | Other discharge diagnosis (n=34) | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|
| Very low (0) n=0 | - | - | - | - | - | - |
| Low (2-5) n=24 | 16 (67%) | 8 (33%) | 96% | 6% | 94% | 9% |
| Medium (6-9) n=222 | 203 (91%) | 19 (9%) | 93% | 26% | 95% | 21% |
| High (10-14) n=276 | 270 (98%) | 6 (2%) | 53% | 18% | 91% | 2% |

# Discussion

Dyspnoea at rest (NYA class IV), absence of COPD/Asthma, renal dysfunction, absence of anaemia and NT-proBNP > 300 pg/ml are independent predictors of a discharge diagnosis of HF in patients admitted to hospital with suspected HF.

In contrast to previous studies, where 18%, 20% and 33% of HF discharge diagnoses were false-positive,[1,3] we found that only 6% of the patients that were admitted with suspected HF did not have HF as the discharge diagnosis after close examination of all available information. This is at least partly attributable to the patient selection typically involved in randomized trials and more the rigorous evaluation (more intensive monitoring) of patients in such studies. In addition, it also reflects the experience of the participating clinics and cardiologists. Because of the low number of non HF discharge diagnoses we limited the number of diagnostic determinants to be evaluated.

Our study identified other determinants of a diagnosis of HF than studies in other settings. Previous studies in an emergency department setting showed that age, history of HF, previous myocardial infarction, hypertension, rales, pulmonal congestion and orthopnea were independent predictors of the diagnosis of HF,[14-16] while in our study NYHA class and several co-morbidities (COPD/asthma, anaemia, renal dysfunction) were the most powerful predictors (table 2). This difference could be explained by the difference in clinical setting. All patients in the present study were admitted with suspected HF and therefore almost all patients had evidence of cardiac disease. In contrast, about half of the patients in the other studies did not have HF at all. A remarkable finding of the present study is that the haemoglobin plasma levels were lower in the patients with other discharge diagnoses. The fact that anaemia causes symptoms similar to HF, notably dyspnoea and fatigue[14] may have led to a, suspected, diagnosis of HF at admission. A similar phenomenon is known from patients with COPD and also shown in our data.[13]

The well established emergency department BNP rule out value of 100 pg/ml and the NT-proBNP rule out value of 300 pg/ml were univariable predictors of the discharge diagnosis HF, but in multivariable analysis only NT-proBNP > 300 pg/ml remained a statistically significant determinant. Our results for NT-proBNP confirm the findings from a recent study by Baggish et al. who developed a score for the diagnosis of HF in an acute HF setting that included elevated NT-proBNP.[15]

The reference ('gold') standard that was used in the present study to classify the discharge diagnosis is not perfect due to subjectivity. However, an outcome panel is a common way to classify the definite diagnosis and it has been used in many other diagnostic studies, including many in the field of heart failure.[4,5,16] Furthermore, according to the Standards for Reporting of Diagnostic Accuracy (STARD) initiative, a consensus panel is the best proxy reference in the absence of an ideal standard.[17] Although by bootstrapping the final model we adjusted the model for over-fitting, this final model and the points score needs to be validated externally in a new sample of patients that is about to be discharged from the hospital after admission for suspected HF.

We observed high positive predictive values and low negative predictive values for our score categories, which indicates that this score is more a test to confirm the discharge diagnosis HF than to reject it. In case of local availability of BNP instead of NT-proBNP, the score can be adjusted, although, as mentioned above, the performance of the model including BNP (ROC area 0.76) is worse than for the model including NT-proBNP (ROC area 0.78) The corresponding score for BNP is: absence of anaemia 2 points, NYHA class IV 4 points, absence of COPD/ asthma 2 points, renal dysfunction 3 points and BNP > 100 pg/ml 3 points.

We conclude that a limited number of readily obtainable data from physical examination or medical history (dyspnoea at rest and absence of COPD/asthma) together with renal dysfunction, and absence of anaemia and the NT-proBNP value > 300 pg/ml may improve the assessment of the discharge diagnosis of patients admitted with suspected HF, and thus optimize therapeutic interventions in these patients after discharge. Although we internally validated the score by means of bootstrapping, it needs to be validated externally in a new sample of patients that is about to be discharged from the hospital after admission for suspected HF, before it can be recommended for clinical practice.

## Ackowledgments

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# Chapter 7

# Low prevalence of BNP levels below 100 pg/ml in heart failure patients at hospital discharge

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# Abstract

**Background:** In acute heart failure (HF) patients presenting at the emergency department, a BNP < 100 pg/ml was found in only 10% of the patients. However, in a more stable outpatient HF population from another study, a BNP < 100 pg/ml was found in as many as 21% of the patients. Therefore, we aimed to investigate the prevalence and characteristics of stabilized patients with B-type Natriuretic Peptide (BNP) < 100 pg/ml before discharge after admission for decompensated HF.

**Methods:** We investigated 601 HF patients who were part of a large-scale multicenter study in the Netherlands. All patients had been admitted for decompensated HF, and BNP levels were measured before discharge, when they had been clinically stabilized. Clinical characteristics of patients with BNP levels < and ≥ 100 pg/ml were compared.

**Results:** Patients were 70 ±12 years old, 61% was male and mean left ventricular ejection fraction (LVEF) was 0.34 ±0.14. Of these patients 10% had BNP levels < 100 pg/ml. Patients with a BNP < 100 pg/ml were similar in terms of age and gender, but had higher LVEF (0.41 ±0.14 versus 0.33 ±0.13, P<0.001), body mass index, hemoglobin and hematocrit concentrations compared to those with BNP levels ≥ 100 pg/ml.

**Conclusions:** In clinically stable patients with a recent admission for decompensated HF, only 10% had BNP levels below 100 pg/ml. These patients with low BNP levels seemed to have less severe HF and more frequently had preserved systolic function compared to patients with BNP levels ≥ 100 pg/ml.


# Introduction

B-type Natriuretic Peptide (BNP) is increasingly used in the diagnosis and prognosis of heart failure (HF).[1-3] In addition, BNP can be used as a discharge criterion and to monitor treatment.[4, 5] A BNP value of 100 pg/ml is considered the optimal value in the diagnosis or exclusion of HF in acute dyspneic patients at the emergency department.[2] In these patients a BNP cut-off value of 100 pg/ml had a sensitivity of 90%, which means that only 10% of HF patients had BNP plasma levels < 100 pg/ml. When the same cut-off value was used in a stable outpatient systolic HF population, classified as NYHA functional class II-III, as many as 21% of patients had BNP levels below 100 pg/ml,[6] which might suggest that the prevalence of patients with BNP levels below this cut-off value is much higher than 10% in stable HF patients at discharge. However, the prevalence of BNP levels < 100pg/ml in clinically stable hospitalized patients remains unknown. Hence, we investigated the prevalence and characteristics of patients with BNP levels < 100 pg/ml classified in NYHA class II-IV, before discharge after admission for HF.

# Methods

## Study population

All patients were included in a multicenter HF trial conducted in the Netherlands (Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure [COACH]).[7]

All these sites (n = 17) were experienced HF centers. Patients were included in COACH if they were admitted for decompensated HF (NYHA II-IV), with HF as the primary diagnosis. Furthermore, patients were required to have evidence of structural underlying heart disease, and had to be at least 18 years of age. Reasons for exclusion were: concurrent inclusion in a study requiring additional visits to research health care personnel; restrictions that make the patient unable to fill in the data collection forms; invasive intervention within the last 6 months (PTCA, CABG, HTX, valve replacement) or planned during the following 3 months; ongoing evaluation for heart transplantation. The design of the study has been described in detail elsewhere.[7] In short, COACH is a randomized controlled trial investigating the effect of education and counseling on readmission for HF and mortality. Of the 1050 patients included in the COACH, 601 patients had BNP plasma levels available at baseline. Main reasons for missing BNP data were: no Triage® BNP meter available (in 5 out of 17 clinics; n = 324), unplanned hospital discharge (n = 75) or death during admission (n = 20). No BNP levels were available at admission, and the investigators and patients of the present study were blinded to BNP results at discharge.

The study was approved by a central Ethical Committee, and all patients provided informed written consent.

### BNP measurement

Blood was collected before discharge between 8:00 AM and 4:00 PM, after patients had been clinically stabilized and were recovered well enough to go home. All patients went home at the planned day of discharge. Five milliliter 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. Within 4 hours after blood collection BNP plasma levels were determined 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 validated in early studies.[8,9] The measurable range of the BNP assays was 5.0- 5000.0 pg/ml.

### Renal function

Serum creatinine was determined from the blood draw before discharge, in the local laboratory at each center. Estimated Glomerular Filtration Rates (eGFR's) were calculated using the Levey – modified Modification of Diet in Renal Disease formula:[10]

$GFR\ (ml/min/1.73m^2) = 186 \times SCr^{-1.154} \times age^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$

Additional demographic and clinical data were collected by chart review.

### Statistical analysis

Differences in clinical characteristics between patients with BNP plasma levels < and ≥ 100 pg/ml were tested using the Mann-Whitney U test or independent samples t-tests. Outcomes were considered statistically significant when $P<0.05$. Values are presented as means ± SD except when stated otherwise.

**Table 1:** Patient characteristics divided by BNP levels.

| | Total (n=601) | BNP<100 pg/ml (n=60) | BNP≥100 pg/ml (n=541) | P-value |
|---|---|---|---|---|
| Age (yrs) | 70 ± 12 | 69 ± 11 | 70 ± 12 | 0.29 |
| Gender (m) | 61% | 58% | 61% | 0.65 |
| Heart failure cause | | | | |
| Ischemic | 38% | 30% | 39% | 0.18 |
| Non-ischemic | 62% | 70% | 61% | 0.18 |
| LVEF | 0.34 ± 0.14 | 0.41 ± 0.14 | 0.33 ± 0.13 | <0.001 |
| Co-morbidities | | | | |
| Hypertension | 34% | 47% | 33% | 0.03 |
| COPD/Asthma | 28% | 30% | 28% | 0.71 |
| Diabetes (type1 or 2) | 28% | 27% | 28% | 0.84 |
| Renal diseases | 7% | 7% | 7% | 1.00 |
| BMI (kg/m2) | 26 ± 5 | 30 ± 6 | 26 ± 5 | <0.001 |
| X-thorax during admission | | | | |
| Pulmonal congestion | 69% | 57% | 70% | 0.04 |
| CT-ratio (n=158) | 0.56 ± 0.08 | 0.53 ± 0.15 | 0.57 ± 0.06 | 0.05 |
| Rales during admission | 87% | 89% | 87% | 0.76 |
| Duration of HF symptoms (yrs) | 2.7 ± 4.2 | 2.7 ± 4.0 | 2.7 ± 4.2 | 0.93 |
| Duration HF admission (days) | 13 ± 11 | 13 ± 8 | 13 ± 11 | 0.55 |
| Medication at admission | | | | |
| Diuretics | 57% | 63% | 56% | 0.29 |
| ACE/ARB | 52% | 60% | 51% | 0.19 |
| Beta-blockers | 39% | 38% | 39% | 0.96 |
| Spironolacton | 16% | 22% | 15% | 0.18 |
| Medication at discharge | | | | |
| Diuretics | 95% | 92% | 95% | 0.21 |
| ACE/ARB | 84% | 83% | 84% | 0.94 |
| Beta-blockers | 61% | 48% | 63% | 0.03 |
| Spironolacton | 50% | 50% | 50% | 0.97 |
| ECG measurements at discharge | | | | |
| Sinus rhythm | 56% | 67% | 55% | 0.08 |
| AF/flutter | 34% | 30% | 35% | 0.48 |
| HR (bpm) | 74 ± 13 | 76 ± 13 | 74 ± 13 | 0.42 |
| Laboratory values at discharge | | | | |
| BNP (median [interquartile range], pg/ml) | 492 (223-952) | 55 (37-79) | 530 (294-1060) | <0.001 |
| Hb (mmol/l) | 8.2 ± 1.2 | 9.0 ± 1.1 | 8.2 ± 1.1 | <0.001 |
| Ht (1/l) | 0.40 ± 0.05 | 0.43 ± 0.05 | 0.40 ± 0.05 | <0.01 |
| eGFR(ml/min1.73m$^2$) | 56 ± 21 | 57 ± 18 | 55 ± 22 | 0.56 |
| Blood pressure at discharge (mm/Hg) | | | | |
| Systolic | 119 ± 22 | 124 ± 22 | 118 ± 21 | 0.05 |
| Diastolic | 69 ± 12 | 73 ± 13 | 68 ± 12 | 0.03 |
| Pulse pressure | 50 ± 17 | 51 ± 17 | 50 ± 17 | 0.48 |
| NYHA at admission (II, III, IV) | 6%, 53%, 41% | 2%, 68%, 30% | 7%, 51%, 42% | 0.23 |
| NYHA at discharge (II, III, IV) | 52%, 45%, 3% | 48%, 50%, 2% | 53%, 44%, 3% | 0.62 |

**Legend table 1:** ACE/ARB= ACE inhibitor or Angiotensin Receptor Blocker, AF= Atrial Fibrillation, BMI= Body Mass Index, BNP= B-type Natriuretic Peptide, COPD= Chronic Obstructive Pulmonary Disease, CT-ratio= Cardio- Thoracic ratio, eGFR= estimated Glomerular Filtration Rate, Hb= Hemoglobin, HF= Heart Failure, HR= Heart Rate, Ht= Hematocryte, LVEF= Left Ventricular Ejection Fraction, NYHA= New York Heart Association functional class.

# Results

## Study population

Demographic and clinical characteristics of the 601 discharged patients are presented in table 1. Mean age of the patients was 70 (± 12) years, and more than half of the population was male (61%) and had a non-ischemic etiology for HF (62%). At admission patients were classified as NYHA functional class II (6%), III (53%) or IV (41%), and were on medical therapy including diuretics (57%), ACE inhibitors/ angiotensin receptor blockers (52%), beta-blockers (39%) and spironolactone (16%). At discharge, patients were classified as NYHA functional class II (52%), III (45%) or IV (3%), and were on medical therapy including diuretics (95%), ACE inhibitors/ angiotensin receptor blockers (84%), beta-blockers (61%) and spironolactone (50%).

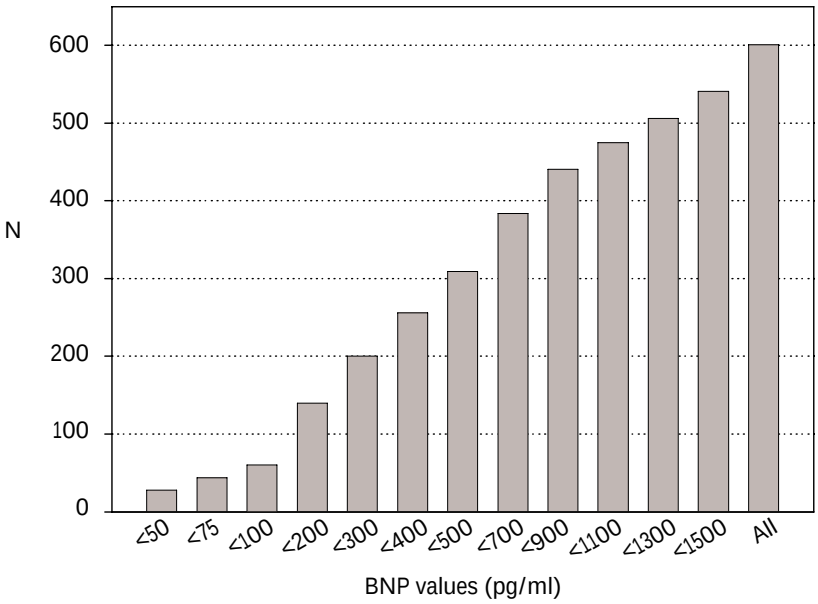
## Prevalence of low BNP levels at discharge after HF hospitalization

Of the 601 HF patients, 60 patients (10%) had BNP plasma levels below 100 pg/ml. Out of these 60 patients, 44 patients (7% of the total population) and 28 patients (5% of the total population) had BNP levels below 75 pg/ml and 50 pg/ml respectively (figure 1).

## Comparison of patients with BNP < and ≥ 100 pg/ml

The median and interquartile range of BNP values in the group of patients with BNP < and ≥ 100 pg/ml were 55 (37-79) and 530 (294-1060) respectively (table 1). Patients with BNP levels below 100 pg/ml showed less pulmonary congestion during hospital admission compared to patients with high BNP levels (57% vs. 70% respectively; P=0.04). At discharge these patients had a significantly higher LVEF (0.41 ± 0.14 vs. 0.33 ± 0.13; P<0.001) and diastolic blood pressure (73 ± 13 mmHg vs. 68 ± 12 mmHg; P=0.02), and a significantly higher prevalence of hypertension (47% vs. 33%; P=0.02) than patients with BNP levels ≥ 100 pg/ml. Furthermore, at discharge body mass index (30 ± 6 vs. 26 ± 5; P<0.001), hemoglobin (9.0 ± 1.1 vs. 8.2 ± 1.1; P<0.001) and hematocrit (0.43 ± 0.05 vs. 0.40 ± 0.05; P<0.01) were significantly higher in patients with low BNP levels compared to patients with high BNP levels. Moreover, patients with low BNP levels less often had received beta-blockers at discharge (48% vs. 63%; P=0.03) compared to patients with high BNP levels. Other variables were not significantly different between the two groups (table1).

**Figure 1:** BNP plasma levels (n=601).




BNP = B-type natriuretic peptide, N = number of patients.

# Discussion

The major finding of the present study is that only 10% of clinically stabilized hospitalized HF patients had pre-discharge BNP plasma levels below 100 pg/ml.

In patients with acute dyspnea, Maisel et al. showed a sensitivity of 90% for a BNP cut-off value of 100 pg/ml to diagnose HF,[2] and Morrison and colleagues showed a sensitivity of 86% for a BNP value of 94 pg/ml to differentiate HF from pulmonary disease.[11] In other words, in these studies 10% and 14% of HF patients had BNP plasma levels below 100 pg/ml and 94 pg/ml respectively.

In an outpatient clinic setting Tang and co-workers found that as much as 21% of chronic symptomatic systolic HF patients had BNP levels below 100 pg/ml.[6] Recently, a low prevalence of low BNP levels was shown in a systematic review that mainly described studies on acute dyspnea and outpatient clinic HF patients. However, the majority of the studies described in this review showed the highest diagnostic accuracy to differentiate between dyspnea due to HF and dyspnea due to other pathology for a cut-off value of 52 pg/ml.[12] Since BNP is related to the severity of HF,[13] it is conceivable that BNP plasma levels are higher in HF patients during acute dyspnea compared to an outpatient clinic setting. In addition, BNP levels are probably higher in acute dyspneic HF patients compared to 'dry BNP levels' in stabilized HF patients.[14] Therefore, the 10% of HF patients with BNP levels below 100 pg/ml that were found in the present study, is lower than expected based on previous literature.[14] When the cut off values of 75 pg/ml and 50 pg/ml were used, 7% and

5% of the patients were found to have BNP levels below these cut-off values respectively. This finding shows that within the group of patients with BNP < 100 pg/ml the distribution of BNP levels was normal, indicating that in this group no majority exists with 'healthy' BNP levels of < 20 pg/ml.[15]

Tang et al. showed that patients with BNP < 100 pg/ml were more likely to be younger, to be female, and to have a non-ischemic etiology, better-preserved cardiac and renal function, and less atrial fibrillation as compared to patients with BNP > 100 pg/ml.[6] The same differences between the groups were found in the present study (table 1), although of these variables only LVEF was statistically significant. This indicates a specific profile of patients with BNP plasma levels < 100 pg/ml. The differences between patients with high and low BNP levels in current population, suggest that patients with BNP < 100 pg/ml had less severe HF, and more often had HF with preserved systolic function.

Moreover, we found significantly higher body mass indexes in the low BNP group, confirming data recently published which have shown that obesity is related to lower BNP values.[16,17] There are two explanations for this consistent finding. First, natriuretic peptide clearance receptors (NPR-C) are abundant in adipose tissue, suggesting that adipocytes participate in the removal of natriuretic peptides from the circulation.[18] A second explanation of lower BNP plasma levels in obese patients may be an impaired natriuretic peptide secretion. In isolated obese Zucker rat hearts, an impaired signal cascade myocardial protein kinase C - MAP kinase - natriuretic peptide secretion was shown, as compared to lean rat hearts.[19] In another study in young, healthy, normotensive obese subjects, an impaired natriuretic peptide secretion was shown in response to saline load.[20]

Logeart et al. showed that patients with a decrease in BNP plasma levels during HF admission had a lower risk on events after discharge compared to patients with unchanged or increased BNP levels during admission.[21] Therefore, the authors recommend a 'decrease of BNP approach' for clinical practice. The present results, however, indicate that a goal of decreasing BNP levels during HF admission below 100 pg/ml is not realistic for most patients.

Altogether, the 10% of heart failure patients that were found to have low BNP levels at discharge in the present study is a remarkably low percentage, when taken into account that 21% of stable outpatient clinic patients had low BNP levels. This finding adds value to the use of BNP in clinical practice in patients recently admitted for HF, and extends the low prevalence of normal BNP levels from acute dyspneic patients[2] to stabilized in hospital HF patients.

## Limitations

The present study was limited by its cross sectional design. BNP plasma levels at hospital admission and post discharge outcomes would have added to the importance of the study. However, an evaluation of the BNP value of 100 pg/m at hospital discharge, adds important knowledge for clinical practice, since this value is increasingly used.

## Conclusion

The present study demonstrated that 10% of patients with a recent admission for decompensated HF have BNP plasma levels 100 pg/ml. These patients seem to have less severe HF and more often have HF with preserved systolic function.

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# Chapter 8

# General discussion and future perspectives

# BNP/ NT-proBNP in heart failure: the holy grail in clinical practice?

After the publication of a large number of studies on the potential beneficial effects of BNP and NT-proBNP in the diagnosis and prognosis of HF, as well enthusiasm about the possible value of BNP/NT-proBNP guided therapy, many physicians have started to use natriuretic peptides in clinical practice. Many questions regarding the application of BNP/NT-proBNP in daily practice, however, have remained unanswered. These include:

- Are BNP and NT-proBNP only elevated in case of HF, or are there other clinical conditions involved that cause elevated plasma levels? In other words, which clinical conditions other than severity of HF are related to BNP and/or NT-proBNP plasma levels?
- Since BNP/ NT-proBNP may be related to age and gender in HF patients, should cut-off values be age and gender specific?
- Which one, BNP or NT-proBNP should be preferred in daily clinical practice?
- Are BNP and NT-proBNP also useful in conditions other than in the differentiation between cardiac and pulmonary dyspnoea at the emergency department?
- Are the cut-off values established in studies in the emergency department setting also valuable at discharge after admission for HF?
- Is BNP/NT-proBNP really useful in the titration of HF medication?

The major findings from the studies presented in this thesis include:

- In HF patients elevated BNP/NT-proBNP levels are clearly associated with increasing age.
- Anaemia and renal dysfunction are related to increased BNP and NT-proBNP levels, independent of the severity of HF.
- Renal dysfunction is relatively stronger related to elevated NT-proBNP levels than to elevated BNP levels.
- BNP is not related to physical dimensions of quality of life, nor to sub maximal functional capacity in HF patients.
- Dyspnoea at rest, absence of COPD/Asthma, renal dysfunction, absence of anaemia and NT-proBNP > 300 pg/ml are independent predictors of a discharge diagnosis HF. These five simple diagnostic predictors were transformed in a scoring rule (range 0 - 14) that can be applied in daily practice.
- 10% of the patients admitted with suspected HF have BNP levels below the well established BNP cut-off value of 100 pg/ml at discharge.

Thus, the studies provided useful information pertaining to the remaining questions mentioned above. Below, several of these issues will discussed in more detail in the context of the total body of evidence and suggestions for future studies are given.

### Single cut off values for BNP and NT-proBNP or should cut off values depend on patient characteristics?

Until now, a single BNP cut-off value to differentiate between a cardiac and pulmonary cause of dyspnoea has been proposed for all patients (100 pg/ml). For NT-proBNP however, both non-stratified and age specific cut-off values have been advocated. In this thesis we showed that BNP and NT-proBNP are not only independently related to age, but also to renal dysfunction and anaemia. Moreover, previous research showed that both BNP and NT-proBNP levels are depressed in case of an elevated body mass index.[1-3] Thus, it could be argued that one should adjust the BNP and NT-proBNP threshold indicating abnormal levels to important influencing factors such as age, renal function, anaemia and body mass index.

Previous research showed that both BNP and NT-proBNP levels are related to age and gender in healthy subjects .[4] In addition, we showed that BNP and NT-proBNP are also related to age in HF patients. The difference between males and females was less pronounced in our study population than in healthy subjects. This finding implicates that only age and not gender should be taken into consideration when interpreting BNP and NT-proBNP results in HF patients. Nevertheless, the correlations between BNP/ NT-proBNP and age were only moderate and comparable to other factors, indicating that it is not necessary to use age specific thresholds. Furthermore, stratification of cut-off values according to age could be problematic because BNP levels are lower in patients with diastolic HF than systolic HF.[5] Consequently, diastolic HF, which is most prevalent in the elderly, will be missed more frequently when these cut-off values are higher for elderly patients.

Since we showed that both BNP and NT-proBNP, are independently associated to anaemia and renal dysfunction, it is important to take these clinical conditions into consideration when interpreting natriuretic peptide plasma levels. Does this also mean that we should adjust BNP/NT-proBNP cut-off values in case these conditions are present? Several investigators studied the influence of renal function on optimal cut-off values, with varying findings. Four studies in patients with acute dyspnoea at the emergency department[6,7] and in patients with a history of myocardial infarction[8,9] found that renal dysfunction stratified cut-off values showed better diagnostic accuracy than a single cut-off value. In contrast, Anwaruddin et al. did not find a significant difference between renal function adjusted and non-adjusted NT-proBNP cut-off values in dyspnoeic patients with suspected HF. Other studies showed an inverse effect of anaemia on BNP levels in patients without HF[10-12] and of anaemia on NT-proBNP in a small group of HF patients.[13] To our knowledge, our study was the first to investigate both relations in one large group of HF patients. Since we found that both BNP and NT-proBNP are higher in anaemic compared to non-anaemic HF patients, the stratification question arises again.

Since, BNP and NT-proBNP are associated to both age and several clinical conditions (apart from anaemia, renal dysfunction and body mass index, natriuretic levels have also been reported to be increased in e.g. COPD patients) it is not useful, if doable at all, to apply specific cut-off values for all of these factors. In addition, the applicability of BNP/NT-proBNP assess-

ments is hampered when thresholds differ across relevant patient categories. We therefore recommend to use single cut-off values in clinical practice, and neither stratify for age, nor for renal function, haemoglobin levels or body mass index, and interpret BNP and NT-proBNP levels in conjunction with the complete clinical assessment of HF patients in clinical practice.

Another implication for clinical practice of our results may be that in some clinical situations it may be wiser to primarily evaluate a patient on the basis of signs and not on the basis of BNP/ NT-proBNP levels. For example, in case of an elderly patient with renal dysfunction and anaemia it is hard to establish whether the elevated natriuretic peptide levels reflect severity of HF or only the severity of his or her co-morbidities.

Undoubtedly, BNP/NT-proBNP are not the miracle predictors of the physical and mental status of HF patients some researchers believe it to be. We, for example, also demonstrated that BNP does not reflect physical dimensions of quality of life, an important target for HF therapy. Our results confirmed the findings of Luther et al. who showed that BNP was not related to health status as measured by the Kansas City Cardiomyopathy Questionnaire.[14] This instrument measured symptoms, physical function, social function, self efficacy and quality of life. In addition we found that BNP was not related to 6-minute walk test (sub maximal functional capacity), a measure that reflects daily activities of elderly patients. For clinical practice, we suggest that quality of life and sub maximal functional capacity should be measured in addition to BNP and the currently available diagnostic tools.

### When should BNP/ NT-proBNP be used?

There is strong supportive evidence for the use of BNP and NT-proBNP in an emergency department setting in differentiating cardiac from pulmonary dyspnoea.[15,16] Additionally, we showed that together with readily available clinical variables such as the severity of HF symptoms at admission (NYHA class IV), the absence of COPD, renal dysfunction and absence of anaemia, a NT-proBNP level exceeding > 300 pg/ml is and independent determinant of the discharge diagnosis HF in patients admitted with suspected HF. Based on these diagnostic predictors we constructed a diagnostic score that could be applied in clinical practice, albeit that external validation is needed before its use on a larger scale can be recommended. When instead of an NT-proBNP assay, a BNP assay is locally available, the score can be adjusted.

We also studied the value of established cut-off values of BNP at discharge after admission for HF. Earlier studies showed that 10%[16] and 21-30%[17,18] of acute dyspnoeic and stable HF patients respectively, had BNP levels below the established threshold of 100 pg/ml. Furthermore, Knebel et al. showed that a decrease in BNP levels during admission was accompanied by recompensation of HF patients that were admitted to the hospital for decompensated HF. Based on these results one might expect that the percentage of false positive results would be higher in HF patients that are recompensated after hospital admission than in decompensated HF patients. However, we found that when using the established BNP cut-off value at discharge, the proportion of false positive HF diagnoses was equal to the proportion in patients with BNP levels below this cut-off value at the emergency depart-

ment (10%). This result indicates that this BNP cut-off value may be useful at discharge after admission for suspected HF. Since we showed that patients with natriuretic peptide plasma levels below the threshold had less severe HF and a preserved systolic function, the cut-off values can possibly be used at discharge after admission for HF for purposes of differentiation between patients with severe and less severe HF and between preserved and suppressed systolic function. This information may give an indication as to whether a patient requires more intensive medical treatment or a more intensive post discharge follow up scheme.

### Should we use either BNP or NT-proBNP (or both?) in clinical practice?

It is hard to give a straightforward answer to the question whether BNP or NT-proBNP should be preferred in clinical practice since both peptides have similar benefits (diagnostic properties in suspected HF) and limitations (influenced by several clinical conditions/ co-morbidities other than HF). A disadvantage of BNP is its stronger relationship to age and a disadvantage of NT-proBNP is that it is more strongly related to renal dysfunction. The preferential use of BNP or NT-proBNP should ideally be based on its clinical purpose (i.e. diagnosis, prognosis or intensive or less-stringent monitoring of therapy), since the most important difference between the two is their half life in blood (20 minutes vs. 120 minutes respectively). For diagnostic and prognostic purposes the two are comparable, even if patient characteristics differentially influence BNP or NT-pro BNP levels, as outlined above. When the aim is to monitor more gradual changes in HF severity over a longer time period, NT-proBNP may be more useful and when quick changes in HF severity should be detected, BNP may be preferred. Furthermore, there are practical issues that are important in the decision to prefer one of the two markers in clinical practice. For example, the Biosite Triage BNP meter is a bedsite meter and the Roche Elecsys NT-proBNP meter is a full automatic laboratory meter. In some situations, a clinician may not have a choice between BNP and NT-proBNP because a laboratory already chose either one of them based on their preferences.

In view of the current available literature, the use of both BNP and NT-proBNP has no additional value for clinical practice.[19]

## Future perspectives

### Clearance of BNP/NT-proBNP

The differences between BNP and NT-proBNP in their association with renal function could be explained in different ways. On the one hand McCullough et al. found that stronger influence of renal function on NT-proBNP may be attributable to differences in clearance. They postulate that in contrast to the renal clearance of NT-proBNP, BNP is mainly cleared from the bloodstream by natriuretic peptide clearance receptors and by neuro endopeptidases. On the other hand, the observed differences between BNP and NT-proBNP are moderate, and this is considered a reflection of structural heart disease and as 'cardiorenal' interaction.[20] Two small studies in healthy young men and in hypertensive patients showed that about 20% of both BNP and NT-proBNP are cleared from the bloodstream by the kidneys.[21,22] This, however, has never been confirmed in a large group of HF patients.

In addition, studies applying micro punction of the efferent and afferent renal arterioles are lacking. By using this method, an exact change in NT-proBNP levels caused by renal filtration can be determined.

### Urine BNP/ NT-proBNP guided treatment

There are indications that NT-proBNP guided treatment may be of additional value in the management of HF.[23] Since plasma levels of NT-proBNP are influenced by many patient characteristics, including co-morbidity, as well as by biological variation, the use of NT-proBNP levels for guidance of HF treatment may be limited due to fluctuations caused by other phenomena than worsening HF.

Since a fraction of NT-proBNP is cleared from the blood by the kidneys, NT-proBNP may also be detected in urine of HF patients. In a study on screening for left ventricular systolic dysfunction Ng et al. showed that NT-proBNP can be detected in urine.[24] NT-proBNP in urine could also be used for guidance of medical treatment. Ideally, this would require accurate NT-proBNP values without fluctuations due to reasons other than worsening HF. In 24 hours urine, an average NT-proBNP value in an individual HF patient on a particularly day, without daily variation, could serve as an indicator of the appropriateness of medical therapy. However, it is known that peptides such as NT-proBNP are broken down in the proximal renal tubule, but it is unknown whether the proportion that is cleared by the kidneys differs according the concentrations of plasma NT-proBNP. Therefore, data on the relationship between plasma NT-proBNP and urine NT-proBNP in HF patients with and without renal dysfunction are needed before trials on urinary NT-proBNP guided HF therapy can be initiated.

### Other options of titration medical treatment

As already stated before, there are indications that NT-proBNP guided HF therapy results in lower mortality and fewer hospitalizations than clinical monitoring alone. Larger trials are underway that are about to either confirm or reject these pilot results. In addition, other ways to guide medical treatment have been proposed. Pilot studies showed that blood volume change or impedance cardiography may be good candidate markers for this purpose.[25,26] Firmer studies are necessary to asses which of these methods could be applied to monitor HF treatment.

### Multivariable prognosis

Until now, only the univariable prognostic value of BNP and NT-proBNP levels, and a multivariable risk score without BNP or NT-proBNP levels[27] have been published. A multivariable risk score including data readily obtainable from physical examination and medical history as well as BNP or NT-proBNP levels could improve the identification of HF patients at increased risk for future cardiovascular events. An optimal risk stratification for HF patients is important to optimize (dosages of) HF medication and the intensity of medical follow up.

# Conclusion

BNP and NT-proBNP have important benefits in the daily management of patients with possible or established HF, including, as shown in this thesis, those patients discharged from hospital after admission for suspected HF. Besides the benefits, however, our studies also revealed important limitations that should be taken into consideration in the decision to assess BNP/ NT-proBNP levels and in the interpretation of the test results.

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# Summary

# Summary

The diagnostic and prognostic properties of B-type Natriuretic Peptide (BNP) and N-terminal proBNP (NT-proBNP) in patients with heart failure have been well established during the past years. Today, measurement of natriuretic peptides is frequently used in clinical practice. However, although very promising, there are several factors that might limit the diagnostic and prognostic use of these peptides. This thesis provided a critical appraisal on the benefits and limitations of the use of natriuretic peptides in heart failure patients.

The primary aims of this thesis were:

1. To assess the influence of age, renal dysfunction, anaemia, functional capacity and quality of life on levels of BNP and/or NT-proBNP.
2. To identify the independent predictors of the discharge diagnosis heart failure, and to develop an easy applicable scoring rule using these independent predictors and BNP and/or NT-proBNP levels.
3. To investigate the value of the currently available cut-off value of BNP levels for exclusion of heart failure in a setting of discharge from the hospital after admission for heart failure.

Since most studies on BNP and NT-proBNP have been performed in emergency department settings and because only little evidence is available on their usefulness in a setting of discharge after admission for heart failure, we studied BNP and NT-proBNP levels in a population of patients that were about to be discharged after admission for suspected heart failure. We described the criteria of this population, which was included in the COACH study, in **chapter 2**.

In healthy subjects, natriuretic peptide levels are higher with increasing age, but it remained unknown whether the same is true for patients with heart failure. In **chapter 3** we described that all studied natriuretic peptides were significantly related to age ($p<0.05$) on multivariate regression analysis, with partial correlation coefficients of 0.18, 0.29, 0.28 and 0.25 for ANP, NT-ANP, BNP and NT-proBNP respectively. The relative increase of both BNP and NT-proBNP with age were more pronounced than the relative increase of ANP and NT-ANP with age ($p<0.01$). Furthermore, the relative increase of BNP with age was markedly larger than of NT-proBNP ($p<0.01$). Levels of all natriuretic peptides were also significantly related to cardiothoracic ratio, renal function and left ventricular ejection fraction.

Other phenomena that may possibly influence BNP and NT-proBNP levels are anaemia (by increasing plasma volume) and renal dysfunction (by decreasing clearance), although this was not been well described in heart failure patients. We therefore aimed to study the influence of anaemia and renal dysfunction on BNP and NT-proBNP levels in heart failure patients. In **chapter 4** we showed that in a heart failure population of 541 patients, 30% (n=159) was anaemic (Hb<7.5 mmol/L for women and Hb<8.1 mmol/L for men). Of the 159 anaemic patients, 73% had renal dysfunction (estimated GFR <60 ml/min/ $1.73m^2$) and of the non-anaemic patients, 57% had renal dysfunction. Multivariable analysis demonstrated that both plasma haemoglobin and estimated GFR were independently related to the level of both BNP and NT-proBNP (standardized beta's of -0.20, -0.13 [BNP] and -0.26, -0.28 [NT-proBNP] respectively, P-values <0.01).

Both BNP and the 6-minute walk test are related to severity and prognosis of heart failure. However, in **chapter 5** we did not find a correlation between BNP and the 6-minute walk test, indicating that BNP and the 6-minute walk test represented different aspects of the clinical syndrome of heart failure (r=0.01, P=0.87). Further results of our study suggested that BNP plasma levels were more related to cardiac function, while the 6-minute walk test reflected functional capacity and physical dimensions of quality of life.

Early validation studies showed that 18% - 33% of patients admitted for suspected heart failure received a false-positive discharge diagnosis of heart failure. We aimed to identify the most important independent predictors of a (false) heart failure discharge diagnosis and to construct a score to improve the discharge diagnosis of heart failure (**chapter 6**). The outcome panel that we put together, identified 6% of our research population that was admitted for suspected heart failure (n=540) with a discharge diagnosis other than heart failure. Univariable predictors of the discharge diagnosis heart failure were dyspnoea at rest, absence of COPD/ asthma, absence of anaemia, renal dysfunction, BNP > 100 pg/ml and NT-proBNP > 300 pg/ml. In multivariable logistic analyses, all of these, except BNP > 100 pg/ml, remained independent predictors of a heart failure discharge diagnosis. The ROC area of a model combining these predictors was 0.78. These independent predictors were combined in a scoring rule to optimize the discharge diagnosis of these patients. This score should be validated in other populations before its use in clinical practice can be recommended

Previous studies in acute heart failure patients presenting at the emergency department, found a BNP < 100 pg/ml in only 10% of the patients. However, in a more stable outpatient heart failure population from another study, a BNP < 100 pg/ml was found in as many as 21% of the patients. Therefore, we aimed to investigate the prevalence and characteristics of stabilized patients with BNP < 100 pg/ml before discharge after admission for heart failure. In **chapter 7** we showed that in our study population consisting of clinically stable patients with a recent admission for heart failure, only 10% had BNP levels below 100 pg/ml. These patients with low BNP levels seemed to have less severe heart failure and more frequently had preserved systolic function compared to patients with BNP levels ≥ 100 pg/ml.

In **chapter 8** we discussed whether different BNP and NT-proBNP cut-off values should be used in different populations, since natriuretic peptides are not only influenced by the severity of heart failure, but by several other factors as well (this thesis). On the other hand, it would be very unpractical to use many different cut-off levels for each group of patients. This means that each outcome level of BNP or NT-proBNP should be interpreted in the light of the other factors that might have influenced this value.

We also discussed the issues of whether we should use either BNP or NT-proBNP in clinical practice, and in which settings these natriuretic peptides can be used. Finally we made several recommendations for future clinically applied research on BNP and NT-proBNP in patients with heart failure.

In conclusion, BNP and NT-proBNP have important benefits in the daily management of patients with possible or established heart failure, including, as shown in this thesis, those patients discharged from hospital after admission for suspected heart failure. Besides the benefits, however, our studies also revealed important limitations that should be taken into consideration in the decision to assess BNP/ NT-proBNP levels and in the interpretation of

# Nederlandse samenvatting

# Samenvatting

In de diagnose en prognose van hartfalen hebben B-type Natriuretisch Peptide (BNP) en N-terminaal proBNP (NT-proBNP) in de afgelopen jaren hun waarde bewezen. Tegenwoordig worden natriuretische peptiden dan ook frequent gebruikt in de klinische praktijk. Hoewel het gebruik van deze natriuretische peptiden veelbelovend is, zijn er echter diverse factoren die de toepassing bij zowel de diagnose als de prognose van hartfalen kunnen beperken. Dit proefschrift leverde een kritische noot over de voor- en nadelen van het gebruik van natriuretische peptiden bij patiënten met hartfalen.

De hoofddoelen van dit proefschrift waren:

1. Het bepalen van de invloed van leeftijd, nierdisfunctie, anemie, functionele capaciteit en kwaliteit van leven op BNP en NT-proBNP spiegels.
2. Het identificeren van onafhankelijke predictoren van de ontslagdiagnose hartfalen en het ontwikkelen van een eenvoudig toepasbare diagnostische score die deze predictoren bevat evenals BNP en/ of NT-proBNP waarden.
3. Het onderzoeken van de gangbare BNP afkapwaarde om hartfalen uit te sluiten bij ontslag uit het ziekenhuis na een opname voor hartfalen.

De meeste studies over BNP en NT-proBNP zijn uitgevoerd op een afdeling Spoedeisende Hulp. Er is slechts weinig bewijs voor het gebruik van BNP en NT-proBNP bij ontslag uit het ziekenhuis na opname voor hartfalen. Daarom hebben we BNP en NT-proBNP waarden onderzocht in een populatie patiënten opgenomen voor verdenking op hartfalen, vlak voor ontslag uit het ziekenhuis. We hebben de criteria van deze populatie, die was geïncludeerd in de COACH studie, evenals het design van de NHS-COACH studie, beschreven in **hoofdstuk 2.**

Bij gezonde proefpersonen zijn natriuretische peptiden waarden hoger naarmate de leeftijd toeneemt. Tot nu toe was echter onduidelijk of deze leeftijdsafhankelijkheid ook bestaat voor patiënten met hartfalen. In **hoofdstuk 3** beschreven we dat alle onderzochte natriuretische peptiden significant gerelateerd waren met leeftijd ($P<0.05$) in een multivariabele analyse. De partiele correlatiecoëfficiënten waren respectievelijk 0,18; 0,29; 0,28 en 0,25 voor ANP, NT-ANP, BNP en NT-proBNP. BNP en NT-proBNP namen relatief meer toe met leeftijd dan ANP en NT-ANP ($P<0,01$). Verder nam BNP relatief meer toe met leeftijd dan NT-proBNP ($P<0,01$). Waarden van alle onderzochte natriuretische peptiden waren ook significant gerelateerd aan CT-ratio, nierfunctie en linker ventrikel ejectie fractie.

Andere factoren die BNP en NT-proBNP waarden mogelijk kunnen beïnvloeden zijn anemie (via een vergroot plasma volume) en nierdisfunctie (via een verminderde klaring). Dit was tot nu toe nog beperkt beschreven in patiënten met hartfalen. In **hoofdstuk 4** hebben we beschreven wat de invloed is van anemie en nierdisfunctie op BNP en NT-proBNP bij patiënten met hartfalen. In een populatie van 541 patiënten met hartfalen lieten we zien dat 30% (n=159) van de patiënten anemisch was (hemoglobine <7.5 mmol/L voor vrouwen en hemoglobine <8.1 mmol/L voor mannen). Van de 159 anemische patiënten had 73% nierdisfunctie (geschatte GFR <60 ml/min/1.73m$^2$); van de patiënten zonder anemie had 57% nierdisfunctie. Multivariaat bleek dat zowel hemoglobine als nierfunctie (geschatte GFR) onafhankelijk gerelateerd waren aan BNP en NT-proBNP waarden (gestandaardiseer-

de beta's van -0.20, -0.13 [BNP] en -0.26, -0.28 [NT-proBNP] respectievelijk, P-waarden <0.01).

BNP en de 6-minuten looptest (die submaximale functionele capaciteit meet) zijn beide gerelateerd aan ernst en prognose van hartfalen. Echter in onze onderzoekspopulatie van 229 patiënten met hartfalen (70 ± 12 jaar oud en 63% mannen) hebben we geen relatie gevonden tussen BNP en 6-minuten looptest (**hoofdstuk 5**). Dit impliceert dat BNP en 6-minuten looptest verschillende aspecten van het klinische syndroom van hartfalen weergeven (r=0.01, P=0.87). Verder waren BNP waarden meer met hartfunctie (linker ventrikel ejectie fractie) gerelateerd en de 6-minuten looptest hield verband met fysieke componenten van kwaliteit van leven.

Eerdere onderzoeken naar de juistheid van de ontslagdiagnose hartfalen hebben aangetoond dat 18% - 33% van de patiënten die waren opgenomen met verdenking op hartfalen uiteindelijk toch niet voor hartfalen waren opgenomen. In **hoofdstuk 6** beschreven we dat in onze populatie slechts 6% van de patiënten die waren opgenomen voor verdenking op hartfalen (n=540) een ontslagdiagnose hadden die anders was dan hartfalen. Een goede ontslagdiagnose hartfalen werd vaker gesteld bij mensen met dyspnoea in rust, afwezigheid van COPD/ astma, afwezigheid van anemie, nierdisfunctie en NT-proBNP > 300 pg/ml. De oppervlakte onder de ROC curve van het logistische regressie model met deze multivariabele predictoren was 0.78. Deze onafhankelijke predictoren hebben we gecombineerd in een score om de ontslagdiagnose hartfalen te optimaliseren. Deze score zal eerst moeten worden gevalideerd in andere populaties voor het gebruik ervan in de klinische praktijk kan worden aanbevolen.

In een onderzoek bij patiënten met acuut hartfalen op een afdeling Spoedeisende Hulp werd in slechts 10% van de patiënten een BNP < 100 pg/ml gevonden. In een onderzoek in een stabiele hartfalen populatie op een polikliniek werd bij 21% van de patiënten een BNP waarde < 100 pg/ml gevonden. Wij onderzochten de prevalentie van stabiele patiënten die vlak voor ontslag uit het ziekenhuis na een opname voor hartfalen een BNP < 100 pg/ml hadden. In **hoofdstuk 7** hebben we laten zien dat slechts 10% van deze populatie een BNP waarde < 100 pg/ml had. Deze patiënten met lage BNP waarden hadden minder ernstig hartfalen en vaker een behouden systolische functie vergeleken met patiënten met BNP waarden ≥ 100 pg/ml.

In de discussie (**hoofdstuk 8**) beschreven we dat het aan de ene kant wenselijk lijkt om verschillende afkapwaarden voor BNP en NT-proBNP te gebruiken in verschillende populaties, aangezien natriuretische peptiden niet alleen door de ernst van het hartfalen worden beïnvloed, maar ook door diverse andere factoren, zoals leeftijd, nierfunctie en anemie (dit proefschrift). In de praktijk is het echter erg onpraktisch om verschillende afkapwaarden te gebruiken voor de verschillende patiëntengroepen. Dit betekent dat elke BNP of NT-proBNP waarde geïnterpreteerd zou moeten worden rekening houdend met de ernst van hartfalen en alle andere beïnvloedende factoren. Verder kwam in de discussie de keuze voor het gebruik van BNP of NT-proBNP aan de orde en bespraken we in welke klinische situaties BNP en NT-proBNP kunnen worden gebruikt. Tenslotte hebben we verscheidene aanbevelingen gedaan voor toekomstig klinisch toegepast onderzoek over BNP en NT-proBNP bij patiënten met hartfalen.

Concluderend hebben BNP en NT-proBNP belangrijke voordelen in de behandeling van

patiënten met mogelijk of vastgesteld hartfalen, inclusief, zoals beschreven in dit proefschrift, de patiënten die op het punt staan te worden ontslagen na opname voor verdenking op hartfalen. Naast de voordelen hebben onze studies echter ook belangrijke beperkingen van het gebruik van BNP en NT-proBNP laten zien, die meegenomen moeten worden bij het besluit of BNP of NT-proBNP waarden bepaald moeten worden. Tevens moeten deze beperkingen in overweging worden genomen bij de interpretatie van de test resultaten.

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# Dankwoord

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