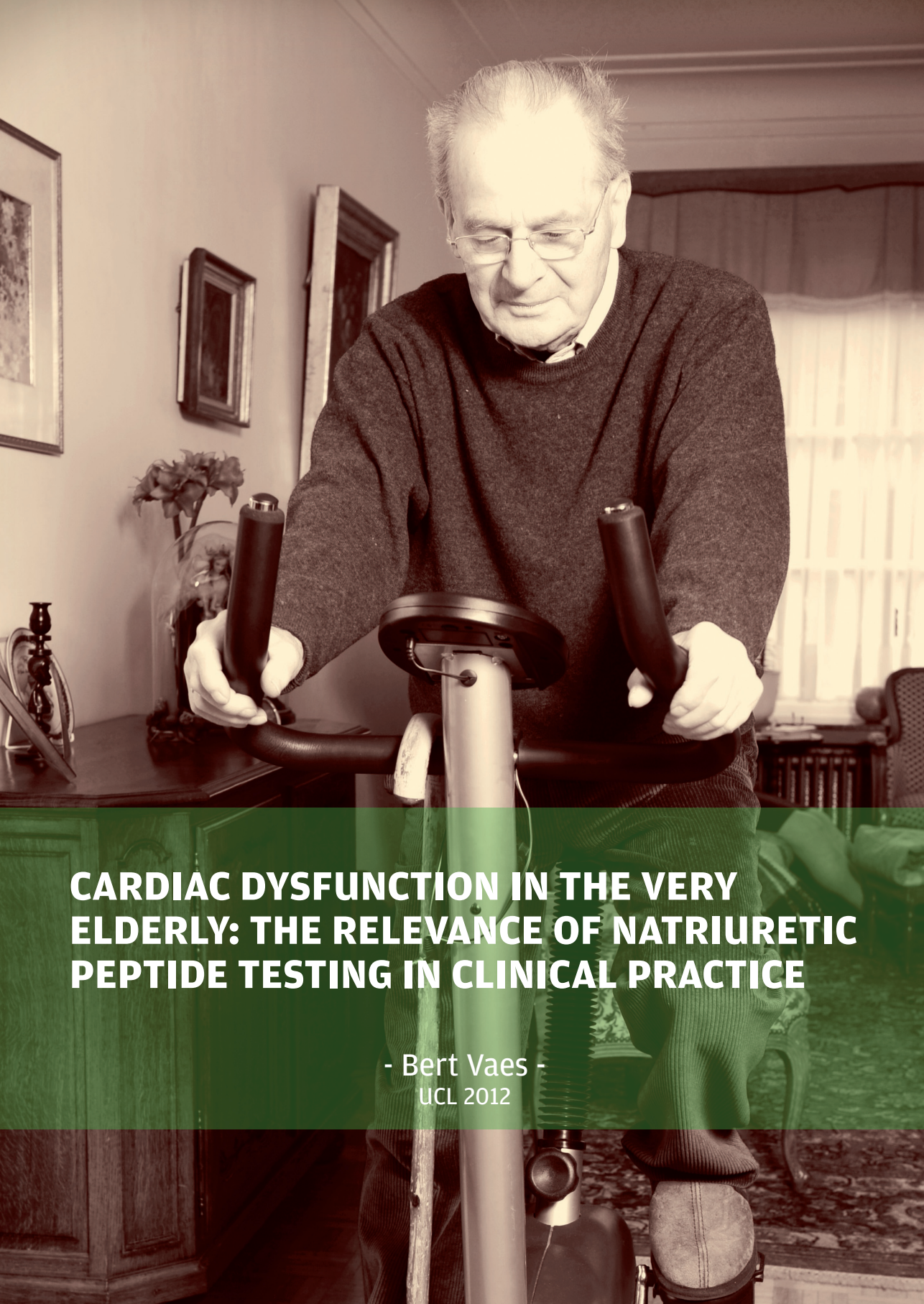

CARDIAC DYSFUNCTION IN THE VERY ELDERLY: THE RELEVANCE OF NATRIURETIC PEPTIDE TESTING IN CLINICAL PRACTICE

- Bert Vaes -
UCL 2012

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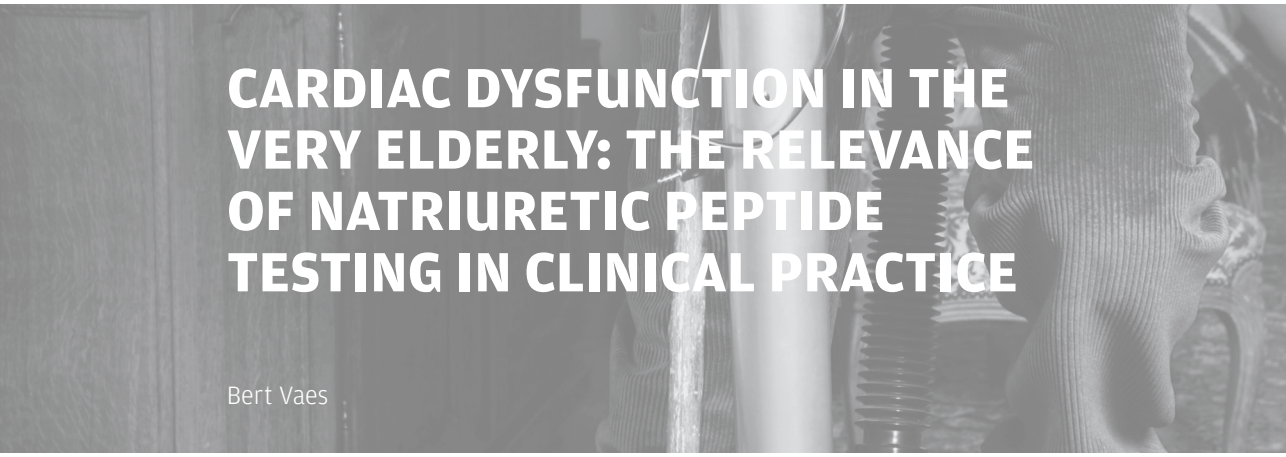

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Bert Vaes

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CARDIAC DYSFUNCTION IN THE VERY ELDERLY: THE RELEVANCE OF NATRIURETIC PEPTIDE TESTING IN CLINICAL PRACTICE

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INTRODUCTION

« The very essence of cardiovascular medicine is the recognition of early heart failure. »

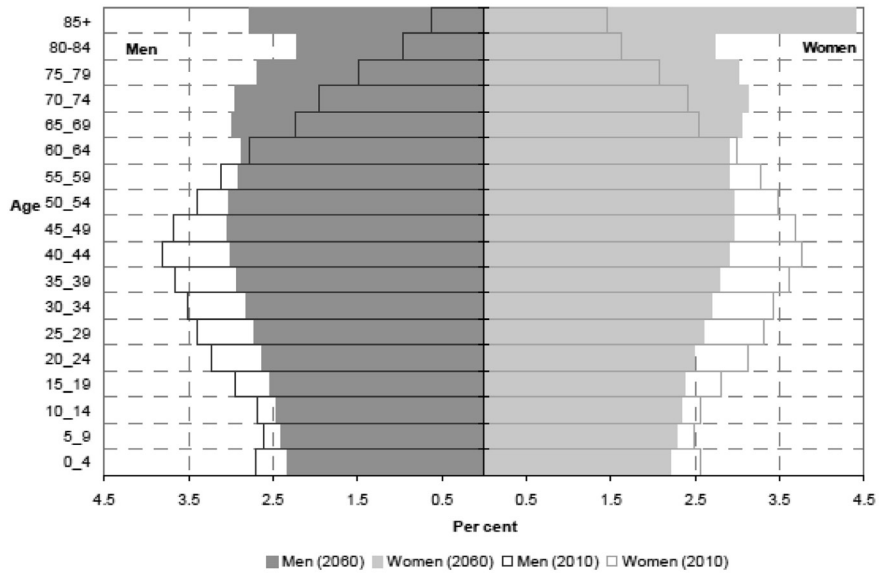
Sir Thomas Lewis, 1933

1.

THE GREY EPIDEMIC

Health care and social security systems in industrialized countries are confronted with ageing populations. In 2010 the median age of the 27 Member States population of the European Union was 40.9 years[1]. The population aged 65 and older accounted for 17.4%, and the proportion of people aged 80 and older for 4.7% of the total population. By 2060 the median age is projected to rise to 47.9 years, 30.0% will be aged 65 and older and the proportion of those aged 80 and older is projected to almost treble (12.1%)[1]. In the coming decades, the large number of ageing baby boomers will swell the number of older people. The baby boom bulge will move up the population pyramid, leaving the middle (population of working age, 20-64), and the base (ages 0-19), considerably narrower in 2060 (Figure 1).

Figure 1. Population pyramids, EU-27, 2010 and 2060[1]



The old age dependency ratio is used as an indicator of the potential level of support needed by older people (aged 65 and older) from the population of working age. The ratio is expressed in terms of the relative size of the older population to the population of working age[2]. This ratio is projected to more than double from 28.4% in 2010 to 58.5% in 2060. The implication is that there will be three persons of working age for every two dependent persons aged 65 years and older, instead of three for one in 2010[1].

This forthcoming "grey epidemic" will lead to a heavy burden of chronic diseases. The prevalence of multimorbidity, the presence of two or more diseases at the same time, increases with age up to 78% in subjects aged 80 and older, with a mean number of prevalent diseases of 3.2 and 3.6 for men and women, respectively[3]. Multimorbidity is associated with poor quality of life, physical disability, intensive health care use, multiple medications, and increased risk of adverse drug events and mortality[4-6]. Optimizing care for this population is a high priority[7]. Marengoni et al. showed heart failure and visual impairment to be associated with the highest number of comorbid diseases in an elderly population aged 77 and older[8].

2.

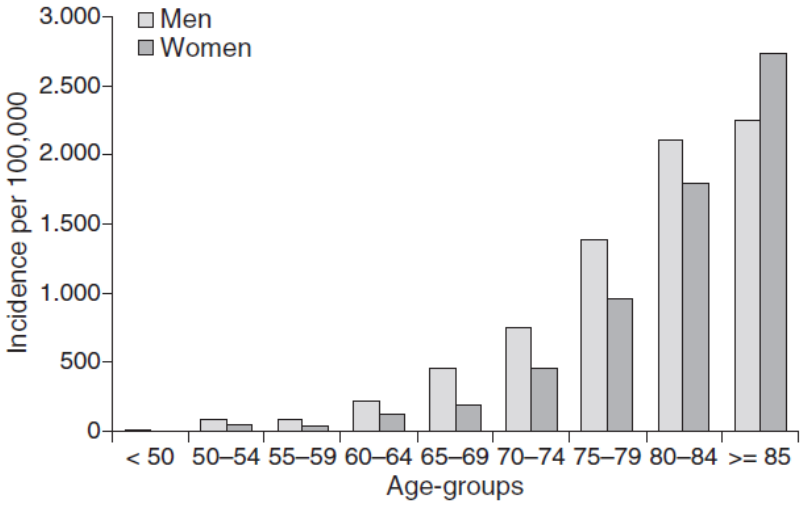
THE BURDEN OF HEART FAILURE IN AN AGEING SOCIETY

There is growing evidence of the progression from risk factors to asymptomatic cardiac dysfunction and eventually symptomatic heart failure and death[9-13]. Improved survival following acute cardiac events has led to an increased prevalence of heart failure[14]. Furthermore, the prevalence increases with age from 2.7% in people aged 65–74 years to 13.0% in those aged 75–84 years[15]. Data on the incidence of heart failure are scarce and mainly originate from the Framingham Study[16]. This study showed the incidence of heart failure nearly doubles every life decade, making this mainly a disease

of the elderly[16]. The incidence of heart failure is estimated at 2-3% in people aged 85 and older[17].

For Belgium, little reliable nationwide data about the prevalence of heart failure are available. Prevalence rates are only available from the Health Interview Surveys, where patients themselves report on their heart failure, or from the follow up studies of coronary patients[18]. Recently, data on the incidence and mortality of heart failure in Belgium were published, prospectively collected during a 2-year period by a group of sentinel practices[19]. The overall yearly incidence of heart failure is estimated at 210 new patients per 100.000 women and 174 per 100.000 men, but increases to more than 2000 patients per 100.000, both for women and men aged 80 and older[19] (Figure 2). The severity of heart failure is generally high at the time of the diagnosis (New York Heart Association [NYHA] Class III or worse) and most patients need to be hospitalised. Moreover, heart failure is fatal for more than one quarter of patients in the first year after the diagnosis[19].

Figure 2. Incidence of heart failure in men and women per age-group in Belgium[19]



3.

HEART FAILURE: A DIAGNOSTIC CHALLENGE IN THE ELDERLY

In young populations, heart failure is most often associated with systolic dysfunction, evidenced by an impaired left ventricular ejection fraction (LVEF). Heart failure with normal LVEF (HFNEF) is relatively uncommon in younger patients but is more prevalent in the elderly. HFNEF is frequently referred to as diastolic heart failure because of the presence of diastolic LV dysfunction evident from abnormal LV relaxation, filling, diastolic distensibility and diastolic stiffness[20]. To date, however, there is no reference standard to indicate diastolic dysfunction in the way that the left ventricular ejection fraction is generally accepted as the reference standard for systolic dysfunction. Furthermore, there is an on-going discussion whether these two pathologies should be considered as a single syndrome, with two phenotypes at the end of the spectrum, or as two separate syndromes, as supported by functional, structural and molecular biological arguments[20].

To date, there is no gold standard for the diagnosis of heart failure. The best reference standard is considered to be the consensus of a panel of experts, that has access to all relevant data and bases its diagnosis on the presence of symptoms and signs typical of heart failure, along with the objective evidence of a structural or functional abnormality of the heart at rest[21]. However, when the above reference standard is used in diagnostic research, there is the danger of incorporation bias and circular thinking. Furthermore, as multimorbidity becomes more prevalent with age, the specificity of typical symptoms and signs of heart failure decreases drastically[22]. Moreover, the prevalence of structural or functional abnormalities of the heart increases with age[23]. Therefore, the presence of severe cardiac dysfunction, objectively measured with echocardiography, was chosen as the reference standard in this thesis.

Echocardiography is currently the diagnostic test of first choice for identifying structural and functional cardiac

abnormalities. However, its availability for the very elderly can be limited, so there is the likelihood of considerable over- and under diagnosis of cardiac dysfunction[24;25]. The diagnostic work-up (e.g. electrocardiogram [ECG], chest X-ray, and echocardiography) in suspected heart failure in geriatric patients is further complicated by immobility and comorbidity[26]. In cases of suspected heart failure, the percentage of referral by the general practitioner decreases as the patient's age increases[27].

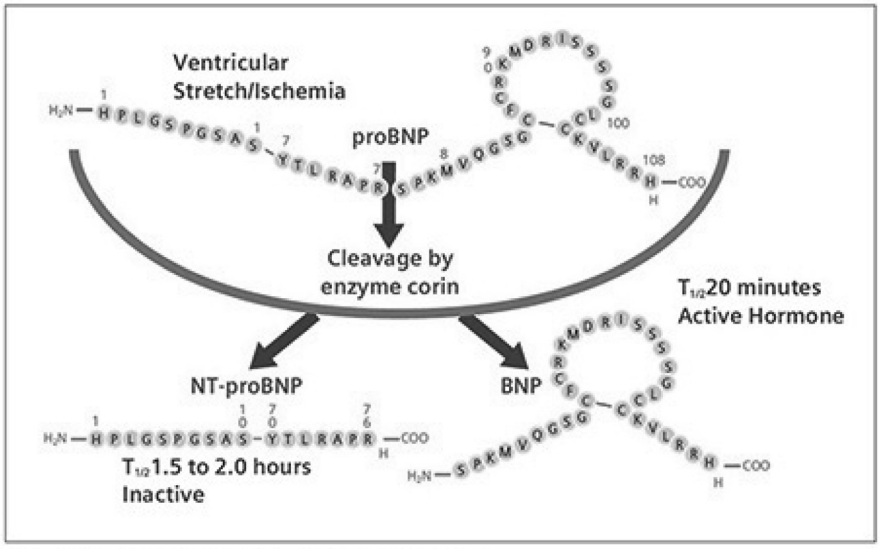
All this emphasises the need for a simple test to identify patients at risk. The measurement of natriuretic peptides has been suggested in screening for left ventricular (LV) dysfunction in high-risk patients, such as the elderly[28;29].

4.

NATRIURETIC PEPTIDES: THE 'ULTIMATE' BIOCHEMICAL TEST FOR HEART FAILURE?

Brain natriuretic peptide (BNP) initially was isolated and named after experiments on the porcine brain[30]
However, with the primary site of synthesis localized to the cardiac ventricular myocytes, the term "B-type" natriuretic peptide is now favoured[31]. In the setting of volume expansion or pressure overload, the resulting wall stress initiates synthesis of pre-proBNP in the ventricular myocardium[32]. Subsequently, the peptide is cleaved first to proBNP, then to the biologically active BNP and the inactive amino-terminal fragment, NT-proBNP[31] (Figure 3). The release of BNP results in improved myocardial relaxation and serves an important regulatory role in response to acute increases in ventricular volume by opposing the vasoconstriction, sodium retention and antidiuretic effects of the activated renin-angiotensin-aldosterone system[33].

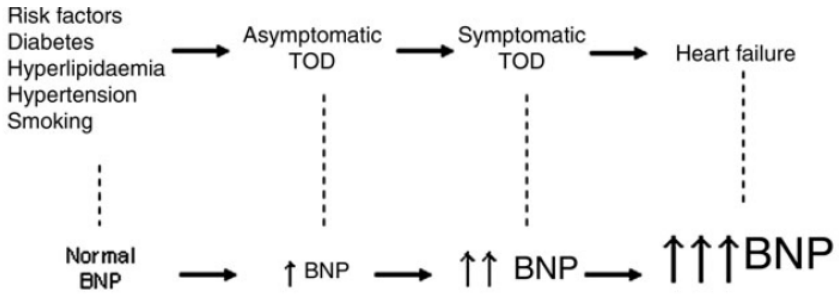
Figure 3. ProBNP cleaved to BNP and NT-proBNP



ProBNP molecule cleaved to BNP and NT-proBNP.

However, it now transpires that BNP is not just an indicator of raised intracardiac pressure and left ventricular dysfunction[34]. When myocardial tissue is damaged by ischaemia, extra BNP is made and released, irrespective of hemodynamic considerations[35]. This has been shown for both symptomatic[36] and asymptomatic individuals[37;38]. Furthermore, natriuretic peptides have been shown to identify left ventricular hypertrophy[39] and LA enlargement and atrial fibrillation[40]. Therefore, it appears that natriuretic peptides may be able to identify all of the main forms of cardiac target organ damage (TOD), and could become an indicator of pancardiac damage, even when it is silent[34]. In the 'cardiovascular continuum' of Braunwald and Dzau[41], it is easy to see how natriuretic peptides could serve as a way of recognizing when longstanding risk factors have produced any form of cardiac damage in an individual, and even how natriuretic peptides increase progressively as the patient goes from silent to symptomatic damage to overt heart failure[34] (Figure 4).

Figure 4. Brain natriuretic peptide release and evolution of cardiovascular disease[34].



In addition, natriuretic peptides have also been investigated as prognostic markers[42], therapeutic agents[43], and indicators to guide treatment of patients with heart failure[44].

Most of the studies investigating the diagnostic accuracy of natriuretic peptides have been performed in emergency settings with acute dyspnoeic patients[31]. However, as many people with substantial cardiac dysfunction are asymptomatic, natriuretic peptides might also be used as a simple screening/case-finding test to identify significant cardiac abnormalities. The success of a population-based screening programme is dependent on disease prevalence, the availability of a screening test that is acceptable, safe and inexpensive, the presence of effective treatment for detected disease, as well as the existence of, and compliance with, a follow-up care system for people at risk or with positive tests[31]. Natriuretic peptides might be attractive candidates for screening the general population for subclinical disease for several reasons. First, left ventricular dysfunction and the other cardiovascular diseases that are detectable by elevated natriuretic peptide levels are common and cause significant morbidity and mortality[45]. Second, natriuretic peptide levels may be elevated early in the disease process, allowing for timely detection of disease prior to symptom onset[46]. Third, early treatment of latent disease with medications such as angiotensin converting enzyme inhibitors improves outcomes by preventing the

development of symptomatic heart failure[47]. Finally, several studies have shown that, in the right setting, screening with natriuretic peptides may prove cost-effective[48;49].

Besides being hospital-based, most studies investigating the diagnostic accuracy of natriuretic peptides have been carried out in younger populations. Because age has been shown to be an important confounder for the plasma level of natriuretic peptides[50], cut-off values used in younger populations should not, perhaps, be applied in old age. Furthermore, multiple factors are known to influence circulating levels of natriuretic peptides, especially in the elderly. The prevalence of possible influencing factors, such as renal dysfunction, chronic obstructive pulmonary disease and diabetes, increases with age[29]. Understanding these factors is a prerequisite for using these peptides optimally to diagnose cardiac dysfunction in the community[51].

In addition, many questions about the implementation of natriuretic peptides in everyday clinical practice remain unresolved. First, cut-off values for natriuretic peptides to identify pancardiac damage are not yet established. Second, the impact of confounders on the test performance of natriuretic peptides for cardiac dysfunction is unclear. Third, the best place for a natriuretic peptide test in the diagnostic algorithm for cardiac dysfunction remains uncertain. Studies estimating the added value of natriuretic peptides beyond history taking and clinical examination or ECG, representing everyday clinical practice, remain extremely scarce. Fourth, there is the question which natriuretic peptide, BNP or NT-proBNP, is best used in general practice.

5.

NATRIURETIC PEPTIDE TESTING IN THE ELDERLY: LIGHTHOUSE IN THE MIST?

Clinicians will be more and more confronted with complex geriatric patients, who often present with multimorbidity and

polypharmacy. Furthermore, the diagnosis of chronic heart failure is notoriously difficult, especially in old age, when many other possible causes for dyspnea, fatigue or peripheral edema may exist. Natriuretic peptides might be an easy, accessible marker to identify patients at risk. However, as shown, many questions about the implications of natriuretic peptides in clinical practice remain unresolved, especially in the elderly. Therefore, this thesis sets out to examine part of the evidence concerning the relevance of natriuretic peptide testing in the elderly in clinical practice.

The thesis consists of two parts. The first part comprises the first three chapters and comes from an intensive collaboration with the Department of Public Health and Primary Care of the Leiden University Medical Center in The Netherlands, analysing data from their Leiden 85-plus Study and performing a systematic review. The second part, chapters 4 to 7, concerns the design of the BELFRAIL study and cross-sectional analysis of data originating from this study.

CHAPTER 1 describes the association between NT-proBNP levels, indicators of general health and functioning, cardiac morbidity and mortality in 274 nonagenarians from the Leiden 85-plus Study. As discussed before, the interpretation of high levels of natriuretic peptides in old age may be blurred by the high prevalence of comorbidities. Therefore, the hypothesis that natriuretic peptides are possibly more a marker of failing general homeostasis, an aspecific indicator of poor health status and poor functioning, rather than a specific marker of cardiac morbidity is further investigated. **CHAPTER 2** reports the findings of a systematic review to evaluate the diagnostic accuracy of plasma natriuretic peptide measurement in elderly patients from the general population. As most evidence using the diagnostic characteristics of natriuretic peptides is derived from hospital-based studies in younger populations, diagnostic cohort and cross-sectional studies on the accuracy of natriuretic peptides for diagnosis of cardiac dysfunction or chronic heart failure in people aged 75 and over in the community are sought for. In **CHAPTER 3** the relationship between NT-proBNP levels and structural and functional cardiac abnormalities is studied in a convenience

sample of "well-functioning" nonagenarians of the Leiden 85-plus Study, and the use of NT-proBNP levels to exclude structural and functional cardiac abnormalities in this age group is evaluated.

CHAPTER 4 presents the methodology of the BELFRAIL study that was designed to investigate further the implementation of natriuretic peptides in daily practice. All 567 study participants, aged 80 and older, were thoroughly examined by their general practitioner and a clinical research assistant, had an echocardiography performed at home by a trained cardiologist and a blood test done in the morning. **CHAPTER 5** describes the prevalence of echocardiographic abnormalities and severe cardiac dysfunction in participants from the BELFRAIL study. Furthermore, the correlation between structural and functional echocardiographic abnormalities and poor physical and cognitive functioning is explored. In **CHAPTER 6** the hypothesis that natriuretic peptides are a marker of pancardiac damage is further investigated. As multiple determinants are known to influence natriuretic peptide levels, the impact of confounders on the diagnostic performance of natriuretic peptides for severe cardiac dysfunction is also studied. Moreover, the diagnostic accuracy of BNP and NT-proBNP is compared. **CHAPTER 7** assesses the added diagnostic value of natriuretic peptides and an electrocardiogram (ECG) beyond previous medical history, anamnesis, physical examination and routine laboratory tests for severe cardiac dysfunction, representing everyday clinical practice. Logistic regression analysis and Classification and Regression Trees (CART) analysis will be used as analytical tools to analyse data from an "intention to diagnose" perspective.

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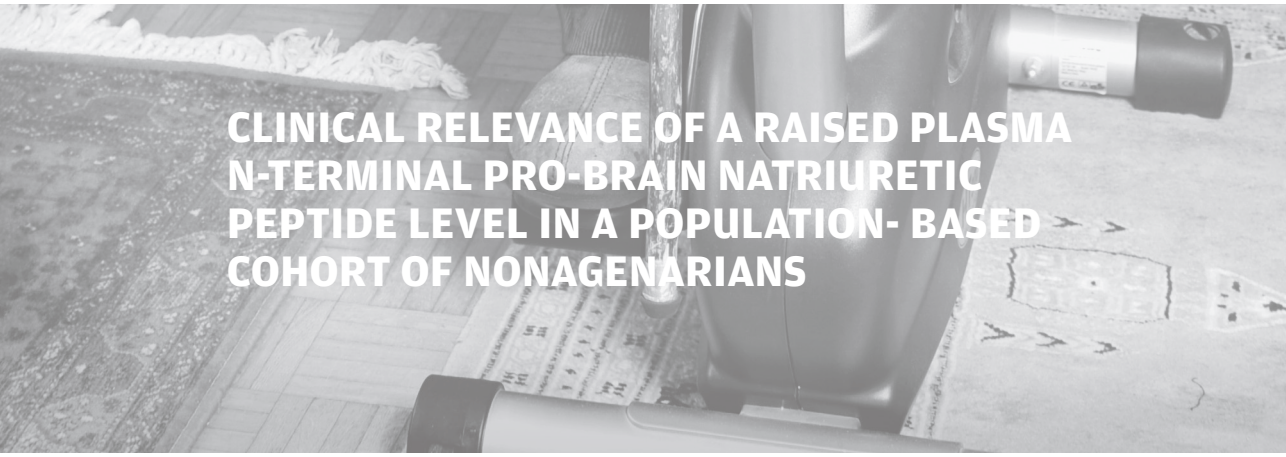
CHAPTER 1



CLINICAL RELEVANCE OF A RAISED PLASMA N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE LEVEL IN A POPULATION- BASED COHORT OF NONAGENARIANS

Bert Vaes, Wouter de Ruijter, Jan Degryse, Rudi GJ Westendorp, Jacobijn Gussekloo

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ABSTRACT

Objectives: To investigate whether plasma NT-proBNP remains a specific marker of cardiac illness in very old age and is able to identify very elderly at high risk for death independent from the presence of known cardiac diagnoses.

Design: Prospective, observational, population-based follow-up study within the Leiden 85-Plus Study of a 2-year birth cohort (1912-1914).

Setting: General population, municipality of Leiden, the Netherlands.

Participants: A total of 274 participants were followed up from age 90 onwards (median follow-up 42.3 months, interquartile range 20.2 to 50.2 months).

Measurements: Plasma NT-proBNP level, indicators of general health and functioning, and specific cardiac diagnoses at age 90 and mortality from age 90 onwards.

Results: Plasma levels of NT-proBNP were not correlated to indicators of poor health or poor functioning. However, the level of NT-proBNP increased significantly with increasing numbers of cardiac diagnoses ($p < 0.001$). High NT-proBNP was associated with overall mortality, both in participants with specific cardiac diagnoses (HR 2.8, 95% CI 1.5–5.2) and without (HR 3.5, 95% CI 1.6–7.5). This was also found for cardiovascular mortality risks (with specific cardiac diagnoses HR 4.1 (95% CI 1.5–11) versus without HR 5.6 (95% CI 1.0–30)) and noncardiovascular mortality risks (with specific cardiac diagnoses HR 1.9 (95% CI 0.84–4.5) versus without HR 3.4 (95% CI 1.3–8.6)).

Conclusion: Plasma NT-proBNP is still a disease specific marker of cardiac illness in nonagenarians and can possibly be used as a predictor of mortality, both in elderly with and without specific cardiac diagnoses.

INTRODUCTION

In our aging society chronic heart failure is becoming more frequent. The prevalence increases with age from 2.7% in people aged 65–74 years to 13.0% in those aged 75–84 years[1]. The diagnosis of chronic heart failure is notoriously difficult, especially in old age when multiple comorbid conditions are present and many other possible causes for dyspnea, fatigue or peripheral edema may exist. Poor availability of routine echocardiography in the community results in considerable over- and under diagnosis of heart failure[2, 3]. This emphasizes the need for a simple, easily applicable test to identify the patients at risk. N-terminal pro-brain natriuretic peptide (NT-proBNP) is gaining recognition as a diagnostic marker for heart failure[4] and a determinant of prognosis[5]. Most studies however investigated the relationship between NT-proBNP and cardiac dysfunction and prognosis in younger populations and were hospital based. Some scarce population-based studies performed in elderly (sub)populations[6-9] found limited evidence for these associations in patients above 75 years old.

Multiple determinants are known to influence circulating levels of natriuretic peptides. An understanding of these determinants is a prerequisite for its optimal use as a diagnostic tool for cardiac dysfunction in the community[10]. However, as the prevalence of possible determinants increases, especially in the very elderly, the usefulness of NT-proBNP may be limited. The interpretation of high plasma levels of NT-proBNP in very old age may be blurred by the high prevalence of comorbidities like renal failure or chronic obstructive pulmonary disease. In line with this, it is unclear whether the association between plasma NT-proBNP and cardiac morbidity, as a precursor of cardiac dysfunction and chronic heart failure, and prognosis holds in very elderly people. Possibly NT-proBNP in very old age is more a marker of failing general homeostasis, an aspecific indicator of poor health status and poor functioning, rather than a specific marker of cardiac morbidity.

Therefore we set out to study the associations between

plasma NT-proBNP and indicators of general health and functioning, cardiac morbidity and mortality in the Leiden 85-plus Study, a prospective population-based cohort of nonagenarians.

METHODS

Study Population

The Leiden 85-plus Study is an observational, prospective population-based study of inhabitants of the city of Leiden, The Netherlands. The study design and characteristics of the cohort were previously described in detail[11]. In short, between September 1997 and September 1999 all
705 members of the 1912 to 1914 birth cohort in the city of Leiden were asked to participate in the month after their 85th birthday. There were no exclusion criteria regarding health status or demographic characteristics. At baseline and yearly up to the age of 90, the participants were visited at their place of residence. A medical history was obtained annually from the participant's general practitioner or nursing home physician, and information on the use of medication was obtained from the participant's pharmacist. All participants in the study gave informed consent and the Medical Ethics Commission of the Leiden University Medical Center approved the study. For the current study, determinants and covariates were measured at age 90 years and participants followed for mortality from age 90 onwards.

Plasma NT-proBNP Levels at Age 90

Plasma levels of NT-proBNP for all participants at age 90 were measured in one batch using the NT-proBNP assay of Roche Diagnostics (Mannheim, Germany) on a Roche Modular E-170 automated immunoanalyzer. The within-run coefficient of variation was less than 2% and total variation was less than 6% at all levels measured (400–13500 pg/mL). Levels of NT-proBNP for men and women were ranked into tertiles separately. Gender-specific tertiles

were composed by combining the tertiles of men with the tertiles of women.

Clinical Characteristics

Each participant's general practitioner (or, if applicable, nursing home physician) was interviewed annually about the patient's medical history, using standardized questionnaires, including questions on present and past cardiovascular and noncardiovascular morbidities. Specific cardiac diagnoses were defined as a positive response from the general practitioner to questions about previously diagnosed myocardial infarction, angina pectoris, arrhythmias or heart failure, or an ECG at age 90 years revealing a prior myocardial infarction (Minnesota Code 1-1 or 1-2, excluding 1-2-8), atrial fibrillation (Minnesota Code 8-3-1) and left ventricular hypertrophy (Minnesota Code 310, 330 or 340)[12]. Other vascular morbidity was defined as a positive response from the general practitioner to questions about previously diagnosed noncardiac vascular morbidity including stroke and peripheral arterial disease.

The cardiovascular risk profile includes diabetes mellitus, diagnosis of hypertension and plasma levels of lipids. Diabetes was considered present in cases of diagnosis in the medical record, a nonfasting glucose level higher than 11 mmol/L, or the use of antidiabetic medication. Blood samples were taken for measurement of total cholesterol, LDL- and HDL-cholesterol and triglycerides. The cutoff level for high total cholesterol was set at 5.0 mmol/L, for high LDL-cholesterol 2.5 mmol/L, for low HDL-cholesterol at 1.0 mmol/L and for high triglycerides at 2.0 mmol/L[13].

Noncardiovascular morbidity was defined as a positive response from the general practitioner to one or more questions about previously diagnosed Parkinson's disease, chronic obstructive pulmonary disease, arthrosis (including rheumatoid arthritis and polymyalgia rheumatica), malignancies and/or hip fracture.

Evaluation of the functional status of participants included measures of cognitive function, subjective well-being, disability and depressive symptoms. Cognitive function was assessed by the

Mini-Mental State Examination (MMSE), with scores ranging from 0 to 30 points (optimal)[14]. A MMSE score below 19 points was considered to be poor cognitive functioning. Subjective well-being was tested with a visual analogue scale (CANTRIL) in those with MMSE > 18 points, scores ranging from 0 to 10 (optimal)[14]. A CANTRIL score below 7 points was considered to be poor. Disability was assessed on the Groningen Activity Restriction Scale (GARS), which is a combination of nine items relating to activities of daily living (ADLs) and nine items relating to instrumental ADLs, scores range from 18 (optimal) to 72 points[14]. A GARS score above 55 points was considered to represent poor functioning. Depressive symptoms were measured in those with MMSE > 18 points, using the 15-item Geriatric Depression Scale (GDS-15), with scores ranging from 0 (optimal) to 15 points[14]. A GDS-15 score above 4 was considered to be poor.

C-reactive protein, hemoglobin levels and renal function were measured as parameters reflecting general health status. Renal function was assessed by renal clearance (GFR, glomerular filtration rate) estimated by the MDRD (Modification of Diet in Renal Disease Study Group)[15]. CRP levels > 4 mg/L, GFR < 60 mL/min/1.73m^2 and hemoglobin levels < 7.5 mmol/L (for women) and < 8.1 mmol/L (for men) were considered to reflect poor health status.

Mortality

All participants were followed for mortality from age 90 years until the census date (11th February 2008) using data from the municipal Register Office. Causes of death were obtained from Statistics Netherlands, where all national death certificates are coded according to the International Classification of Diseases and Related Disorders, 10th revision (ICD-10)[16]. The causes of death were divided into cardiovascular (ICD-10 codes I00–I99) and noncardiovascular causes (all other ICD-10 codes). The assignment of cause of death was made independently of any study results.

Possible Confounding Variables

Possible confounding variables are body mass index

(BMI), renal dysfunction, hemoglobin levels and heart failure medication[17–20]. BMI at age 90 years was assessed by measuring height and weight and data on relevant cardiovascular medication including diuretics, beta-blockers, ACE inhibitors, angiotensin II receptor blockers and digitalis were included.

Data Analysis

Odds ratios (OR) with the corresponding 95% confidence intervals (CI) were calculated by logistic regression analysis with the first (lowest) tertile of NT-proBNP as the reference group, and adjusted for height, weight, renal clearance, hemoglobin level and cardiovascular medication.
Linear regression analysis was used to examine the association between Log-transformed levels of NT-proBNP and gender and number of cardiac diagnoses.

After stratification for presence of specific cardiac diagnoses, gender-specific tertiles of NT-proBNP were plotted in Kaplan–Meier curves representing cumulative mortality during follow-up, and compared using a log-rank test. Mortality risks with corresponding 95% confidence intervals, stratified for presence of specific cardiac diagnoses, were calculated in a Cox proportional hazard model and adjusted for height, weight, renal clearance, hemoglobin level and cardiovascular medication.

Data analysis was performed using SPSS 14.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

At 90 years of age 323 individuals of the initial cohort of 599 who participated at age 85 had died. NT-proBNP was determined in 274 of the remaining 276 individuals. Their sociodemographic, functional and clinical characteristics are described in Table 1. Most participants lived at home (61.9%), showed no severe cognitive impairment (73.4%) and were not .

Table 1. Sociodemographic data, functional status and clinical characteristics of participants at age 90 years (n = 274)

Sociodemographic data	
Male	76 (27.7%)
Institutionalized	104 (38.1%)
Education ≤ 6 yrs primary school	170 (62.0%)
Income < €750/month	139 (51.1%)
Functional status	
Cognitive impairment (MMSE ≤ 18)	72 (26.6%)
Poor well-being (CANTRIL < 7)	51 (25.8%)
Dependent in daily living (GARS ≥ 56)	68 (25.1%)
Depression (GDS-15 ≥ 5)	48 (24.0%)
Clinical characteristics	
Cardiovascular morbidity	180 (65.7%)
Specific cardiac diagnoses[a]	167 (60.9%)
Other vascular morbidity[b]	44 (16.4%)
Noncardiovascular morbidity[c]	175 (63.9%)
Anemia	62 (23.9%)
CRP > 4 mg/mL	110 (40.9%)
GFR < 60 mL/min/1.73m²	143 (52.2%)

[a]Including history of myocardial infarction (clinical or ECG), angina pectoris, arrhythmias, heart failure, and ECG with atrial fibrillation or left ventricular hypertrophy. [b]Including history of stroke and peripheral vascular disease. [c]Including history of Parkinson's disease, chronic obstructive pulmonary disease, arthritis (including arthrosis, rheumatoid arthritis and polymyalgia rheumatica), malignancies and hip fracture.

strongly dependent on others in activities of daily living (74.9%). There was a high burden of cardiovascular (65.7%) and noncardiovascular (63.9%) morbidity. Specific cardiac diagnoses were present in 60.9% of participants.

Plasma NT-proBNP was higher for men than for women

(770.1 pg/mL (IQR 236.35 to 2017.5 pg/mL) versus 405.9 pg/mL (IQR 235.7 to 882.35 pg/mL), Mann–Whitney, $p = 0.019$), also after adjustment for weight, height, GFR, hemoglobin, cardiovascular medication and presence of cardiovascular morbidity ($p = 0.003$). Plasma levels of NT-proBNP were not correlated to indicators of poor health or poor functioning, except a higher risk of renal impairment in participants in the highest tertile compared with those in the first tertile (OR 3.3, 95% CI 1.6–7.0) (Table 2).

Table 3 shows the differences in cardiovascular characteristics between participants based on the tertiles of NT-proBNP. Participants in the highest tertile had an increased burden of cardiovascular morbidity (OR 9.7, 95% CI 3.6–26). When stratified into "specific cardiac diagnoses" and "other vascular morbidity", presence of specific cardiac diagnoses was strongly associated with the highest levels of NT-proBNP (OR 9.7, 95% CI 3.8–25). Participants with the highest plasma levels of NT-proBNP had an increased risk of having a history of myocardial infarction (OR 3.4, 95% CI 1.3–8.4) and arrhythmias (OR 2.2, 95% 1.0-4.7), and showed a significantly higher prevalence of heart failure (OR 2.7, 95% CI 1.1–6.5). Specific cardiac diagnoses, as investigated by an electrocardiogram, showed a higher prevalence of atrial fibrillation (OR 20, 95% CI 4.8–83) and left ventricular hypertrophy (OR 3.7, 95% 1.0–13) for participants in the highest tertile. The prevalence of a clear ECG at the age of 90 was 16.1%. The odds ratio for a clean ECG was significantly lower for participants in the highest tertile (OR 0.093, 95% CI 0.024–0.36). The median level of NT-proBNP raised with increasing number of specific cardiac diagnoses (Jonckheere-Terpstra, $p < 0.001$): 306.7 pg/mL (IQR 172.2 to 507.0 pg/mL) for 0 diagnoses, 447.8 pg/mL (IQR 239.5 to 1249.3 pg/mL) for 1 diagnosis, 748.8 pg/mL (IQR 348.9 to 1934.8 pg/mL) for 2 diagnoses, 982.9 pg/mL (IQR 368.0 to 2293.0 pg/mL) for 3 diagnoses and 1779.5 pg/mL (IQR 510.4 to 5258.0 pg/mL) for ≥4 diagnoses. The association between NT-proBNP and number of cardiac diagnoses remained significant after adjustment for gender, weight, height, GFR, hemoglobin and cardiovascular medication ($p < 0.001$).

Table 2. The correlation between levels of plasma NT-proBNP and indicators of poor health and poor functioning in participants aged 90 years (n=274).

	Gender-Specific Tertiles of NT-proBNP			P for trend
	T1 (n = 91)	T2 (n = 92)	T3 (n = 91)	
Noncardiovascular morbidity[a]	1	1.4 (0.71 – 2.8)	1.2 (0.59 – 2.6)	0.54
Anemia[b]	1	1.5 (0.60 – 3.6)	2.1 (0.84 – 5.2)	0.11
CRP > 4 mg/L	1	1.6 (0.82 – 3.3)	2.0 (0.94 – 4.2)	0.069
GFR < 60 mL/min/1.73m² [c]	1	1.6 (0.81 – 3.0)	3.3 (1.6 – 7.0)	0.002
Institutionalized	1	0.86 (0.43 – 1.7)	1.2 (0.59 – 2.6)	0.62
Cognitive impairment (MMSE ≤ 18)	1	1.2 (0.54 – 2.8)	1.2 (0.48 – 2.9)	0.70
Poor well-being (CANTRIL < 7)	1	1.4 (0.62 – 3.4)	1.3 (0.47 – 3.4)	0.59
Dependent in daily living (GARS ≥ 56)	1	1.0 (0.41 – 2.4)	1.0 (0.39 – 2.8)	0.94
Depressive symptoms (GDS-15 ≥ 5)	1	0.98 (0.40 – 2.4)	1.7 (0.64 – 4.7)	0.32

Data are presented as Odds Ratios with corresponding 95% Confidence Intervals, adjusted for height, weight, renal function (MDRD), hemoglobin and cardiovascular medication. Q1 was used as reference. Second and highest tertile cutoff values: 347.5 pg/mL and 1771.0 pg/mL in men and 284.0 pg/mL and 675.3 pg/mL in women. [a]Including history of Parkinson's disease, chronic obstructive pulmonary disease, arthritis (including arthrosis, rheumatoid arthritis and polymyalgia rheumatica), malignancies and hip fracture. [b]Hemoglobin < 7.5 mmol/L for women, < 8.1 mmol/L for men, adjusted for height, weight, renal function (MDRD) and cardiovascular medication. [c] Adjusted for height, weight, hemoglobin and cardiovascular medication.

Table 3. The association between plasma NT-proBNP and cardiovascular characteristics in participants aged 90 years (n = 274).

	n (%)	Gender-Specific Tertiles of NT-proBNP			P for trend
		T1 (n = 91)	T2 (n = 92)	T3 (n = 91)	
Cardiovascular morbidity	180 (65.7)	1	1.3 (0.67 – 2.4)	9.7 (3.6 – 26)	< 0.001
Specific cardiac diagnoses[a]	167 (60.9)	1	1.4 (0.75 – 2.7)	9.7 (3.8 – 25)	< 0.001
Myocardial infarction (clinical and ECG)	57 (20.8)	1	0.89 (0.33 – 2.4)	3.4 (1.3 – 8.4)	0.007
Angina pectoris	58 (21.6)	1	0.90 (0.38 – 2.1)	1.9 (0.81 – 4.4)	0.14
Arrhythmias	77 (28.6)	1	0.83 (0.39 – 1.8)	2.2 (1.0 – 4.7)	0.045
Diagnosis of heart failure Table	59 (21.9)	1	1.5 (0.63 – 3.5)	2.7 (1.1 – 6.5)	0.030
ECG-findings					
Atrial fibrillation on ECG	33 (12.1)	1	0.69 (0.11 – 4.5)	20 (4.8 – 83)	< 0.001
Left ventricular hypertrophy	30 (10.9)	1	2.4 (0.71 – 8.5)	3.7 (1.0 – 13)	0.042
Normal ECG	44 (16.1)	1	0.60 (0.27 – 1.3)	0.093 (0.024 – 0.36)	< 0.001
Other vascular morbidity[b]	44 (16.4)	1	1.3 (0.50 – 3.5)	1.4 (0.48 – 4.0)	0.55
Stroke	21 (7.8)	1	0.72 (0.16 – 3.3)	0.96 (0.19 – 4.9)	0.91
Peripheral arterial disease	29 (10.8)	1	2.2 (0.70 – 7.1)	2.3 (0.67 – 7.9)	0.20
Cardiovascular risk profile					
Diabetes mellitus*	45 (18.4)	1	1.8 (0.76 – 4.1)	1.0 (0.39 – 2.8)	0.88
Hypertension**	151 (56.1)	1	1.2 (0.59 – 2.3)	1.8 (0.85 – 3.9)	0.14
Cholesterol ≥ 5 mmol/L	164 (59.9)	1	0.99 (0.48 – 2.0)	0.56 (0.26 – 1.2)	0.15
LDL ≥ 2.5 mmol/L	193 (70.7)	1	0.64 (0.29 – 1.4)	0.48 (0.21 – 1.1)	0.083
HDL < 1 mmol/L	19 (6.9)	1	0.34 (0.057 – 2.0)	0.96 (0.21 – 4.3)	0.96
Triglycerides ≥ 2 mmol/L	50 (18.2)	1	1.1 (0.47 – 2.4)	0.40 (0.13 – 1.2)	0.14
BMI > 25kg/m² (n = 151)***	151 (64.3)	1	0.52 (0.26 – 1.0)	0.29 (0.14 – 0.62)	0.001

Data are presented as Odds Ratios with corresponding 95% Confidence Intervals, adjusted for height, weight, renal function (MDRD), hemoglobin and cardiovascular medication. Q1 was used as reference category. [a]Including history of myocardial infarction (clinical or ECG), angina pectoris, arrhythmias, heart failure, and ECG with atrial fibrillation or left ventricular hypertrophy. [b]Including history of stroke and peripheral vascular disease. *According to GP OR (nonfasting) glycemia > 11 mmol/L OR diabetes medication. **History of hypertension according to GP. ***Adjusted for renal function (MDRD), hemoglobin and cardiovascular medication.

The median follow-up was 42.3 months (interquartile range 20.2 to 50.2 months). During follow-up 170 deaths (62%) occurred; 58 participants (34%) died from cardiovascular causes and 107 (63%) from noncardiovascular causes. The specific cause of five deaths (3%) remains unknown. Figure 1 presents the cumulative mortality for gender-specific tertiles of NT-proBNP from age 90 years onwards, stratified for the presence of specific cardiac diagnoses. Increasing plasma levels of NT-proBNP were associated with increasing cumulative mortality in both strata (Log-rank test, $p < 0.001$). This association was not only present for overall mortality, but also for both cardiovascular and noncardiovascular mortality, independent from the presence of specific cardiac diagnoses (Figure 1). After adjustment for known confounding variables the hazard ratio (HR) for risk of mortality from all causes for the highest tertile compared with the lowest tertile was 2.8 (95% CI 1.5–5.2) in the group with and 3.5 (95% CI 1.6–7.5) in the group without specific cardiac diagnoses (Table 4). Similar results were observed for cardiovascular mortality risk (adjusted HR 4.5 (95% CI 1.5–11) and adjusted HR 5.6 (95% CI 1.0–30), for the group with and without specific cardiac diagnoses, respectively) and noncardiovascular mortality risk (adjusted HR 1.9 (95% CI 0.84–4.5) and adjusted HR 3.4 (95% CI 1.3–8.6), for the group with and without specific cardiac diagnoses, respectively) (Table 4).

DISCUSSION

In a large population-based sample of 90-year-old participants, we found a strong and specific correlation between plasma NT-proBNP and specific cardiac diagnoses. More specifically high plasma levels of NT-proBNP were correlated with a history of myocardial infarction, arrhythmias and heart failure, and with atrial fibrillation and left ventricular hypertrophy on ECG. Moreover, the level of NT-proBNP increased significantly with the number of cardiac diagnoses. We found NT-proBNP to be a good predictor for both cardiovascular and noncardiovascular mortality in individuals

at age 90 and above, both in elderly with and without specific cardiac diagnoses.

To date, there are few published data on the relationship between natriuretic peptides, morbidity and mortality in the very elderly. Wallen et al. showed that high BNP concentrations were predictive for atrial fibrillation, ischemic heart disease and congestive heart failure in a community-based population of 85-year-old people[21]. In a more heterogeneous and younger population (range 45–91 years) Galasko et al. showed that left ventricular hypertrophy, ischemic heart disease, atrial fibrillation, valvular heart disease and peripheral vascular disease were independent predictors of raised NT-proBNP concentrations[22]. Some studies have already reported the association between high plasma levels of natriuretic peptides and increased total and cardiovascular mortality, not only in the elderly from the general population[7, 23], but also in selected elderly populations such as healthy community-dwelling elderly[24], patients in nursing homes[6] and elderly patients in general practice with heart failure[25]. Our results are in line with these studies

Although in our study high levels of NT-proBNP were specifically correlated with presence of specific cardiac diagnoses, plasma NT-proBNP was associated with both cardiovascular and noncardiovascular mortality, and was able to predict mortality in participants with and without specific cardiac diagnoses. How can we explain the prognostic characteristics for mortality of NT-proBNP that we found in this study population? Participants in the highest tertiles were not functionally more disabled, did not have more noncardiovascular or other vascular morbidities, nor did they have a higher cardiovascular risk profile than participants in the lower tertiles. Concentrations of natriuretic peptides are related to left ventricular filling pressures[26] and wall stress[27]. Our data showed that an increasing level of NT-proBNP possibly indicates the severity of cardiac illness. In participants without known cardiac morbidity elevated levels of NT-proBNP possibly reflect unknown cardiac morbidity or imminent heart failure. In a 90-year-old patient with severe pneumonia, not only clinical heart failure but also imminent

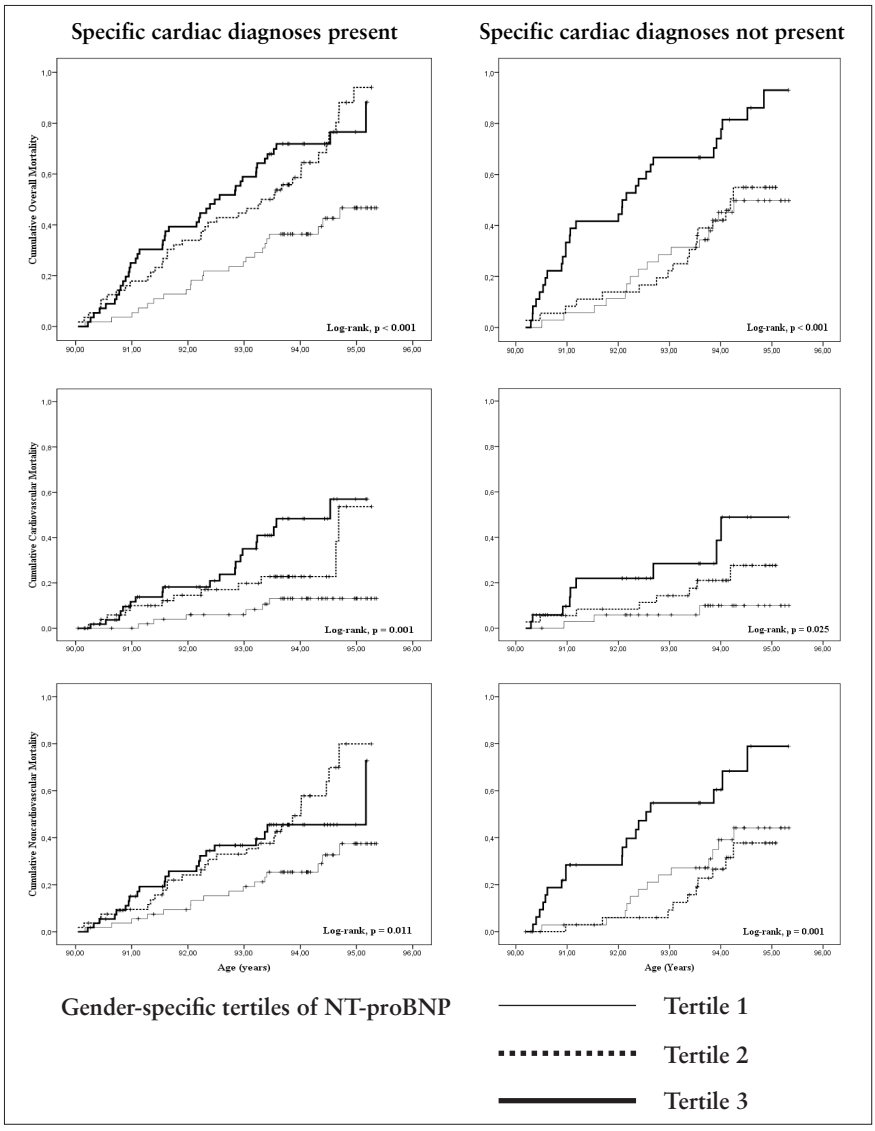

Figure 1. Cumulative overall, cardiovascular and non cardiovascular mortality based on genderspecific tertiles of NT-proBNP stratified for presence of specific cardiac diagnoses. Second and highest tertile cutoff values: 912.8 pg/mL and 2348.0 pg/mL in men and 326.2 pg/mL and 876.3 pg/mL in women, with specific cardiac diagnoses. Second and highest tertile cutoff values: 211.1 pg/mL and 460.7 pg/mL in men and 209.7 pg/mL and 408.4 pg/mL in women, without specific cardiac diagnoses.

Table 4. Overall and cause-specific mortality risks depending on plasma NT-proBNP from age 90 upwards, stratified for presence of specific cardiac disorders.

Specific cardiac diagnoses present	Gender-Specific Tertiles of NT-proBNP			P for trend
	T1 (n = 55)	T2 (n = 56)	T3 (n = 56)	
Observed number of deaths (n)	23	41	42	
Overall Mortality	1	2.5 (1.4 – 4.4)	2.8 (1.5 – 5.2)	0.001
Cardiovascular Mortality	1	2.3 (0.84 – 6.5)	4.1 (1.5 – 11)	0.005
Noncardiovascular Mortality	1	2.7 (1.3 – 5.5)	1.9 (0.84 – 4.5)	0.093
Specific cardiac diagnoses not present	**Gender-Specific Tertiles of NT-proBNP**			**P for trend**
	T1 (n = 35)	T2 (n = 36)	T3 (n = 36)	
Observed number of deaths (n)	16	18	30	
Overall Mortality	1	1.1 (0.50 – 2.5)	3.5 (1.6 – 7.5)	0.003
Cardiovascular Mortality	1	4.2 (0.85 – 21)	5.6 (1.0 – 30)	0.034
Noncardiovascular Mortality	1	0.57 (0.20 – 1.6)	3.4 (1.3 – 8.6)	0.045

Hazard Ratios and corresponding 95% Confidence Intervals were estimated by Cox proportional hazard models, adjusted for weight, height, renal function (MDRD), hemoglobin and cardiovascular medication.

cardiac dysfunction indicates a decreased cardiac reserve and the pneumonia could have more serious consequences including death.

Our study is the first to investigate the predictive value of NT-proBNP in a population-based sample of the very old independent from the presence of specific cardiac diagnoses. The Leiden 85-plus Study is a population-based prospective follow-up study with extensive functional and clinical measurements and virtually complete follow-up for mortality. Our study is the first to show that NT-proBNP is not a marker of failing general homeostasis, as measured with indicators of poor health or poor functioning, but remains a disease specific marker of cardiac illness in a population of the very old presenting a high burden of comorbidity. It could be seen as a limitation that we have no data to correlate plasma levels of NT-proBNP to objective echocardiographic measurements, but because we decided to do all data collection of the Leiden 85-plus Study during home visits to improve participation rates and reduce drop outs, this was not technically feasible. Comorbidities may have been underdiagnosed, since they were not actually assessed but reported by the general practitioner. Since any underreporting was independent from plasma levels of NT-proBNP, this is not underlying our results. There was possibly a non-differential misclassification of cause of death, but the assignment of cause of death was made independently of any study results.

CONCLUSION

Plasma NT-proBNP remains a disease specific marker of cardiac illness in nonagenarians and can possibly be used as a predictor of mortality independent from the presence of known cardiac diagnoses. However, further research is needed to investigate the diagnostic accuracy of NT-proBNP for cardiac dysfunction in the very old, as well as the possibilities and effect of NT-proBNP guided treatment for those with high levels of plasma NT-proBNP.

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Author Contributions: Westendorp and Gussekloo were responsible for study concept and design, as well as acquisition of subjects and data. All authors participated in analysis and interpretation of data and preparation of the manuscript.

Sponsor's Role: The sponsor had no role in the design, methods, subject recruitment, data collection, analysis, or preparation of the manuscript.

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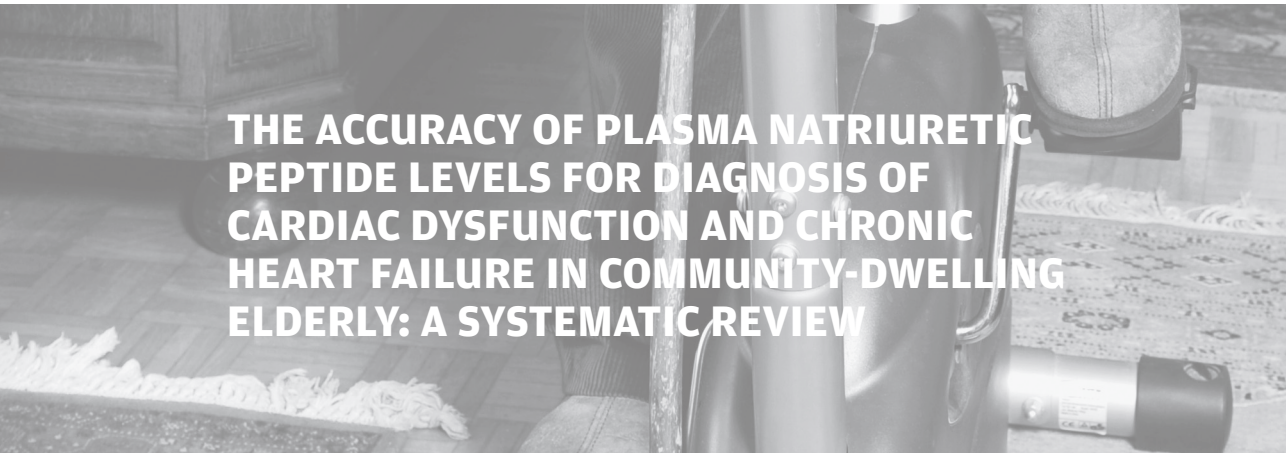
CHAPTER 2



THE ACCURACY OF PLASMA NATRIURETIC PEPTIDE LEVELS FOR DIAGNOSIS OF CARDIAC DYSFUNCTION AND CHRONIC HEART FAILURE IN COMMUNITY-DWELLING ELDERLY: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Measurement of plasma natriuretic peptide levels has been proposed as a simple, accessible test to assist the diagnosis of cardiac dysfunction and heart failure. Most studies have been hospital-based and have investigated the relationship between natriuretic peptides and cardiac dysfunction or heart failure in younger populations.

Objective: We performed a systematic review to evaluate the diagnostic accuracy of plasma natriuretic peptide measurement in elderly patients from the general population.

Methods: Electronic searches of MEDLINE and EMBASE from January 1985 to May 2008 were performed. Diagnostic cohort and cross-sectional studies on the accuracy of natriuretic peptides for diagnosis of cardiac dysfunction or chronic heart failure in people aged 75 and over in the community were included. The quality of the selected studies was assessed with the modified QUADAS tool and the data extracted by two independent reviewers.

Results: Five studies were included. The general quality of the studies was moderate. The extracted data could not be pooled. Negative likelihood ratios for cardiac dysfunction ranged from 0.09 to 0.29.

Conclusion: We found limited evidence supporting the use of plasma natriuretic peptide measurement for diagnosis of cardiac dysfunction or heart failure in the elderly of 75 years and over in the general population. Important questions about the implementation of plasma natriuretic peptide measurement in daily practice remain unresolved.

INTRODUCTION

In our ageing society the burden of chronic heart failure is rising. The prevalence increases with age from 0.7% in people aged 55–64 years to 2.7% in those aged 65–74 years and 13.0% in those aged 75–84 years[1]. Heart failure not only has negative consequences for functional status and well-being but also leads to increased mortality[1]. However, diagnosing chronic heart failure is notoriously difficult, especially in the elderly who often have multiple co-morbidities and may present with many other possible causes for dyspnoea, fatigue or peripheral oedema. With increasing average patient age, primary care physicians will become increasingly important as the principal diagnosticians and treating physicians. In this setting poor availability of routine echocardiography leads to considerable over- and under-diagnosis of heart failure[2, 3]. This emphasizes the need for a simple test, easily applicable in primary care settings, to identify the elderly patients at risk and to initiate timely treatment to reduce mortality and improve quality of life.

Over the last decade, brain natriuretic peptide (BNP) and its amino-terminal portion N-terminal pro-brain natriuretic peptide (NT-proBNP) have been extensively studied. Not only their accuracy as diagnostic markers for cardiac dysfunction and heart failure[4-9] but also their possible applications as prognostic markers[10] and therapeutic agents[11] have been investigated. However, most studies are hospital-based and have investigated the relationship between natriuretic peptide levels and cardiac dysfunction or heart failure in younger populations. Because age has been shown to be an important confounder for the plasma level of natriuretic peptides[12, 13], cut-off values used in younger populations cannot be applied in old age. In addition, because of a different prevalence (pre-test probability) of cardiac dysfunction and heart failure in inpatient and outpatient settings, results from hospital-based studies cannot be extrapolated to primary care settings.

Therefore we performed a systematic review to investigate the accuracy of plasma natriuretic peptide levels for diagnosis of cardiac dysfunction and heart failure in community-dwelling people aged 75 and over.

METHODS

Search question and search strategy

A "PIRT" (**P**atient–**I**ndex test–**R**eference test–**T**arget condition), analogous to the "PICO"[14] (**P**atient–**I**ntervention–**C**omparison–**O**utcome) for systematic reviews of interventional studies, was created for systematic review of diagnostic studies. To create a homogeneous study population of elderly patients, we searched for population-based studies that included only patients aged 75 years and over, or studies with subgroup analysis of patients aged 75 years and over. Only studies that were based in the general population or studies with participants referred for further investigation by a general practitioner were included. Natriuretic peptides represented the index test of the search and no restriction for a specific type of test was used. Because of the absence of a gold-standard test for cardiac dysfunction and heart failure, all possible reference tests were included. The target condition was cardiac dysfunction, systolic and/or diastolic, and chronic heart failure. Based on the results of the search, subgroup analyses for index and reference test and target condition were performed to guarantee homogeneity.

MEDLINE (PubMed) and EMBASE data from January 1985 to 31 May 2008 were searched for all studies of the accuracy of natriuretic peptides for diagnosis of cardiac dysfunction or chronic heart failure. To have a large safety net a broad search strategy based only on the index test and target condition was constructed. In MEDLINE, the MeSH term "Aged" was added. The search strategy for MEDLINE and EMBASE is available from the authors. Additional searching of reference lists of relevant articles and reviews was performed.

Selection of studies

Both population-based diagnostic cohort and cross-sectional studies were included, with no language restrictions. Case-control studies, studies investigating acute dyspnoea or acute heart failure, studies in specific patient populations (e.g., patients with chronic

obstructive pulmonary disease, diabetics) and studies examining the use of natriuretic peptides as prognostic markers or therapeutic agents were all excluded.

The first reviewer (B.V.) divided the resulting articles into three categories (definitely excluded, included and in doubt) based on title and abstract. All studies in the last two categories, plus a random selection of the excluded articles, were checked by the second reviewer (W.R.). Disagreements were resolved by consensus or by a third reviewer (J.D.). A log of the excluded articles, with the reasons for exclusion, was kept.

Quality assessment

Two reviewers (B.V. and W.R.) independently assessed the quality of the selected studies with the modified QUADAS tool[15]. Five extra items, relevant for this systematic review, were added (Table 1).

Data extraction

Each reviewer independently extracted the data from the selected studies. If multiple cut-off values for the natriuretic peptide were presented, the cut-off value giving the greatest sum of sensitivity and specificity was used. For each cut-off value sensitivity, specificity and positive and negative likelihood ratio were reported. The negative likelihood ratio ((1–sensitivity)/specificity) and positive likelihood ratio (sensitivity/(1–specificity)) for all the included studies was calculated, if it was not already available. The likelihood ratio was used to convert the pre-test probability (prevalence) of cardiac dysfunction or heart failure into a post-test probability, which takes the result into account[16]. The post-test probability is the probability that the patient has cardiac dysfunction or heart failure, given a negative or positive test result. The post-test probability for a negative and positive test result (PTP- and PTP+, respectively) was calculated by dividing the post-test odds (likelihood ratio ´ (pre-test probability/(1–pre-test probability))) by (post-test odds + 1). The negative predictive value (NPV) equals one minus the post-test probability of a negative test. The positive predictive value (PPV)

equals the post-test probability of a positive test.

The decision whether to pool the data was based on the number of studies found and the observed differences in index test and target condition used.

Table 1. Modified QUADAS tool and extra items

1. Was the spectrum of patients representative of the patients who will receive the test in practice?
2. Is the reference standard likely to correctly classify the target condition?
3. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
4. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
5. Did patients receive the same reference standard regardless of the index test result?
6. Was the reference standard independent of the index test (i.e., the index test did not form part of the reference standard)?
7. Were the index test results interpreted without knowledge of the results of the reference standard?
8. Were the reference standard results interpreted without knowledge of the results of the index test?
9. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
10. Were uninterpretable/intermediate test results reported?
11. Were withdrawals from the study explained? a. If a cut-off value has been used, was it established before the study was started (pre-specified cut-off value)? b. Is it unlikely that the technology of the index test has changed since the study was carried out? c. Was treatment withheld until both the index test and reference standard were performed? d. Were data on observer variation for the reference test reported and within an acceptable range? e. Were data on instrument variation for the index test reported and within an acceptable range?

RESULTS

The search strategy and results are presented in Figure 1. Five studies that met the inclusion criteria were identified[17-21]. Four population-based studies[22-25] that included participants, or a subgroup of participants, with a mean or median age of 75 years and older, were excluded because they also included patients younger than 75 in their analysis. We differentiated between studies of non-selected populations[17-20], including symptomatic and asymptomatic participants, and a selected population, including only symptomatic participants[21]. Two articles concerned the same study population, but one article analysed the accuracy of BNP[17] and the other NT-proBNP[19] for the diagnosis of cardiac dysfunction.

Table 1 shows the description of the individual items from the "extended" modified QUADAS tool and Table 2 reports the evaluation of each item in the selected studies. The general quality of the studies was moderate, with no study scoring less than 9/16 and a maximum score of 11/16. Item (b) was scored by a specialist in the field. The BNP test from Shionogi[17,18] was considered to be outdated. Several important items were unclear or missing. The study by Sivakumar *et al.*[21] was carried out in an outpatient echocardiography service in a district general hospital, but it was unclear whether the participants were referred only by general practitioners or also by hospital physicians. Most studies did not mention the time period between index test and reference test, so it was impossible to evaluate whether a progression or recovery bias or a treatment paradox was present in these studies. Item 7 was scored "unclear" for all included studies, because it was not mentioned whether the laboratory doctor who interpreted the level of natriuretic peptide was blinded for the results of the reference test. No study used a pre-specified cut-off value. Most studies used discriminatory values derived from Receiver Operating Characteristic analysis.

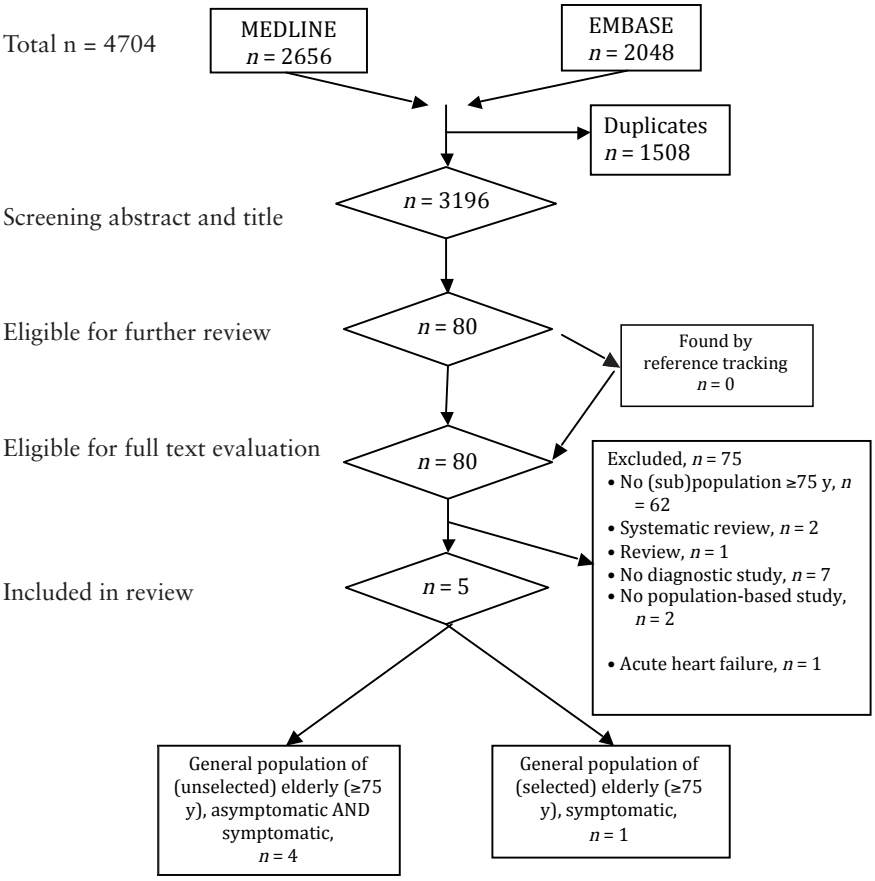

Figure 1. Retrieval of eligible studies: flowchart

Table 3 shows the results for studies from an unselected study population. Hedberg *et al.*[18] included only participants of 75 years old, whereas the other three studies included a subgroup analysis of participants aged 75 years and over. Costello-Boerrigter *et al.*[19] and Abhayaratna *et al.*[20] used NT-proBNP as the index test while Redfield *et al.*[17] and Hedberg *et al.*[18] used BNP. All four used echocardiography as the reference test. An ejection fraction (EF) ≤ 40% was mostly used as the cut-off value. Hedberg *et al.*[18] used the wall motion index that corresponded best to EF < 40% as the target

condition. Abhayaratna *et al.*[20] used a combination of systolic (EF ≤ 40% or EF ≤ 50%) and diastolic dysfunction as target condition. This explains the higher prevalence of the target condition found by Abhayaratna *et al.*[20]. It was not possible to determine the prevalence of the target condition for the study of Redfield *et al.*[17] although this study used the same study population as did Costello-Boerrigter *et al.*[19], because the number of participants receiving one particular index test was different in each study. No statistical analysis for heterogeneity was performed because of the low number of articles found.

Table 2. Qualification of the articles with the modified QUADAS tool and extra items

	1	2	3	4	5	6	7	8	9	10	11	a	b	c	d	e
Unselected population																
Abhayaratna, 2006[20]	+	+	?	+	+	+	?	?	+	–	–	–	+	?	+	+
Costello-Boerrigter 2006[19]	+	+	+	+	+	+	?	+	+	–	–	–	+	+	–	+
Hedberg, 2004[18]	+	+	?	+	+	+	?	+	+	+	+	–	–	?	+	+
Redfield, 2002[17]	+	+	+	+	+	+	?	+	+	?	?	–	–/+	+	–	+
Selected population																
Sivakumar, 2006[21]	?	+	?	+	+	+	?	+	+	+	+	–	+	?	–	–

+ = present; – = not present; ? = unclear

We found negative likelihood ratios ranging from 0.13 to 0.29. The diagnostic impact of natriuretic peptide measurement as expressed by the likelihood ratios depends on the prevalence of the target condition in the population involved (pre-test probability), giving a reduction of a pre-test probability of 21% to a post-test probability of 5.7% for the study of Abhayaratna et al.[20] and a reduction of a pre-test probability of 4.7% to a post-test probability of 0.64% for the study of Costello-Boerrigter et al.[19]. The post-test probability of a positive test was less acceptable, ranging from 21.0 to 59.7%, depending on the pre-test probability.

Because of a different target condition, the diagnostic accuracy for NT-proBNP as determined by Costello-Boerrigter et al.[19] and Abhayaratna et al.[20] is difficult to compare. Costello-Boerrigter et

al.[19] found acceptable gender-specific sensitivities and specificities for systolic dysfunction. Abhayaratna et al.[20] found gender-specific negative likelihood ratios and PTP- in the same range as Costello-Boerrigter et al.[19], for a combined target condition of systolic and diastolic dysfunction with lower cut-off values. Because a 2×2 table could not be extracted from the subgroup analysis by Redfield et al.[17] , the data could not be pooled with that of the study by Hedberg et al.[18]. Hedberg et al.[18] found a negative likelihood ratio for systolic dysfunction in the same range as Redfield et al.[17] with a much lower cut-off value. With this low cut-off value, they found a low PTP- of 1.7% and a low PTP+ of 34.8%.

The one study concerning a selected population investigated the utility of NT-proBNP in a cohort of 100 very elderly (range 75–94 years) patients with suspected cardiac disorders referred for echocardiography[21]. For the diagnosis of systolic dysfunction (EF < 50%, prevalence 25%) the area under the curve (AUC) was 0.71 (95% CI 0.69–0.89). An NT-proBNP level of 424 pg/mL had a sensitivity of 96%, a specificity of 45% and a positive and negative likelihood ratio of 1.75 and 0.09 respectively. The post-test probability for a positive test was 36.8%, the post-test probability for a negative test 2.9%. The authors found that patients with diastolic dysfunction or failure had lower plasma concentrations of NT-proBNP than patients without cardiac dysfunction.

Table 3. Search results for an unselected population ≥ 75 years old

	Abhayaratna, 2006[20]				Costello-Boerrigter, 2006[19]		Hedberg, 2004[18]	Redfield, 2002[17]			
Sample size ≥ 75 y	301				275		407	?			
% Men ≥ 75 y	51.5				?		49.6	?			
Target Condition	EF ≤ 40% or advanced DD-NEF		EF ≤ 50% or advanced DD-NEF		EF ≤ 40%		LVSD, WMI that best corresponded to EF < 40%	EF ≤ 40%			
Prevalence Target Condition, n/tot (%)	Men 20/155 (13)	Women 23/146 (16)	Men 32/155 (21)	Women 28/146 (19)	13/275 (4.7)		28/407 (6.9)	?			
Index test	NT-proBNP, Roche				NT-proBNP, Roche		BNP, Shionogi	BNP, Biosite		BNP, Shionogi	
	Results										
Cut-off value	Men	Women	Men	Women	Men	Women	> 73 pg/mL	Men	Women	Men	Women
	452	375	426	375	1024	879		356	219	672	528
	pg/mL	pg/mL	pg/mL	pg/mL	pg/mL	pg/mL		pg/mL	pg/mL	pg/mL	pg/mL
AUC	0.86	0.89	0.84	0.91			0.88				
Sens (%)	85	83	81	86	89	75	79	78	75	78	75
Spec (%)	79	83	80	86	84	86	89	90	86	93	92
LR+	4.1	4.8	4.2	6.3	5.6	5.4	7.2	7.8	5.4	11.1	9.4
LR–	0.19	0.21	0.23	0.17	0.13	0.29	0.24	0.24	0.29	0.24	0.27
PTP+ (%)	38.0	47.8	52.8	59.7	21.6	21.0	34.8				
PTP– (%)	2.7	3.8	5.7	3.8	0.64	1.4	1.7				

EF: ejection fraction; DD-NEF: diastolic dysfunction with normal ejection fraction; LVSD: left ventricular systolic dysfunction; WMI: wall motion index: AUC: area under curve; Sens: Sensitivity; Spec: Specificity; LR+: positive likelihood ratio: LR–: negative likelihood ratio; PTP+: post-test probability of positive test; PTP–: post-test probability of negative test.

DISCUSSION

In this systematic review we investigated the accuracy of plasma natriuretic peptide levels for diagnosis of cardiac dysfunction and chronic heart failure in community-dwelling elderly patients aged 75 and over. Limited data were retrieved from a broad search strategy that included some 3000 articles. The five studies we found delivered limited information about the use of natriuretic peptide analysis as a tool for diagnosis of cardiac dysfunction and chronic heart failure in our target population. In general, the studies we found confirmed earlier observations in other populations that natriuretic peptide levels can best be used to exclude cardiac dysfunction or chronic heart failure[8].

Age is an important confounder for the plasma level of natriuretic peptides[12, 13]. The mechanisms underlying the age-related increase have not been fully elucidated, although renal impairment, myocardial fibrosis and subtle diastolic dysfunction, not detectable by current techniques, have been suggested[17, 26]. Systematic reviews published in this field have not used age as an inclusion criterion, nor has a subgroup analysis based on age been performed[4-9]. Only Ewald *et al.*[9] examined the effect of age on test performance, but they pooled results of studies in which the mean age of participants was less than 80 years. Our systematic review is the first to use age as a selection criterion.

Several unclear issues regarding the diagnostic abilities of natriuretic peptides in the elderly remain. First, most studies that investigated the diagnosis of chronic heart failure have ignored prognostically significant diastolic dysfunction[27]. Heart failure and preserved left ventricular ejection fraction (HFPEF) is relatively uncommon in younger patients but increases in importance in the elderly. It has, however, been debated whether diastolic and systolic heart failure are separate pathophysiological entities, as diastolic impairment at rest is a common if not universal accompaniment of left ventricular systolic dysfunction[28]. To date there is no reference standard to indicate diastolic dysfunction in the way that the left ventricular ejection fraction is generally accepted as the reference

standard for systolic dysfunction. Furthermore, no specific treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HFPEF and management of HFPEF should be aimed at causes of diastolic dysfunction such as myocardial ischaemia, hypertension and diabetes, and precipitating factors like atrial fibrillation[28].

Second, multiple determinants are known to influence circulating levels of natriuretic peptides, potentially limiting their use as diagnostics, especially in the very elderly, who often present with multiple co-morbidities. An understanding of the determinants affecting natriuretic peptide levels is a prerequisite for their optimal use as a tool for diagnosis of cardiac dysfunction or chronic heart failure in the community[29]. When ordering a natriuretic peptide test in patients with atrial fibrillation or renal impairment, physicians should realize that plasma levels can be raised without accompanying echocardiographic evidence of abnormal cardiac structure or function[20].

Third, as for every day clinical practice, several considerations should be taken into account when interpreting the results from our systematic review:

- In most studies retrieved in this systematic review, natriuretic peptide levels were used as a screening test, not as a diagnostic tool for heart failure or high-risk patients. So far, cost effectiveness studies into such screening are lacking.
- The place of the natriuretic peptide test in the diagnostic algorithm is still unclear. The results of our analysis indicate that natriuretic peptide levels are most efficient in excluding cardiac dysfunction or chronic heart failure. Studies estimating the added value of natriuretic peptides beyond history taking and clinical examination or ECG, representing everyday clinical practice, remain extremely scarce.
- Regarding the choice of natriuretic peptide test, it has been shown that NT-proBNP is more stable than BNP[30], and may have lower intra-individual and inter-individual variation[31].
- Cut-off values vary considerably between studies, with

important effects on test characteristics. Rutten *et al.* even suggest the use of 'double' cut-off values, one exclusionary ('rule out') and one confirmatory ('rule in')[32].

- Gender is a known confounder for natriuretic peptides, which are found to be higher in women than in men[33]. However, in elderly patients gender-specific cut-off values appeared to be higher in men[17, 19, 20].

In conclusion, we found limited evidence for the usefulness of natriuretic peptide measurement for the diagnosis of cardiac dysfunction or heart failure in elderly patients aged 75 and over from the general population. Important questions about the implementation of the natriuretic peptide test in daily practice remain unsolved. This systematic review emphasizes the importance of future research on the diagnostic accuracy of natriuretic peptide levels in elderly people in the community, not only because of the high accessibility of measuring natriuretic peptides (as opposed to echocardiography) in primary care, but also because the forthcoming epidemic of heart failure will predominantly affect elderly people.

CONFLICTS OF INTEREST

This study received no external research funding or commercial sponsorship. The authors have no conflicts of interest to declare.

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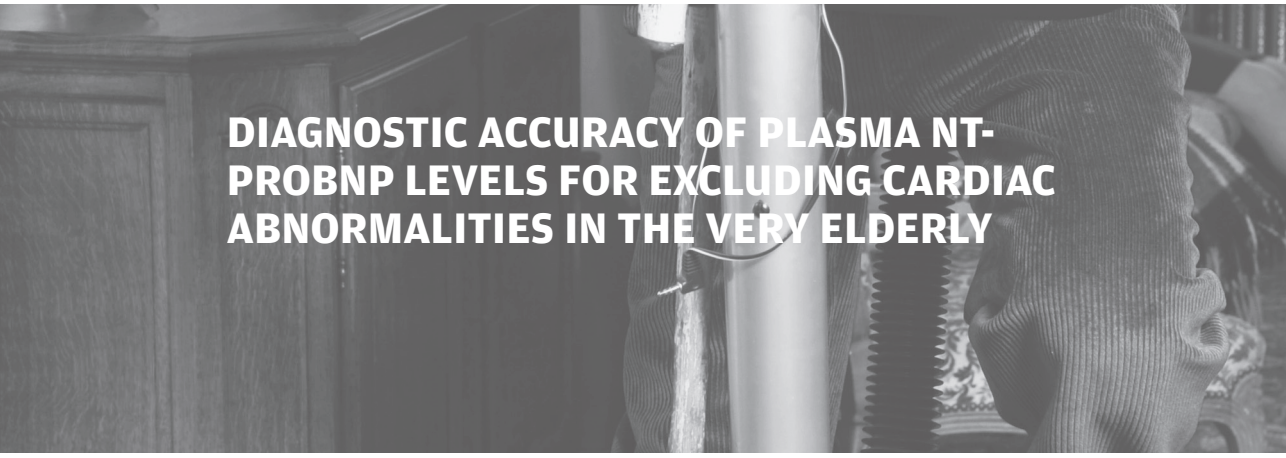
CHAPTER 3



DIAGNOSTIC ACCURACY OF PLASMA NT-PROBNP LEVELS FOR EXCLUDING CARDIAC ABNORMALITIES IN THE VERY ELDERLY

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ABSTRACT

Background: In the elderly the diagnosis of chronic heart failure is often challenging and the availability of echocardiography can be limited. Plasma levels of NT-proBNP are valuable tools to diagnose patients with heart failure. However, the performance of this biomarker to detect cardiac abnormalities in the very elderly remains unclear. The aims of this study were to investigate the relation between NT-proBNP and cardiac abnormalities and to evaluate the use of NT-proBNP to exclude structural and functional cardiac abnormalities in a community-based sample of "well-functioning" nonagenarians.

Methods: A diagnostic cross-sectional study embedded within the Leiden 85-plus Study in the municipality of Leiden, the Netherlands. Plasma NT-proBNP levels were measured and 2-dimensional echocardiography was performed in a subgroup of 80 well-functioning nonagenarians. Linear regression analysis was used to explore the relation between NT-proBNP and cardiac abnormalities and ROC curve analysis was used to assess the performance of NT-proBNP to exclude cardiac abnormalities. The upper limit of the lowest tertile of NT-proBNP was used as a cut-off value.

Results: Plasma NT-proBNP levels were associated with abnormal left ventricular (LV) dimensions, LV systolic and diastolic function, left atrial enlargement and valvular heart disease. LV mass, E/A ratio and degree of aortic regurgitation were identified as independent predictors of NT-proBNP. NT-proBNP levels were higher with greater number of echocardiographic abnormalities ($P < 0.001$). A cut-off level of 269.5 pg/mL identified patients with abnormal LV dimensions or depressed LV systolic function (sensitivity 85%, negative predictive value (NPV) 77%, area under the curve 0.75 (95% CI 0.64–0.85)). In addition, high NPV were found for LV systolic dysfunction, left atrial enlargement, severe valvular heart disease and pulmonary hypertension. The test performance of NT-proBNP to exclude any echocardiographic abnormality showed a

sensitivity of 82% and a NPV of 65%.

Conclusions: In this convenience sample of well-functioning nonagenarians NT-proBNP was related to a wide variety of functional and structural echocardiographic abnormalities. Moreover, NT-proBNP could be used to exclude echocardiographic abnormalities in well-functioning nonagenarians and might be used to indicate who needs to be referred for further cardiovascular examination.

BACKGROUND

Chronic heart failure is becoming more frequent in our aging societies. The prevalence of heart failure increases with age from 0.7% in people aged 55–64 years to 13.0% in those aged 75–84 years[1]. In the elderly, the diagnosis of chronic heart failure is often challenging when there are multiple comorbidities and many other possible causes for dyspnoea, fatigue or peripheral oedema can be present. Echocardiography is currently the diagnostic test of first choice for identifying structural and functional cardiac abnormalities. However, its availability for the very elderly can be limited, so there is the likelihood of a considerable over- and underdiagnosis of heart failure[2, 3]. This emphasises the need for a simple test to identify patients at risk.

Plasma levels of BNP (brain natriuretic peptide) and NT-proBNP (N-terminal pro-brain natriuretic peptide) are valuable tools to diagnose patients with heart failure. These measures have shown to provide prognostic information of mortality and major cardiovascular events, not only in patients with chronic heart failure or coronary artery disease but also in the general population, and this can improve patient management[4-8]. In addition, the measurement of these natriuretic peptides has been proposed in screening for left ventricular (LV) dysfunction in high-risk patients, such as the elderly[9, 10].

However, multiple factors are known to influence the

circulating levels of natriuretic peptides. The prevalence of possible influencing factors, like renal dysfunction and anemia, increases in the very elderly[11, 12]. An understanding of these is a prerequisite for the optimal use of these levels as a tool for diagnosing cardiac dysfunction in the community[13]. In the Leiden 85-plus Study a strong and specific correlation between plasma NT-proBNP and various cardiac diagnoses, like atrial fibrillation and myocardial infarction, was found in nonagenarians[14]. However, the performance of this biomarker to detect structural and functional cardiac abnormalities in this subgroup of subjects remains unclear. Therefore, the aims of the present study were first, to study the relation between plasma NT-proBNP levels and structural and functional cardiac abnormalities in a convenience sample of 80 "well-functioning" nonagenarians; second, to evaluate the use of plasma NT-proBNP levels to exclude structural and functional cardiac abnormalities in this age group.

METHODS

Study Population

The Leiden 85-plus Study is an observational, prospective population-based study of inhabitants of the city of Leiden, The Netherlands. The study design and characteristics of the cohort have been described in detail[15]. In brief, between September 1997 and September 1999 all 705 members of the 1912–1914 birth cohort in the city of Leiden were asked to participate in the month after their 85th birthday. There were no exclusion criteria regarding health status or demographic characteristics. At baseline and yearly up to the age of 90, the participants were visited at their place of residence. For the current study, a convenience sample of 82 participants was invited for echocardiography. The study nurse invited those participants who were physically able to visit the research centre and whose cognitive function allowed them to undergo various technical investigations. All but one underwent echocardiography. All participants in the study gave

informed consent and the Medical Ethics Commission of the Leiden University Medical Centre approved the study.

Functional and Clinical Characteristics

Evaluation of the functional status of participants included measures of cognitive function, subjective well-being, disability and depressive symptoms. Cognitive function was assessed by the Mini-Mental State Examination (MMSE), with scores ranging from 0 to 30 points (optimal)[16]. Subjective well-being was tested with a visual analogue scale (CANTRIL) in those with MMSE >18 points, with scores ranging from 0 to 10 (optimal)[16]. Disability was assessed on the Groningen Activity Restriction Scale (GARS), which is a combination of nine items relating to activities of daily living (ADLs) and nine items relating to instrumental ADLs: scores range from 18 (totally independent) to 72 points (totally dependent)[16]. Depressive symptoms were measured in those with MMSE >18 points, using the 15-item Geriatric Depression Scale (GDS-15), with scores ranging from 0 (optimal) to 15 points[16]. Each participant's general practitioner (or, if applicable, his/her nursing home physician) was interviewed annually about the patient's medical history, using standardised questionnaires including questions on present and past cardiovascular and non-cardiovascular morbidities. Specific cardiac diagnoses were defined as the presence of a medical history of myocardial infarction, angina pectoris, arrhythmias or heart failure, or an electrocardiogram (ECG) at age 90 years revealing a prior myocardial infarction (Minnesota Code 1-1 or 1-2, excluding 1-2-8), atrial fibrillation (Minnesota Code 8-3-1) or LV hypertrophy (Minnesota Code 310, 330 or 340)[17]. Other vascular morbidity was defined as the presence of a diagnosed noncardiac vascular morbidity including stroke and peripheral arterial disease. Non-cardiovascular morbidity was defined as the presence of a medical history of Parkinson's disease, chronic obstructive pulmonary disease, arthrosis (including rheumatoid arthritis and polymyalgia rheumatica), malignancies and/or hip fracture.

Plasma Levels of NT-proBNP at Age 90

Blood samples were taken within the month after every participant's 90th birthday, and were kept frozen at -80°C. In 2006 plasma levels of NT-proBNP were measured in one batch using the NT-proBNP assay of Roche Diagnostics (Mannheim, Germany) on a Roche Modular E-170 automated immunoanalyser. The within-run coefficient of variation was less than 2% and total variation was less than 6% at all levels measured (400–13500 pg/mL).

Echocardiography

All patients were imaged between January and September 2004, in stable hemodynamic conditions. In the majority of the patients, transthoracic echocardiography was performed the same day of the blood tests. In patients who underwent echocardiography at a different day, no cardiac events were recorded between the two tests. The echocardiographic evaluation was performed by one experienced observer blinded to the NT-proBNP levels.

All patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed system/Vivid Seven, General Electric-Vingmed, Milwaukee, WI, USA) equipped with a 3.5-MHz transducer. Echocardiographic images were acquired at a depth of 16 cm in the parasternal and apical views. Left ventricular (LV) dimensions were measured from M-mode images at the parasternal long-axis view. The LV ejection fraction was derived using the Teichholz formula[18]. Left ventricular diameters were indexed to the body surface area. Left ventricular mass was measured according to the formula proposed by Devereux et al. and indexed to the body surface area[19]. Left ventricular hypertrophy was defined by an LV mass index >149 g/m^2 in men and >122 g/m^2 for women[20].

Left ventricular diastolic function was assessed from pulsed-wave Doppler recordings of the transmitral inflow, measuring the early (E) and atrial (A) wave peak velocities and the E/A ratio[21]. In addition, left atrial dimensions were measured as a morphologic expression of diastolic function[22]. Left atrial anteroposterior diameter was measured from M-mode images at the parasternal

long-axis view and left atrial volume was derived according to the cube formula and indexed to body surface area[20].

The function of the mitral, aortic and tricuspid valves were evaluated with color Doppler echocardiography after optimising the gain and Nyquist limit. Standard continuous and pulsed-wave Doppler recordings were acquired. Stenotic and regurgitant valve diseases were evaluated according to semiquantitative and quantitative methods recommended by the American Society of Echocardiography[23]. When tricuspid regurgitation was present, pulmonary artery pressure was estimated using the modified Bernoulli equation[21].

Confounding Variables

As previously described, plasma levels of NT-proBNP are influenced by gender, body mass index (BMI), renal dysfunction, anemia and medications for heart failure[11, 12, 24, 25]. Therefore, these parameters were defined as possible confounding variables. BMI at age 90 years was assessed by measuring the subject's height and weight. Renal function was estimated using the criteria of the Modification of Diet in Renal Disease Study Group[26]. Anemia was defined as hemoglobin levels <7.5 mmol/L for women and <8.1 mmol/L for men. Data on relevant cardiovascular medications were gathered from each participant's pharmacist, including any use of diuretics, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers or digoxin.

Data Analysis

Echocardiographic parameters were compared between tertiles of plasma NT-proBNP using the Jonckheere–Terpstra test or the Chi-squared test with linear-by-linear association.
Plasma levels of NT-proBNP were log-transformed and the association with echocardiographic parameters was explored further using linear regression analysis corrected for confounding variables. Analysis of variance (ANOVA) testing was used to compare the mean LogNT-proBNP values between different categories of increasing number of cardiac abnormalities.

The performance of NT-proBNP to exclude structural and functional abnormalities was assessed using receiver operating characteristic (ROC) curve analysis. The upper limit of the lowest tertile was used as a cut-off value for NT-proBNP and the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were calculated. The highest cut-off value with an NPV of 100% was reported. Data analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The initial cohort consisted of 599 participants at age 85 years. A total of 276 individuals survived up to the age of 90 years. Plasma levels of NT-proBNP were determined in 274 participants. Both echocardiographic data and plasma NT-proBNP levels were available in 80 well-functioning subjects. The prevalence of cardiovascular and non-cardiovascular comorbidities was similar for patients with and without echocardiography (Table 1). There was a difference in NT-proBNP levels between both groups ($P > 0.05$), but the upper limit of the lowest tertile was in the same range (269.5pg/mL vs 306.7pg/mL).

Most patients showed normal LV end-diastolic diameter (n = 69, 86%) and had a preserved LV ejection fraction (n = 73, 91%). According to current criteria, LV hypertrophy was present in 35% (n = 9) of men and 45% (n = 23) of women (Table 2).

Patients in the highest plasma NT-proBNP tertile showed significantly larger LV dimensions, higher values of LV mass and a higher E/A ratio together with a larger left atrial volume (Table 3). In addition, a higher prevalence of significant mitral and aortic valve regurgitation was observed in patients in the highest NT-proBNP tertile, together with higher values of pulmonary artery pressure.

Table 1. Sociodemographic, functional and clinical characteristics of participants with and without echocardiography at age 90 years

	Echocardiographic examination		P*
	Yes (n = 80)	No (n = 194)	
	n (%)		
Sociodemographic characteristics			
Male	26 (33)	50 (26)	0.28
Institutionalized	17 (21)	87 (45)	<0.001
Education ≤ 6 years primary school	38 (48)	132 (68)	0.002
Income ≤ 750€	34 (43)	105 (54)	0.09
Functional characteristics			
Cognitive impairment (MMSE ≤ 18)	0 (0)	72 (38)	<0.001
Poor well-being (CANTRIL < 7)	16 (20)	35 (29)	0.14
Dependent in daily living (GARS ≥ 56)	4 (5)	64 (34)	<0.001
Depression (GDS-15 ≥ 5)	11 (14)	37 (31)	0.003
Clinical characteristics			
Cardiovascular morbidity	48 (60)	132 (68)	0.22
Specific cardiac diagnoses[a]	47 (59)	120 (62)	0.63
Atrial fibrillation on ECG	8 (10.0)	25 (13)	0.49
Diagnosis of heart failure	20 (25)	39 (21)	0.43
Other vascular morbidity[b]	11 (14)	33 (18)	0.45
Cardiovascular risk factors			
Hypertension	47 (59)	104 (55)	0.58
Diabetes mellitus type II	10 (13)	35 (21)	0.12
Non-cardiovascular morbidity[c]	49 (61)	126 (65)	0.56
BMI > 25 kg/m²	50 (65)	101 (64)	0.88
GFR < 60 mL/min/1.73 m²	43 (54)	100 (52)	0.74
Anemia[d]	11 (15)	51 (28)	0.014
Cardiovascular medication[e]	34 (43)	97 (50)	0.26
NT-proBNP in pg/mL (median, IQR)	389.5 (220.7–779.1)	471.9 (252.8–1655.3)	0.10‡

[a]Including a history of myocardial infarction (clinical or by ECG), angina pectoris, arrhythmias, heart failure and ECG with atrial fibrillation or left ventricular hypertrophy.
[b]Including a history of stroke and peripheral vascular disease.
[c]Including a history of Parkinson's disease, chronic obstructive pulmonary disease, arthritis (including arthrosis, rheumatoid arthritis and polymyalgia rheumatica), malignancies or hip fracture.
[d]Hemoglobin < 7.5 mmol/L for women, < 8.1 mmol/L for men.
[e]Including any use of diuretics, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers or digoxin
* Independent Student's t-test; ‡, Mann–Whitney U test; IQR, inter quartile range.

Table 2. Echocardiographic Characteristics in Well-Functioning Nonagenarians (n = 80)

	Median (IQR)	Normal value *
LV dimensions and systolic function		
LV EDD index (mm/m²)	28 (24 – 31)	≤ 33
LV ESD index (mm/m²)	17 (14 – 20)	-
Interventricular septal wall thickness (mm)	13 (10 – 14)	≤10
Posterior wall thickness (mm)	11 (10 – 13)	≤10
LV Ejection fraction (%)	67 (60 – 77)	≥50
LV Mass index (g/m²)		
Men	132 (105 – 160)	≤149
Women	116 (96 – 145)	≤122
LV diastolic function		
E/A ratio	0.7 (0.6 – 0.8)	–
Indexed left atrial volume (ml/m²)	24 (14 – 33)	≤40
Estimated PAP (mmHg)	34 (30 – 37)	≤40
Valvular function	**Prevalence, n (%)**	
Mitral stenosis	0 (0)	
Mitral regurgitation	58 (72)	
Mild	20 (25)	
Moderate	24 (30)	
Severe	14 (17)	
Aortic stenosis	14 (17)	
Mild (mean ΔP < 25 mmHg)	9 (11)	
Moderate (mean ΔP 25 – 40 mmHg)	4 (5)	
Severe (mean ΔP > 40 mmHg)	1 (1)	
Aortic regurgitation	38 (48)	
Mild	15 (19)	
Moderate	17 (21)	
Severe	6 (8)	
Tricuspid stenosis	0 (0)	
Tricuspid regurgitation	25 (31)	
Mild	8 (10)	
Moderate	4 (5)	
Severe	13 (16)	

Abbreviations: ΔP, pressure gradient; IQR, inter quartile range (25% - 75%); EDD, end-diastolic diameter; ESD, end-systolic diameter; LV, left ventricular; PAP, pulmonary artery pressure.
* References: 20, 29.

Linear regression analyses with LogNT-proBNP as the dependent variable and all echocardiographic parameters as independent variables showed that LV mass, E/A ratio and the degree of aortic regurgitation were independent predictors of NT-proBNP after adjusting for confounding variables (Table 3). Two multivariate regression models were used to evaluate the independent determinants of NT-proBNP plasma levels: one including pulmonary artery pressure and another one without.

The mean LogNT-proBNP was higher with greater number of echocardiographic abnormalities (ANOVA, P < 0.001) (Figure 1). Back transformation yielded the following NT-proBNP levels: 238.2 pg/mL for a normal echocardiographic result, 362.2 pg/mL for patients with one echocardiographic abnormality, 527.2 pg/mL with two and 833.7 pg/mL for patients with three or more.

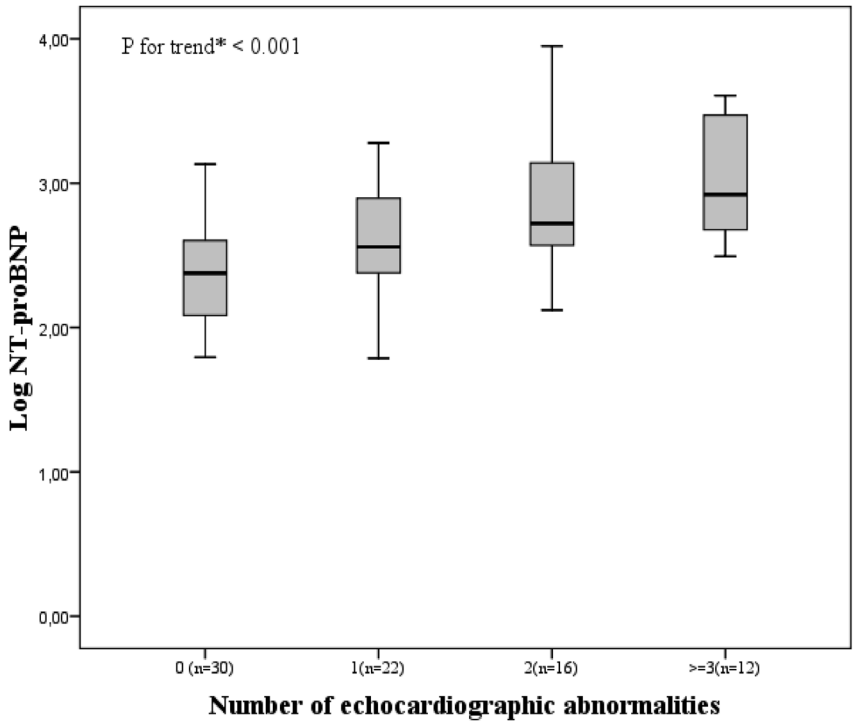

Figure 1. Relationship between LogNT-proBNP and number of cardiac abnormalities at age 90.

Error bars in these box-and-whisker plots show the mean and 95% confidence intervals of LogNT-proBNP at age 90 related to total amount of cardiac abnormalities, including LVEDD > 33 mm/m², EF < 50%, indexed left atrial volume > 40 ml/m², LV hypertrophy (men > 149 g/m², women > 122 g/m²), presence of severe mitral regurgitation, presence of severe aortic regurgitation, presence of severe aortic stenosis or PAP ³ 40 mmHg. *, by ANOVA.

Because NT-proBNP levels did not differ between men and women (501.1 pg/mL (IQR 211.3–1468.3 pg/mL) and 349.5 pg/mL (IQR 214.9–682.5 pg/mL) respectively (Mann–Whitney, *P* = 0.14)) and gender was no independent predictor of NT-proBNP in the linear regression analysis (*P* = 0.88), no gender-specific cut-off values were used (Table 4). The prespecified NT-proBNP cut-off value of 269.5 pg/mL identified LV dilatation, hypertrophy or systolic dysfunction with sensitivity, specificity, PPV and NPV of 84%, 48%, 59% and 77%, respectively. By reducing the cut-off value to 130 pg/mL, the NPV increased to 100%. The prespecified cut-off value was able to exclude an EF < 50 with an NPV of 92%.

To identify left atrial enlargement, severe valvular heart disease and pulmonary hypertension, the prespecified cut-off value yielded a high sensitivity and NPV but low specificity and PPV. An NT-proBNP cut-off value of 61 pg/mL excluded the presence of severe valvular heart disease.

The test performance of NT-proBNP to exclude severe valvular heart disease and/or LV systolic dysfunction showed a sensitivity of 84% and a NPV of 85%. In addition, the diagnostic accuracy of NT-proBNP to exclude any echocardiographic abnormality (n = 50) was calculated. If only the participants with an NT-proBNP level > 269.5pg/mL (n = 54) would be referred for echocardiography, 9 cases would be missed (18%) and 13 negative echoes (0 abnormalities) would be done (43%).

Table 3. Correlation between NT-proBNP levels and echocardiographic parameters

	Tertiles of NT-proBNP*			P for trend	Adjusted B (95% CI) Model 1**, adj R^2=0.19 Model 2£, adj R^2=0.35	P
	1 (n =26)	2 (n = 27)	3 (n = 27)			
LV dimensions and systolic function						
LV EDD (mm)	42 (39 – 51)	47 (43 – 54)	51 (45 – 56)	0.003	-0.042 (-0.088 – 0.005)	0.081
LV ESD (mm)	27 (22 – 31)	28 (27 – 33)	32 (29 – 37)	0.002	0.034 (-0.030 – 0.099)	0.29
LV Ejection fraction (%)	69 (60 – 79)	67 (61 – 72)	67 (53 – 74)	0.24	0.006 (-0.017 – 0.030)	0.59
LV Mass index (g/m²)						
Men	213 (182 – 287)	236 (177 – 260)	268 (209 – 372)	0.068	0.003 (0.000 – 0.005)	0.045
Women	160 (142 – 190)	212 (169 – 242)	213 (160 – 260)	0.008		
Left ventricular diastolic function						
E/A	0.61 (0.51 – 0.70)	0.72 (0.61 – 0.78)	0.70 (0.56 – 1.1)	0.016	0.45 (0.026 – 0.87)	0.038
Left atrial volume (ml)	30.1 (22.1 – 40.0)	43.6 (25.6 – 55.3)	50.3 (33.8 – 73.6)	0.002	0.001 (-0.003 – 0.004)	0.67
Significant heart valvular disease						
Mitral regurgitation ≥ moderate	4 (11%)	18 (47%)	16 (42%)	0.003	-0.046 (-0.14 – 0.045)$	0.32
Aortic regurgitation ≥ moderate	3 (13%)	8 (35%)	12 (52%)	0.014	0.11 (0.002 – 0.21)$	0.046
Any aortic stenosis	7 (50%)	3 (21%)	4 (29%)	0.25	-0.008 (-0.022 – 0.005)$	0.23
Estimated PAP (mmHg)	33 (26 – 36)	33 (29 – 37)	37 (33 – 40)	0.015	0.008 (-0.020 – 0.035)£	0.56

Abbreviations: EDD, end-diastolic diameter; ESD, end-systolic diameter; LV, left ventricular; PAP, pulmonary artery pressure.

*Echocardiographic parameters (median (IQR)) compared between gender-specific tertiles of NT-proBNP using the Jonckheere-Terpstra test (continuous variables) or the Chi-Square test with linear-by-linear association (proportions). Median values of NT-proBNP levels were 143.2 pg/mL (IQR 103.3–220.7 pg/mL) in the first tertile, 380.6 pg/mL (IQR 326.2–499.4 pg/mL) in the second tertile and 1324.0 pg/mL (IQR 762.4–2832.0 pg/mL) in the third tertile.

** Linear regression analysis with LogNT-proBNP as dependent variable and all echocardiographic measurements (except estimated PAP) as independent variables, adjusted for gender, BMI, renal function, anemia and medications for heart failure (n = 56).

$ In the linear regression analysis the degree of mitral and aortic regurgitation were expressed as ordinal variables (1 to 4) and aortic stenosis was expressed as a continuous variable using the aortic valve peak gradient.

£ Linear regression analysis with LogNT-proBNP as dependent variable and all echocardiographic measurements AND estimated PAP as independent variables, adjusted for gender, BMI, renal function, anemia and medications for heart failure (n = 37).

Table 4. Test characteristics for NT-proBNP levels (cut-off 269.5 pg/mL) for detecting structural and functional cardiac abnormalities in nonagenarians

	Prevalence n (%)	AUC (95% CI)	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Abnormal LV dimensions (LVEDD index ≥33 mm/m^2 or LV hypertrophy) and/or LV systolic dysfunction	38 (48)	0.75 (0.64–0.85)	84	48	59	77*
LV systolic dysfunction (EF<50)	7 (9)	0.67 (0.42–0.92)	71	33	9	92*
Indexed left atrial volume ≥ 40ml/m^2	12 (15)	0.74 (0.60–0.88)	92	36	21	96$^£$
Severe valvular heart disease$^\#$	21 (26)	0.71 (0.58–0.84)	90	41	35	92$^\$$
PAP ≥40 mmHg	10 (13)	0.85 (0.72–0.98)	100	35	28	100
Severe valvular heart disease and/or LV systolic dysfunction (EF<50)	25 (31)	0.68 (0.55–0.81)	84	40	39	85$^\$$
Any severe echocardiographic abnormality	50 (63)	0.77 (0.66–0.88)	82	57	76	65$^\$$

Area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) calculated for an NT-proBNP cutoff value of 269.5 pg/mL.
Abbreviations: EDD, end-diastolic diameter; LV, left ventricular; EF: ejection fraction; PAP, pulmonary artery pressure; CI, confidence intervals.
An NT-proBNP cut-off value of 130 pg/mL (*), 236 pg/mL ($^£$) and 61 pg/mL ($^\$$) increased the NPV to 100%.
$^\#$ Severe mitral or aortic stenosis, severe mitral regurgitation and severe aortic regurgitation.

DISCUSSION

In this convenience sample of well-functioning nonagenarians we showed NT-proBNP is not just an indicator of increased cardiac pressure but is related to a wide variety of functional and structural echocardiographic abnormalities. This confirms the hypothesis that natriuretic peptides could possibly be used to identify 'pancardiac' damage, even when it is silent[27]. In a previous study in this cohort NT-proBNP was found to be a good predictor for both cardiovascular and noncardiovascular mortality, both in elderly with and without specific cardiac diagnoses. This indicated elevated plasma NT-proBNP levels possibly reflect unknown cardiac morbidity or imminent heart failure[14]. In this convenience sample 18 of 33 patients (56%) without specific cardiac diagnoses had one or more echocardiographic abnormality. Moreover, increasing levels of NT-proBNP were related to the number of echocardiographic abnormalities.

A recent systematic review concluded important questions about the implementation of measuring plasma NT-proBNP in daily practice remain unsolved for the diagnosis of cardiac dysfunction in elderly patients aged 75 and over from the general population[28]. The present study confirms that low plasma NT-proBNP levels are most efficient in excluding echocardiographic abnormalities in well-functioning nonagenarians. Possibly the level of NT-proBNP might be used to indicate who needs to be referred for further cardiovascular examination including echocardiography.

Some limitations should be acknowledged. First, we were not able to correlate plasma levels of NT-proBNP to echocardiographic measurements for the entire cohort. Seen the small sample of well-functioning nonagenarians we should be careful to generalize the findings of the present study to the entire population of well-functioning nonagenarians. Second, there was no available data on the symptomatology of the participants. However, participants in the convenience sample only differed in functional status, but had the same burden of cardio-vascular comorbidities compared to the limited-functioning elderly. Third, the fact the NT-proBNP levels

were determined in 2006 after being frozen might have influenced the absolute value, but it is unlikely that it has affected the ranking, with regard to the NPV. In addition, the applicability of current echocardiographic cut-off values to nonagenarian subpopulations may be debatable since the thresholds for normal values are usually derived from younger subpopulations. Finally, LVEF measured with biplane Simpson's methods was not systematically available in all patients.

CONCLUSIONS

In conclusion, this study showed plasma NT-proBNP is related to a wide variety of functional and structural echocardiographic abnormalities in well-functioning nonagenarians. Furthermore, low values of NT-proBNP were able to exclude echocardiographic abnormalities and could be used to identify nonagenarians that need to be referred for further cardiovascular examination.

LIST OF ABBREVIATIONS

BNP: Brain natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide; ROC: Receiver operating characteristic; LV: Left ventricular; CI: Confidence intervals; MMSE: Mini-Mental State Examination; GARS: Groningen Activity Restriction Scale; ADLs: Activities of daily living; GDS-15: 15-item Geriatric Depression Scale; BMI: Body mass index; ANOVA: Analysis of variance; NPV: Negative predictive value; PPV: Positive predictive value; ΔP: Pressure gradient; SD: Standard deviation; IQR: Inter quartile range; EDD: End-diastolic diameter; ESD: End-systolic diameter; PAP, Pulmonary artery pressure.

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COMPETING INTERESTS

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AUTHOR'S CONTRIBUTIONS

JG had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. JG and RGJW are responsible for the study concept and design. BV and VD performed the statistical analysis and drafted the manuscript. All authors participated in the analysis and interpretation of the data and critically revised the manuscript.

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CHAPTER 4

THE BELFRAIL (BF_{C80+}) STUDY: A POPULATION-BASED PROSPECTIVE COHORT STUDY OF THE VERY ELDERLY IN BELGIUM

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ABSTRACT

Background: In coming decades the proportion of very elderly people living in the Western world will dramatically increase. This forthcoming "grey epidemic" will lead to an explosion of chronic diseases. In order to anticipate booming health care expenditures and to assure that social security is funded in the future, research focusing on the relationship between chronic diseases, frailty and disability is needed. The general aim of the BELFRAIL cohort study ($BF_{C80+)}$ is to study the dynamic interaction between health, frailty and disability in a multi-system approach focusing on cardiac dysfunction and chronic heart failure, lung function, sarcopenia, renal insufficiency and immunosenescence.

Methods/Design: The BF_{C80+} is a prospective, observational, population-based cohort study of subjects aged 80 years and older in three well-circumscribed areas of Belgium. In total, 29 general practitioner (GP) centres were asked to include patients aged 80 and older. Only three exclusion criteria were used: severe dementia, in palliative care and medical emergency. Two sampling methods for the recruitment of patients were used. Between November 2, 2008 and September 15, 2009, 567 subjects were included in the BF_{C80+} study. Every study participant was invited to undergo four study visits. The GP recorded background variables and medical history and performed a detailed anamnesis and clinical examination. The clinical research assistant performed an extensive examination including performance testing, questionnaires and technical examinations. Echocardiography was performed at home by a cardiologist. A blood sample was collected in the morning. Follow-up reporting of hard outcome measures including mortality, hospitalization and morbidity was organized. A second data collection is planned after 18 months.

Discussion: The BF_{C80+} was designed to acquire a better understanding of the epidemiology and pathophysiology of chronic diseases in the very elderly and to study the dynamic interaction

between health, frailty and disability in a multi-system approach. The wide variety of dimensions investigated in the BF_{C80+} will enable us not only to investigate in depth the relationship between the different physiological systems but also to initiate new research questions based on this unique database of community-dwelling elderly.

BACKGROUND

Health care and social security systems in industrialized countries are confronted with ageing populations. By 2050, 10% of people living in Belgium will have reached the age of 80 or older[1]. This forthcoming "grey epidemic" will lead to an explosion of chronic diseases. This situation has stimulated researchers to focus their efforts on studying relationships between chronic diseases, frailty and the development of disability[2, 3]. Fried et al.[4] have clearly shown that there is an overlap between chronic diseases, frailty and disability. In this regard the concept of frailty fulfils an important role. Although there are a large variety of models, definitions and criteria, a consensus view exists that considers frailty as a multidimensional geriatric syndrome with biological, physiological and psychosocial components, and as a state of increasing vulnerability and loss of adaptability to stress[5,6]. Campbell and Buchner[7] described frailty as a condition or syndrome which results from a multi-system reduction in reserve capacity to the extent that a number of physiological systems are close to, or past, the threshold of symptomatic clinical failure. A better understanding of the dynamic process leading from health to frailty and eventually disability is of primary interest if preventive interventions are planned.

In Belgium general practitioners (GPs) have a prominent place in the health care system. More than 95% of the population is reported to consult the same GP or practice (duo or group) in case of health problems. More than 90% of people aged 65 and older have at least one contact with their GP every year, with an average

of 11.9 contacts per year at the age of 75 and older[8].

The general aim of the BELFRAIL cohort study is to acquire a better understanding of the epidemiology and pathophysiology of chronic diseases in the very elderly and to study the dynamic interaction between health, frailty and disability in a multi-system approach. Therefore the BF_{C80+} focuses on different systems; (1) cardiac dysfunction and chronic heart failure, (2) lung function, (3) sarcopenia, (4) renal insufficiency and (5) immunosenescence and the profile of immune risk.

Cardiac dysfunction and chronic heart failure

In our ageing society the burden of chronic heart failure is rising. The prevalence increases with age from 0.7% in people aged 55–64 years to 2.7% in those aged 65–74 years and 13.0% in those aged 75–84 years[9]. Heart failure not only has negative consequences for functional status and well-being but also leads to increased mortality[9]. However, diagnosing chronic heart failure is notoriously difficult, especially in the elderly who often have multiple comorbidities and may present with many other possible causes for dyspnoea, fatigue or peripheral oedema. With increasing average patient age, primary care physicians will become increasingly important as the principal diagnosticians and treating physicians. In this setting, poor availability of routine echocardiography leads to considerable over- and under-diagnosis of heart failure[10, 11]. This emphasizes the need for a simple test, easily applicable in primary care settings, to identify elderly patients at risk and to initiate timely treatment to reduce mortality and improve quality of life. Over the last decade, brain natriuretic peptide (BNP) and its amino-terminal portion N-terminal pro-brain natriuretic peptide (NT-proBNP) have been extensively studied. However, a recent systematic review found limited evidence for the usefulness of natriuretic peptide measurement for the diagnosis of cardiac dysfunction or heart failure in community-dwelling elderly patients aged 75 and over and concluded that important questions about the implementation of the natriuretic peptide test in daily practice remain unsolved[12]. The BF_{C80+} was conceived (1) to examine further the diagnostic accuracy

of natriuretic peptides for cardiac dysfunction in elderly people in the community and (2) to develop an algorithm, easily applicable in primary care, for the diagnosis of chronic heart failure in the very elderly by estimating the added value of natriuretic peptides and ECG beyond history taking and clinical examination.

Lung function

With regard to the burden of respiratory diseases in the elderly, many fundamental issues remain unresolved. Few reliable data are available concerning the prevalence of chronic obstructive pulmonary disease (COPD) and asthma[13], and the global initiative for chronic obstructive lung disease (GOLD) criteria[14] for the diagnosis of COPD have been debated and appear not to be meaningful in the elderly[15]. Moreover, the lack of clear reference data for the very elderly makes assessment of pulmonary function a real challenge[16, 17]. Predictive models for spirometric variables have been proposed but are based on very small samples that are rarely representative of the population in an area[18]. Two aims of the BF_{C80+} study are (1) to collect respiratory reference data from a large sample of the elderly population in Belgium in order to develop an adapted predictive model (regression equation that allows computation of predicted values) and (2) to gain better insight into the prevalence of respiratory symptoms and obstructive lung disease in octogenarians. Clustering with other chronic diseases will also be studied, and the ability of older patients to perform good-quality spirometric tests will be investigated.

Sarcopenia

Sarcopenia has been described as an age-related decline in muscle mass in older people[19]. Current definitions of sarcopenia include both a loss of muscle strength and a decline in functional quality in addition to the loss of muscle protein mass[20]. However, it is unclear whether a decline in functional capacity results from the loss of muscle mass and/or the qualitative impairment of the muscle tissue[21]. The age-associated changes in muscle mass explain less than 5% of the variance in the change in strength with ageing[20].

Sarcopenia is associated with many adverse outcomes like increases in morbidity, falls, institutionalization and onset of disability[22]. It has been suggested that the contribution of muscle mass to certain outcomes may be primarily because of its association with muscle strength[20]. Decreased strength, most often grip strength, has been identified as an important sign of frailty[23]. Grip strength appears to be a robust predictor of functional decline, disability and mortality[19]. In the BF_{C80+} the relationship between grip strength, muscle mass and clinical outcome will be studied. Also the relationship with nutritional status, performance tests and biological indicators will be investigated.

Renal insufficiency

Chronic kidney disease (CKD) is increasingly recognized as an important problem in public health because of its high prevalence[24] and its association with increasing mortality, cardiovascular events and hospitalizations[25]. "Gold standard tests" based on ethylenediaminetetraacetic acid (EDTA), inulin, iohexol or diethylene triamine pentaacetic acid (DTPA) clearance that aim to measure the glomerular filtration rate (GFR) are difficult to perform in clinical practice. Cockcroft and Gault[26] developed a method to estimate renal function based on the serum creatinine value and the patient's body weight and age. Since then, many researchers have tried to find a better formula based on serum creatinine or cystatin C[27]. However, none of these methods has been validated in a large population of community-dwelling elderly patients. The aims of the BF_{C80+} are, first, to achieve a better understanding of the prevalence, complications and evolution of CKD in elderly patients, and second, to identify the most accurate existing method or to develop a new method, applicable in clinical practice, to estimate the GFR in elderly patients.

Immunosenescence and the immune risk profile

Deterioration of the immune system with ageing, referred to as immunosenescence, is believed to be a prominent pathophysiological feature of frailty[28]. The hallmarks of immunosenescence are a

decrease in adaptive immunity and increased low-grade chronic inflammatory status, which has been referred to as inflamm-ageing. The former results in a decreased ability to effectively control infectious diseases and a generally poor response to vaccination, while inflamm-ageing seems to underlie most of the age-related diseases (e.g. atherosclerosis, dementia, sarcopenia, diabetes, etc.) and has been shown to be related to mortality of all causes in older persons[29, 30]. The chronological age at which immunosenescence becomes clinically important is most likely influenced by many factors, including the pathogen load to which individuals are exposed throughout life. There is considerable evidence that human cytomegalovirus (CMV) in particular plays an important role in immune modulation later in life[31]. Understanding how and why immune responsiveness changes in humans as they age is essential for developing strategies to prevent or restore dysregulated immunity and assure healthy aging. Therefore, we will explore the complex relationship between immunosenescence and frailty, disease and death in the BF_{C80+}. Furthermore, we will investigate the role of CMV and other pathogens in the process of immunosenescence and the mechanisms underlying it.

METHODS

Study design and setting

The BF_{C80+} is a prospective, observational, population-based cohort study of subjects aged 80 years and older in three well-circumscribed areas in Belgium. The study protocol was approved by the Biomedical Ethics Committee of the Medical School of the Université Catholique de Louvain (UCL) of Brussels, Belgium (B40320084685).

Sample size calculations were based on the first focus of this study: to determine the diagnostic accuracy of clinical signs and symptoms for heart failure. Therefore the sample size calculation was based on the following premises: 1) the expected prevalence of "cardinal" symptoms (i.e. dyspnoea, fatigue, peripheral oedema)

of CHF in octogenarians of 30%, 2) the worst-case scenario in which none of these criteria would have any diagnostic value (i.e. proportion of any symptom of 0,5) and taking into account an acceptable confidence interval of 90%, and 3) assuming a prevalence of CHF of 15% in octogenarians. The sample size for the BF_{C80+} was estimated on 420 subjects. Taking into account a refusal rate of not more than 10% and a yearly mortality rate of 10% a sample size of 550 was proposed.

General practitioners in three Belgian areas were invited to participate in the study. In Wallony (région de Dinant), Brussels and Flanders (Druivenstreek), respectively, 17, 2 and 10 GP centres agreed to participate. Participating centres were invited to a training meeting in order to standardize the recording of the medical history, anamnesis and clinical examination. The GP centres received study information with a detailed study protocol and a CD-ROM with visual and audio examples of the clinical examination and recent guidelines on heart failure and hypertension.

The participating centres were asked to include patients aged 80 and older in the cohort. Only three exclusion criteria were used: (1) dementia (known mini-mental state examination (MMSE) < 15/30), (2) in palliative care and (3) medical emergency. Two sampling methods for the recruitment of patients were used. Two GP centres were asked to include all eligible patients. The remaining 27 centres were asked to include a maximum of three consecutive patients during a three-week interval. In these three weeks the GP also planned his visit. This interval was repeated five times so every participating centre included a maximum of 15 patients. Every interval of recruitment was started on a different day to avoid selection bias.

On November 2, 2008 the inclusion period was started in Wallony. All participating centres in this area recruited patients according to the second sampling method, thus a maximum of 15 patients. On February 28, 2009 inclusion was stopped in Wallony. On March 16, 2009 the inclusion period was started in Flanders and Brussels. One centre in Flanders and one centre in Brussels recruited all eligible patients. The remaining centres (Flanders (n = 9), Brussels

(n = 1)) recruited patients according to the second sampling method. On September 15, 2009 inclusion was stopped in Flanders and Brussels.

Visit by the general practitioner

Eligible patients were first flagged by the GP and received an information letter about the study. After providing informed consent, patients entered the study population. In the weeks after flagging, the GP recorded the social situation, medical history and medication for each patient and undertook a detailed anamnesis and clinical examination.

The social anamnesis consisted of questions about ethnic group, marital status, type of living (at home or institutionalized), level of education and professional history. The GP was asked to record important antecedents in the medical history of the study subjects and to list the medical problems for which the subject was currently followed. Afterwards, a detailed recording of non-cardiovascular and cardiovascular comorbidities took place.

Non-cardiovascular morbidities were defined as a positive response from the GP about the presence of thyroid problems, anaemia, asthma, COPD, Parkinson's disease, arthritis, osteoarthritis, documented osteoporosis, malignancies, depression and renal insufficiency. A distinction was made between an active and cured pathology. Active status was defined as being present (even if well controlled by treatment) or having occurred less than six months ago. The GP was asked whether the subject had had a knee or hip replacement or had undergone important surgery less than or more than 12 months ago. Tetanus, pneumococcal and influenza vaccination status was registered.

Cardiovascular morbidities were defined as a positive response for the presence of hypertension, diabetes mellitus, hyperlipidaemia, history of angor pectoris or myocardial infarction, known cardiomyopathy, history of transient ischaemic attack (TIA) or cerebro-vascular accident (CVA), peripheral arterial disease, history of decompensated heart failure, atrial fibrillation, valvular disease or history of oedema of the lower extremities. If present, details

were requested about the date of diagnosis, the diagnostic pathway and nature of treatment. The GP was asked to report important cardiovascular intervention or surgery (percutaneous transluminal coronary angioplasty (PTCA) or stenting, coronary, valvular or arterial surgery, or the placement of cardiac device) less than or more than 12 months ago.

Current medication was recorded by the GP.

A structured and standardized anamnesis was performed and included questions about symptoms of angina pectoris (at rest or during exercise), dyspnoea (Medical Research Council (MRC) scale), fatigue, orthopnoea, cough (nocturnal or diurnal), wheezing, oedema of the lower extremities, palpitations, loss of appetite, smoking status, alcohol intake, recent changes in symptoms, recent weight change and alteration of mental and psychological status.

The clinical examination consisted of a blood pressure measurement in the sitting position on both arms that was repeated after 2 min. The GP used his or her own blood pressure meter. Heart rate (with auscultation over 30 s, x2), heart rhythm (regular or irregular) and breathing rate at rest (with observation over 30 s, x2) were measured. Heart auscultation was performed to detect an S3, S4 or cardiac murmur (systolic or diastolic). The apex beat was palpated with the patient in a supine and lateral position, and if present the GP was asked to describe whether it was displaced (outside the mid-clavicular line in supine position), enlarged (> 2 fingers) or sustained (in left lateral position). Lung auscultation was performed to detect crepitations, wheezing and rhonchi. The carotid arteries were auscultated to detect a murmur and the peripheral arteries (femoral, popliteal and dorsal and tibial arteries) were palpated. The jugular venous pressure (JVP) was measured in a 45° reclining position and noted if raised (> 3 cm between the angle of Louis (manubrio-sternal joint) and the highest level of jugular (internal or external) vein pulsation). In the same position, the presence of hepatojugular reflux was checked for. Hepatojugular reflux was present when the vertical height of the JVP increased by more than 1 cm and remained elevated for as long (15–20 s) as pressure was applied to the epigastrium. The GP was asked to

determine whether hepatomegaly or oedema of the lower extremities was present and if he or she had a suspicion of ascites.

Finally, the GP was asked whether, in his or her opinion, the patient suffered from chronic heart failure, and to determine his or her degree of certainty (2, 10, 25, 50, 75, 90 or 98% certain). The reason why the GP thought chronic heart failure was or was not present was noted and the New York Heart Association (NYHA) class scored for those patients with a suspicion of chronic heart failure.

The practice in Flanders that included all eligible patients also determined an ankle–brachial index with the patient in supine position with oscillometric pressure measurements using a standard automated blood pressure cuff system (SCVL-2007, Diegel Healthworks®, Auckland, New Zealand).

Visit by the clinical research assistant

After inclusion of a patient, the data manager made an appointment for the clinical research assistant (CRA) to visit the patient. Three CRAs were trained to perform an extensive examination with performance testing, questionnaires and technical examinations. The French-speaking patients were visited by a French-speaking CRA (n = 1) and the Dutch-speaking patients by a Dutch-speaking CRA (n = 2). This visit lasted between 90 and 150 minutes depending on the general state of the patient. The following tests and questionnaires were performed by the CRA:

- Biometry: circumference of upper arm, calf and upper leg, skin fold of upper arm, calf and upper leg, weight, height, span width and knee height.
- Blood pressure: electronically measured (Omron 705IT®, Omron, Japan) in sitting position on both arms and repeated after 2 min.
- Vision: asking the respondent "are you able to recognize someone's face at a distance of four metres?"[32].
- Hearing: asking the respondent "are you able to follow a conversation with one and four persons?" both with a hearing aid if needed[32].

- Incontinence: asking the respondent whether he or she lost urine unintentionally[33].
- Performance testing: the performance-based tests of physical function included timed measures of walking speed, rising from a chair, putting on and taking off a cardigan, and maintaining balance in a tandem stand. The performance tests have been used in several studies and have been shown to be a reliable and valid measure of physical functioning[34, 35]. For the walking test, respondents were asked to walk 3 metres, turn around, and walk back the 3 metres as quickly as possible. For the chair-stand test, respondents were asked to fold their arms across their chest and to stand up from a sitting position and sit down five times as quickly as possible. For the cardigan test, respondents were asked to put on and take off the cardigan. For the ability to maintain balance in tandem stand the respondent was asked to put the heel of one foot in front of the other and to stand still as long as possible.

Categories of performance were created for each set of performance measures to permit analyses that included those unable to perform a task. For the walking test, chair-stand test and cardigan test, those who could not complete the task were assigned a score of 0. Those completing the task were assigned scores of 1 to 4, corresponding to the quartiles of time needed to complete the task, with the fastest time scored as 4. For the balance in tandem stand a score of 0 was assigned to those who were unable to perform the test or maintained the tandem stand for less than 3 seconds (< 3 s). For those maintaining a tandem stand for more than 3 seconds but less than 10 seconds (3–9.99 s) a score of 1 was assigned and for those maintaining the tandem stand for 10 seconds or more a score of 2. A summary performance scale, ranging from 0 to 14, was created by summing the category scores.

- Activities of daily living (ADL): functional limitations were assessed by asking the respondent to describe the degree of difficulty they had with six activities of daily living (ADL): climbing stairs, walking 5 min outdoors without resting, getting up and sitting down in a chair, dressing and undressing oneself, using own or public transportation, and cutting one's own toenails[36-38]. Response

categories ranged from (1) "No I cannot" to (5) "Yes without difficulty." The total score was calculated by summing the scores of all activities and ranged between 6 and 30.

- LASA Physical Activity Questionnaire (LAPAQ)[39]: the LAPAQ is a face-to-face questionnaire (http://ssg.scw.vu.nl/lasa) that covers the frequency and duration of walking outside, bicycling, gardening, light household activities, heavy household activities, and a maximum of two sport activities during the previous two weeks. Walking and bicycling for transportation purposes are considered as common daily activities, and not as sport activities. The duration of the activities assessed with the LAPAQ was categorized into six groups. The duration of the activities, 0, 1–15, 16–30, 31–60, 61–120 and > 120 min per day, were assigned scores 0, 1, 2, 3, 4 and 5 (called the duration score), respectively. The total score of the LAPAQ for each activity in two weeks was calculated by multiplying the frequency of the activity by the duration score. For instance, eight walking sessions of 45 min each in two weeks corresponded to eight ´ duration score 3 = 24. If the activity was performed several times per day, the total duration of that activity per day was calculated. For example, 45 walking sessions of 10 min each in two weeks corresponded to (45x10)/14 = 32 min of walking per day. In this example the score for walking was 14x duration score 3 = 42. The total activity was calculated by summing the scores of the individual activities over two weeks.
- Geriatric Depression Scale (GDS-15): the 15-item Geriatric Depression Scale (GDS-15) is the shortened, less time-consuming version of the 30-item GDS which has been especially designed to screen for depression in the elderly[40]. Both the long and the short form of the GDS focus on functional and mood symptoms of depression rather than on potentially misleading somatic features. Several studies have validated the use of the GDS-15 for screening for depressive disorders in old age in geriatric inpatients[41], outpatients[42] and in primary care[43]. It has been shown that the GDS-15 has a good accuracy in screening for depression in the community-living very elderly[44].
- MMSE[45]: cognitive function was assessed by the MMSE, with

scores ranging from 0 to 30 points (optimal). The test evaluates in a global way cognitive efficiency by examining orientation in time and space, short- and middle-term memory, calculation, comprehension and constructive praxis. Any score greater than or equal to 25 points is effectively normal (intact). Below this, scores can indicate severe (≤ 9 points), moderate (10–20 points) or mild (21–24 points) deficits[46]. The raw score may also need to be corrected for educational attainment and age.

- Barthel Index[47]: the Barthel Index consists of 10 items that measure a person's daily functioning, specifically the activities of daily living and mobility. The items include feeding, moving from chair to bed and return, grooming, transferring to and from a toilet, bathing, walking on a level surface, going up and down stairs, dressing, and continence of bowels and bladder. The assessment can be used to determine a baseline level of functioning and can be used to monitor improvement in activities of daily living over time. The items are weighted according to a scheme developed by the authors[47]. The person receives a score based on whether they have received help while doing the task. The scores for each of the items are summed to create a total score, with a maximum score of 100. The higher the score the more "independent" the person. Independence means that the person needs no assistance for any part of the task.
- Tinetti test[48]: the Tinetti test comprises a series of tests that measures subjects' gait and balance in order to estimate the risk of falls. Subjects were scored 0 to 2 on the individual items, with 0 representing the most impairment and 2 representing independence. The individual items were combined into three measures: (1) an overall gait score (12 points), (2) an overall balance score (16 points) and (3) a gait and balance score (28 points). Subjects who scored 25 to 28 were classified as at low risk of falls. Those who scored 19 to 24 points were classified as at moderate risk of falls and those who scored 18 or below were classified as at high risk of falls.
- IADL-E Lawton: the ability of subjects to perform instrumental activities of daily living (IADL-E) was measured using the scale developed by Lawton and Brody[49]. The instrument consists

of eight items (ability to use telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications and ability to handle finances) and has been widely accepted as a valid and reliable measure for use in elderly community populations. One item was added, namely the ability to repair and maintain the house. The scale was completed by the CRA during a home visit using the "best available" information, which included self-report, CRA observation, or proxy report. Responses were recorded for each item. To improve the sensitivity of the scale, the trial altered the scoring of each item from the original two-point scale to scores which ranged from 1 to 4. Scores increased with level of dependence, and the same scoring system was used for both sexes. If it was impossible to score an item, this item was excluded from the overall score. Scores ranged from 9/36 (independent) to 36/36 (complete dependency).

- IADL (Katz-score): the Katz Index of Activities of Daily Living is an assessment tool that is frequently used with the geriatric population in many settings, including patients' homes[50]. It is used to measure function and how it changes over time in older people who have chronic illnesses. The Katz scale considers six basic domains: bathing, dressing, toileting, ambulating or transferring, continence and feeding. For each of the six function domains, five possible function levels are scored ranging from complete independence (6/30) to complete dependence (30/30).
- The Groningen Frailty Indicator (GFI): this is a short 15-item questionnaire aiming to identify patients that have diminished reserves in one or more of the core domains of functioning[51, 52]. These domains are: mobility, physical fitness, comorbidity, weight loss, vision, hearing, cognition and psychosocial resources. It has empirically been shown that all these domains are associated with a variety of adverse outcomes. The current view on the clinical measurement of frailty encompasses the whole person's functioning and physiology, emphasizing the interaction of physical and psychosocial systems[53]. The GFI builds on the assumption that strong interaction effects often exist between different weaknesses of older patients, reinforcing each other into a downward spiral of

further decline.

- Sense of coherence: the concept of sense of coherence (SOC) was put forward by Aaron Antonovsky in 1979 to explain why some people become ill under stress and others stay healthy[54-56]. It arose from the salutogenic approach, that is, the search for the origins of health rather than the causes of disease. The SOC is defined as: "The extent to which one has a pervasive, enduring though dynamic, feeling of confidence that one's environment is predictable and that things will work out as well as can reasonably be expected." In other words, it is a mixture of optimism and control. It has three components: comprehensibility, manageability and meaningfulness. Comprehensibility is the extent to which events are perceived as making logical sense, that they are ordered, consistent and structured. Manageability is the extent to which a person feels they can cope. Meaningfulness is how much one feels that life makes sense and challenges are worthy of commitment. For this study the 13-item scale was used. Every item was scored with a Likert scale ranging from 1 to 7, generating a total scale range from 13–91, a high score representing a strong SOC. Before calculating the total score, five items were reversed according to the original codebook as presented by Antonovsky[57]. The division into a low and high/medium group was dichotomized at the lower tertile.
- Locus of Control (LOC): locus of control refers to the extent to which individuals believe that they can control events that affect them. Individuals with a high internal locus of control believe that events result primarily from their own behaviour and actions. Those with a high external locus of control believe that powerful others, fate, or chance primarily determine events. The Multidimensional Health Locus of Control (MHLC) Form A, developed by Wallston and Wallston in 1978, was used[58]. The MHLC, which is a six-point Likert scale, contains 18 questions classified into three subscales: Internal HLC, Powerful-Others HLC, and Chance HLC. Each subscale contains six questions. For each question subjects chose one out of six answers ranging from "strongly agree" to "strongly disagree".
- Grip strength: grip strength was measured in the dominant

hand using a JAMAR® Plus digital handheld dynamometer. Three attempts at maximal squeeze were recorded.

- Basic spirometry: this was performed using a Spirobank spirometer (MIR, Rome, Italy). This is a hand-held instrument for lung function tests that has been wired into a computer. Winspiro software (MIR) compares the measured values with reference tables and automatically calculates the reproducibility of the performed spirometry in accordance with European Respiratory Society guidelines[59]. The CRA enthusiastically demonstrated the correct manoeuvres before the patient attempted them. The minimum number of forced vital capacity (FVC) manoeuvres required to meet quality goals is three, but since older patients require an average of five, up to eight manoeuvres were performed when needed in order to meet the goals. When patients appeared to be exhausted the test was interrupted.
- Electrocardiogram (ECG): a 12-lead ECG was recorded on a QRS Universal ECG device (QRS Diagnostic, Plymouth, USA, www.qrsdiagnostics.com). QRS medical devices are manufactured under an ISO 13485 Registered Quality Management System. The Universal ECG device is FDA approved and CE Marked in accordance with medical device directive (MDD) 93/42/EEC. An automated protocol was produced by the QRS Diagnostic software based on the "Louvain" diagnostic algorithm[60]. Each ECG was digitally stored and analysed off-line by an experienced cardiologist according to the Minnesota Code Classification System for Electrocardiographic Findings.
- Bio-electrical impedance (BIA): BIA is based on the relationship between the volume of a conductor and its electrical resistance. We used BIA mainly to estimate skeletal muscle mass[61]. Validated formulas appropriate for assessment of fat-free mass (FFM) and skeletal muscle mass (SMM) in the elderly were used as suggested by Duerenberg et al.[62]. The BODYSTAT 1500 MDD device (Bodystat LTD, Douglas, Isle of Man, UK) was used and dual-frequency measurements were performed with patients in a supine position. Patients wearing a pacemaker were excluded from the procedure.

- Exhaled NO: Nitric oxide (NO) is detectable in the exhaled air of humans. An increase in the concentration of exhaled nitric oxide (eNO) has been found in asthmatic patients including those with mild disease[63]. Levels of eNO parallel the inflammatory process in the asthmatic airway[64]. Recommendations for standardized procedures for measurements of exhaled lower respiratory nitric oxide have been published by the American Thoracic Society[65]. The NIOX MINO portable device (Aerocrine, Solna, Sweden, www.aerocrine.com) was used. The device produces an auditory and visual feedback signal to guide patients. Patients were encouraged to perform a 10-second exhalation manoeuvre. When this appeared difficult, a 6-second procedure was accepted.

Echocardiography

Echocardiograms were performed at home using a commercially available portable system (CX50, Philips, Andover, Massachusetts, USA) with M-mode, 2-dimensional, and pulsed, continuous-wave and colour-flow Doppler capabilities. Echocardiograms were performed by a cardiology fellow fully trained in echocardiography. All patients were examined in left lateral decubitus. A complete examination comprising standard parasternal short and long axis, apical and subcostal 2D views was performed according to the recommendation of the American and European society of Echocardiography[66]. Colour, pulsed and continuous Doppler were used to assess the presence and severity of valvular lesions. Diastolic function was assessed using mitral flow velocities obtained by pulsed Doppler or pulsed tissue Doppler at the level of the mitral annulus. Additional apical and parasternal views for assessment of tissue velocity (colour tissue Doppler) and deformation (2D strain or speckle tracking) were also recorded. Still frames for M-Mode, continuous and pulsed Doppler and cineloops for assessment of left ventricular (LV) function were digitally stored on DVD and later transferred to a workstation. All the measurements were performed off-line using Xcelera software (Philips, Andover, Massachusetts, USA). LV function was calculated by the Simpson biplane method. Tissue velocity and

deformation were analysed using Q lab software (Philips, Andover, Massachusetts, USA).

Laboratory tests

Several blood specimens were collected on each patient after fasting (between 7.00 AM and 10.30 AM), and immediately stored in a refrigerated container until arrival in the central laboratory (< 3h after blood collection). Plasma (EDTA, heparin) or serum samples were obtained after centrifugation. They were separated as aliquots (n: 4-6, depending on the volume obtained) and immediately stored frozen at -80°C until analysis. The analytical process was organized to avoid several freeze-thaw cycles. The biomarkers investigated included a wide range of cardiac, renal, thyroïd, bone metabolism, nutritional and inflammatory biomarkers, such as BNP and NTpro-BNP, TSH and free T4, creatinine and cystatin C, HDL- and LDL-cholesterol, total-cholesterol and triglycerides, hemoglobin, calcium, 25-hydroxyvitamin D, parthyroid hormone, phosphorus, transthyretin (prealbumin), IGF1, osteocalcin, usCRP, CMV IgG, a series of trace elements (including aluminium, zinc, copper, selenium, manganese, nickel, etc.), Clara Cell proteins (CC16) and surfactant protein D (SPD). A large panel of inflammatory biomarkers and cytokines (12 Cytokines Array 1) was analyzed using Biochip arrays on the Evidence Investigator™ analyzer (Randox Laboratories Limited, Crumlin, UK). The combination of immobilised ligands specific to different bio-markers, chemiluminescent immunoassays and charged coupled device camera enables to analyze simultaneously the 12 cytokines using a limited volume of serum (100 µL).

All measurements were performed in the laboratories of the Cliniques universitaires St Luc, Brussels, except the CC16 and SPD assays, determined in the laboratory of the Louvain centre for Toxicology and Applied Pharmacology (LTAP, Université Catholique de Louvain, Medical School, Brussels) in accordance with strict quality controls programmes and proficiency testing schemes. The UniCel® Dxl 800 Immunoassay System (Beckman-Coulter, Brea, USA) was used to determine the BNP, Parathyroid hormone

(PTH), TSH, and free T4 concentrations; the Dade-Dimension® Xpand (Siemens, Deerfield, USA) was used to measure the NTpro-BNP concentration (NTpBNP); the UniCel® DxC 800 Synchron (Beckman-Coulter, Brea, USA) was used to measure creatinine, HDL- and LDL-cholesterol, Total-cholesterol, triglycerides, calcium, phosphorus, transthyretin, usCRP, and cystatin C. The Sysmex XE-2100 automated hematology analyser (Milton Keynes, UK) was used to measure the hemoglobin concentrations. The CMV IgG concentrations were measured on the ARCHITECT® i4000SR (Abbott Diagn, Abbott Park, Illinois, USA). The 25-OH-Vitamin D, IGF1, and osteocalcin were measured on the LIAISON® (Diasorin, Saluggia, Italy). Twenty three trace metal elements were simultaneously measured by Inductively Coupled Plasma Mass Spectrometry (ICP-MS), on a 7500 Series ICP-MS system (Agilent Technologies, Santa Clara, USA). CC16 and SPD were determined by ELISA using a Tecan plateform (Männedorf, Switzerland) and reagents kits from BioVendor (Brno, Czech Republic).

Table 1 displays the main characteristics of the assays, including the biological matrix, reagents kits, normal ranges, inter-assay imprecision (CV%), and the limits of detection (LOD). The list of the 12 cytokines analyzed together with their sensitivity is reported in Table 2.

Table 1. Main characteristics of the analytical methods used for the laboratory tests

Test (unit)	Analyser/kits	Matrix	Reference range	Reproducibility CV%	LOD
BNP (pg/mL)	DxI 800/Biosite	Plasma EDTA	5–100	5.4–6.7	1
NT-proBNP (pg/mL)	Dimension/Siemens	Serum	< 450 (> 75 yrs)	3.9–4.3	NR
TSH (µU/mL)	DxI 800/Beckman	Serum	0.2–3.5	3.72–4.96	0.003
Free T4 (ng/dL)	DxI 800/Beckman	Serum	0.9–1.8	4.3–8.8	0.5
Parathyroid hormone (pg/ml)	DxI 800/ Beckman	Serum	16–81	2.8–6.4	1
Creatinine (mg/dL)	DxC 800/Beckman	Serum	0.6–1.4	1.7–9.5	0.05
Cystatin C (mg/L)	DxC 800/Gentian	Serum	0.5–1.0	2.95 – 4.38	<0.1
HDL (mg/dL)	DxC 800/Beckman	Plasma heparin	> 60	2.1–3.4	5
Total cholesterol (mg/dL)	DxC 800/Beckman	Plasma heparin	< 200	1.48–1.6	5
Triglycerides (mg/dL)	DxC 800/Beckman	Plasma heparin	< 150	2.2–2.6	10
Haemoglobin (g/dL)	Sysmex XE-2100	Whole blood	12–17	0.5–1.0	<1.0
Calcium (mg/dL)	DxC 800/Beckman	Serum	8.6–10.0	1.0–2.2	2
Phosphorus (mg/dL)	DxC 800/ Beckman	Serum	2.4–4.7	0.6–3.0	0.5
Transthyretin (mg/dL)	DxC 800/Beckman	Serum	18–38	3.6–4.2	2
usCRP (mg/dL)	DxC 800/Beckman	Serum	< 0.3	4.1–5.1	0.02
CMV IgG (A.U./L)	Architect i4000/Abbott	Plasma EDTA	< 6 (normal) 6–15 (suspicion)	5.9–6.2	NA
25-OH-Vitamin D (ng/mL)	Liaison/Diasorin	Serum	30–100	5.2–8.4	< 5.0
IGF1 (ng/mL)	Liaison/Diasorin	Serum	70–140 (> 75 yrs)	5.8–6.1	< 15
Osteocalcin (ng/mL)	Liaison/ Diasorin	Serum	3–7	7.4–7.6	< 1.0
Aluminium (µg/dL)	ICP-MS, Agilent/NA	Plasma heparin*	0.2–1.0	8.9	0.1
Copper (µg/dL)	ICP-MS, Agilent/NA	Plasma heparin*	70–170	1.22	3.0
Zinc (µg/dL)	ICP-MS, Agilent/NA	Plasma heparin*	70–120	1.39	5
Selenium (µg/dL)	ICP-MS, Agilent/NA	Plasma heparin*	5–15	1.18	0.5
CC16	ELISA	Serum	2–20	4–9	1.0
SPD	ELISA	Serum	50–150	4.2–9.8	0.2

CV: coefficient of variation; LOD: limit of detection; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide; NR: not reported; TSH: thyroid stimulating hormone; HDL: high-density lipoprotein; usCRP: ultrasensitive C-reactive protein; CMV IgG: cytomegalovirus immunoglobulin G; NA: not applicable; IGF: insulin-like growth factor; * special sampling tubes free of aluminium and other trace elements; CC16: Clara cell protein 16; SPD: surfactant protein

Table 2. Panel of cytokines measured on the evidence investigator ™ analyzer (Randox) with their respective analytical ranges, imprecision and sensitivities

Cytokine Array I panel	Assay range	Imprecision CV%	LOQ
Interleukin-1 α (IL-1 α) (pg/mL)	0–500	5.9–10.7	0.8
Interleukin-1 β (IL-1 β) (pg/mL)	0–250	7.0–13.1	1.6
Interleukin-2 (IL-2) (pg/mL)	0–3000	7.2–10.0	4.8
Interleukin-4 (IL-4) (pg/mL)	0–900	6.4–10.0	6.6
Interleukin -6 (IL-6) (pg/mL)	0–900	8.7–15.4	1.2
Interleukin-8 (IL-8) (pg/mL)	0–3000	8.7–10.1	7.9
Interleukin-10 (IL-10) (pg/mL)	0–1000	6.1–9.4	1.8
Epidermal Growth Factor (EGF) (pg/mL)	0–900	4.0–7.4	2.9
Interferon-γ (IFN- γ) (pg/mL)	0–1500	9.1–13.4	3.5
Monocyte Chemotactic Protein-1 (MCP-1) (pg/mL)	0–1500	5.6–14.7	13.2
Tumour Necrosis Factor- α (TNF- α) (pg/mL)	0–1500	8.1–13.0	4.4
Vascular Endothelial Growth Factor (VEGF) (pg/mL)	0–3000	6.0–13.4	14.6

CV: coefficient of variation; LOQ: limit of quantification as the lowest concentration with imprecision < 20% for 20 replicates

Study population

Between November 2, 2008 and September 15, 2009, 567 subjects were included in the BF_{C80+} (Figure 1). Three hundred subjects were included using the first sampling method and 267 using the second sampling method. All study participants underwent at least one study visit and 546 participants underwent all visits. Table 3 shows the socio-demographic characteristics of the study population. Women represented 63.1% (n = 358) of the

study population and had a mean age of 85.0 ± 3.9 years. Male participants had a mean age of 84.3 ± 3.3 years. The majority of study participants lived at home (89.9%) and had a low level of education (69.5% ≤ lower secondary education). Of the participants living at home 188 (36.9%) received professional help and 84 (16.5%) professional care at home.

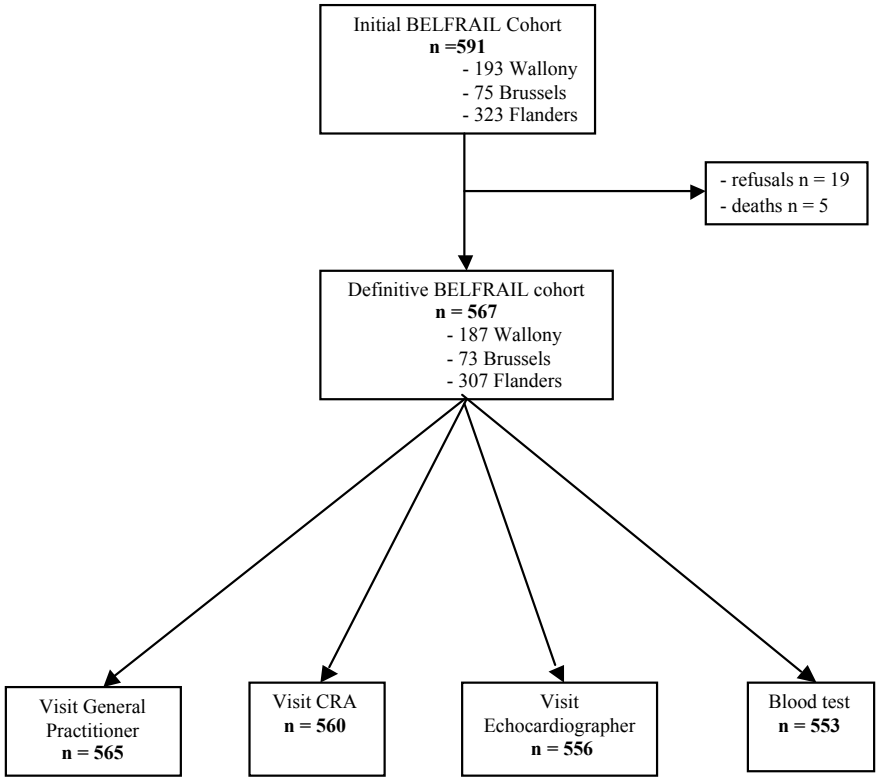

Figure 1. Inclusion of study participants

Table 3. Socio-demographic data of participants in the BELFRAIL cohort (n = 567)		
	n (%)	**Belgian population, %**
Male	209 (36.9)	33.5
Age		
Women 80–84	204 (36.0)	36.8
Women 85–89	116 (20.5)	20.6
Women ≥ 90	38 (6.7)	9.2
Men 80–84	130 (22.9)	21.5
Men 85–89	66 (11.6)	9.4
Men ≥ 90	13 (2.3)	2.7
Current Family Situation		
Married	239 (42.5)	
Divorced	11 (2.0)	
Widow(er)	281 (49.9)	
Single	20 (3.6)	
Other	12 (2.1)	
Institutionalized	57 (10.1)	
Level of Education		
Without qualifications	5 (0.9)	
Primary school	207 (36.8)	
Lower secondary education	179 (31.8)	
Higher secondary education	98 (17.4)	
College	55 (9.8)	
University	17 (3.0)	
Professional help at home	188 (36.9)	
Care at home	84 (16.5)	

There was a high burden of comorbidity in the population under study. Only six participants (1.1%) were free of any pathology. Non-cardiovascular morbidity was reported in 459 participants (81.2%) (Table 4) and cardiovascular morbidity in 524 participants (92.7%) (Table 5). Figure 2 shows that a high proportion of the study population had three or more non-cardiovascular (26.4%) or cardiovascular (53.5%) pathologies.

Table 6 shows the time between the different study visits.

Table 4. Non-cardiovascular morbidity of participants in the BELFRAIL cohort (n = 567)

	Active pathology* n (%)	Cured pathology n (%)	Unknown$, n (%)
Thyroid dysfunction	51 (9.0)	23 (4.1)	1 (0.2)
Hypofunction	47 (8.4)	5 (0.9)	2 (0.4)
Hyperfunction	1 (0.2)	15 (2.7)	3 (0.5)
Anaemia	50 (8.9)	23 (4.1)	0 (0)
Asthma	27 (4.8)	7 (1.2)	5 (0.9)
COPD	65 (11.5)	–	12 (2.1)
Parkinson's disease	16 (2.8)	–	3 (0.5)
Arthritis	28 (5.0)	23 (4.1)	1 (0.2)
Osteoarthritis	324 (58.0)	–	4 (0.7)
Osteoporosis	125 (22.5)	–	17 (3.1)
Cancer	43 (7.6)	73 (12.9)	5 (0.9)
Depression	74 (13.1)	32 (5.7)	8 (1.4)
Renal insufficiency	64 (11.4)	5 (0.9)	9 (1.6)
Hip prosthesis£	73 (13.0)	–	–
Knee prosthesis£	44 (7.8)	–	–

*Present (even if well controlled by treatment) or having occurred less than six months ago; $Unknown or doubt by general practitioner; £Less or more than 12 months ago.

Table 5. Cardiovascular morbidity in participants in the BELFRAIL cohort (n = 567)

	n (%)	Objectified*, n (%)	Unknown$, n (%)
Hypertension	396 (70.1)	–	2 (0.4)
Hyperlipidaemia	245 (44.0)	–	3 (0.5)
Diabetes	107 (18.9)	–	4 (0.7)
Angina pectoris	93 (16.5)	58 (62.4)	24 (4.3)
Myocardial infarction	62 (11.0)	59 (95.2)	6 (1.1)
Cardiomyopathy	56 (10.0)	–	–
TIA	58 (10.5)	34 (58.6)	9 (1.6)
CVA	46 (8.3)	40 (87.0)	5 (0.9)
Peripheral arterial disease	52 (9.2)	43 (82.7)	15 (2.7)
Episode of decompensated heart failure	60 (10.6)	47 (78.3)	7 (1.2)
Episode of atrial fibrillation	113 (20.1)	–	5 (0.9)
Chronic atrial fibrillation	58 (10.3)	–	–
Valvular disease	140 (24.9)	135 (96.4)	7 (1.2)
Peripheral oedema	237 (43.8)	–	5 (0.9)

*The general practitioner was asked to report if the pathology was objectified at the time of the diagnosis; $Unknown or doubt by general practitioner.

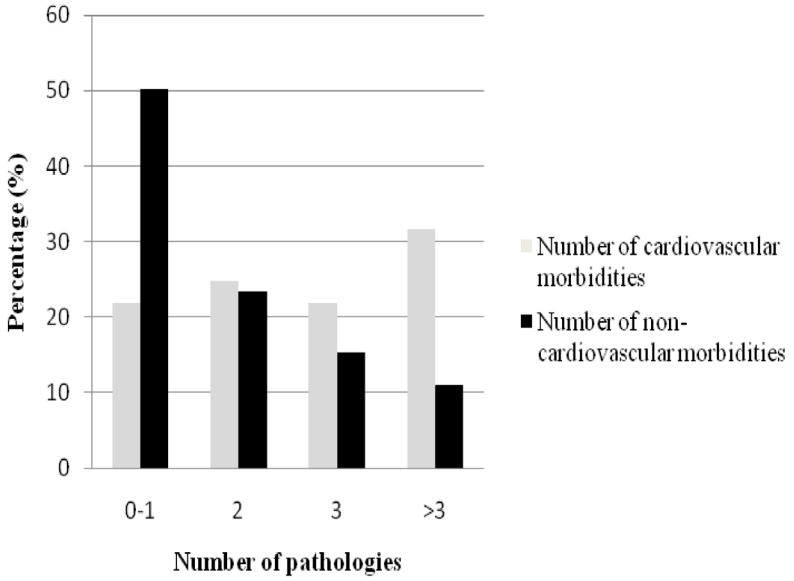

Figure 2. Number of comorbidities

Table 6. Time in days between different study visits

	Median [IQR]
GP–CRA	21 [10–37]
GP–blood test	28 [14–43]
GP–echocardiography	29 [14–43]
CRA–echocardiography	7 [3–15]
CRA–blood test	7 [4–16]
Blood test–echocardiography	3 [1–13]

IQR: interquartile range

Table 7 describes the basic functional status of participants in the BF_{C80+}. In general, there was a low prevalence of functional limitations in the population under study, with 9.8% having a score ≤ 15 on the ADL scale and 10% having a score > 10 on the IADL scale. A large number of subjects had a high score on the GDS-15 questionnaire, with 20.6% scoring ³ 5. Only 15 subjects (2.9%) had an MMSE score ≤ 15. In 8.7% of the study participants, an increased risk of falls according to the Tinetti test was found.

Table 7. Functional status of the BF_{C80+} population (n = 567)

	N	Median [IQR]	Cut-off value	n (%)
ADL	559	25 [21–27]		
GDS-15	557	2 [1–4]	≥ 5	115 (20.6)
MMSE	557	28 [25–29]	≥ 25	443 (79.5)
			21–24	70 (12.6)
			10–20	39 (7.0)
			≤ 9	5 (0.9)
Tinetti	549	27 [24–28]	25–28	406 (74.0)
			19–24	95 (17.3)
			≤ 18	48 (8.7)
IADL	559	6 [6–8]		

ADL: Activities of Daily Living; GDS-15: 15-item Geriatric Depression Scale; MMSE: Mini-Mental State Examination; IADL: Instrumental Activities of Daily Living; IQR: interquartile range.

Follow-up

In October 2009 a basic report for every included patient was sent back to inform the GP. This report included the measurements of height and weight, blood pressure measurements, the results of the performance tests, ADL, MMSE, GDS-15, Barthel's Index and Tinetti test, the unvalidated electronically generated results of the spirometry and ECG and a basic report on major cardiac abnormalities found with echocardiography.

After a follow-up period of a maximum 16 months (March 2010 for Wallony and July 2010 for Flanders and Brussels), and yearly thereafter, a detailed follow-up questionnaire will be sent to the participating GP centres. The GPs will be asked to fill out a questionnaire for every included patient describing his/her health status. The questionnaire includes questions on mortality and cause of mortality, episodes (> 1 day) and cause of hospitalization, change of living and family situation and new comorbidities (fall, cardiovascular event, heart failure, new diagnosis of cancer, renal replacement therapy) that occurred in the past 16 months. The GPs will be asked to report changes in treatment and to record if they

changed the management of the patient based on the basic report that was sent back. For every included patient, the GP will be asked if he agrees that the patient can be contacted for the follow-up examination.

In May 2010 (Wallony) and September 2010 (Flanders and Brussels) every participant will be contacted again for the follow-up examination. The follow-up examination will include anthropometric measurements, evaluation of blood pressure, vision, hearing, incontinence, anamnesis, performance testing, ADL, GDS-15, MMSE, Tinetti Test, GFI, LOC, grip strength, spirometry, ECG, bio-electrical impedance, exhaled NO, echocardiography and new blood tests.

Data check and analysis

Data entry of all questionnaires and examination forms is done by the data manager. Data is inserted with FileMaker® Pro 8.0 (FileMaker Inc., Santa Clara, CA, USA) or Microsoft Excel®. The quality of data entry is systematically verified by a trained researcher in order to detect errors. SPSS 16.0 (SPSS Inc., Chicago, IL, USA) will be used for data analysis. Analyses will combine cross-sectional and prospective approaches. The prospective analyses will be performed on the entire cohort. Outcome measures will be registered for every patient that underwent at least one module of the assessment. The variety of dimensions included in the BF_{C80+} will enable us to correct for a wide range of factors in the analyses and multivariate models.

For the cross-sectional part of the study, very few data are missing. For most variables, less than 5% of data are missing. Only the following variables have more missing data: calf skin fold (n = 55, 9.7%), sense of coherence (n = 70, 12.3%), locus of control (n = 71, 12.5%), bio-electrical impedance (n = 278, 49.0%) and exhaled NO (n = 311, 54.9%).

Future analysis and publications from this cohort will be carried out using the STROBE criteria [67].

DISCUSSION

In the BELFRAIL Cohort Study we were able to include 567 participants who underwent a thorough multi-dimension investigation in order to take a detailed "medical photograph" of every included subject. We were able to construct a cohort representative in gender and age of the very elderly living in Belgium. The mean age of women and men older than 80 living in Belgium (84.9 years and 83.9 years, respectively)[68] was comparable to the mean age found in this cohort. Moreover, the fact that participants were included by their GP enabled us to create a heterogeneous population representative of the very elderly since more than 90% of people aged 80+ in Belgium regularly see their GP.

This is the first cohort study of very elderly people living in Belgium. To our knowledge this is also the first cohort of elderly in which a large set of technical examinations (ECG, spirometry, echocardiography, bio-electrical impedance, etc.) was done at home or in a nursing home. People aged 80+ are the fastest growing segment of the population in industrialized countries, and their number will peak in 2050. Research trying to understand the complexity of the geriatric patient is needed in order to anticipate booming health care expenditures and guarantee future fundable social security. Therefore, the BF_{C80+} was designed to acquire a better understanding of the epidemiology and pathophysiology of chronic diseases in the very elderly, and to study the dynamic interaction between health, frailty and disability in a multi-system approach.

The BF_{C80+} focuses on cardiac dysfunction and chronic heart failure, lung function, sarcopenia, renal insufficiency and immunosenescence. This wide variety of dimensions will enable us not only to investigate in depth the relation between these different systems but also to instigate new research questions with this unique database of community-dwelling elderly.

LIST OF ABBREVIATIONS USED

GP: general practitioner; CRA: clinical research assistant; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide; ECG: electrocardiogram; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; GFR: glomerular filtration rate; CMV: cytomegalovirus; UCL: Université Catholique de Louvain; CD: compact disc; MMSE: Mini-mental state examination; TIA: transient ischaemic attack; CVA: cerebro-vascular accident; PTCA: percutaneous transluminal coronary angioplasty; MRC: Medical Research Council; JVP: jugular venous pressure; NYHA: New York Heart Association; ADL: activities of daily living; LAPAQ: LASA physical activity questionnaire; GDS: geriatric depression scale; IADL-E: instrumental activities of daily living; IADL: index of activities of daily living; GFI: Groningen frailty indicator; SOC: sense of coherence; LOC: locus of control; MHLC: multidimensional health locus of control; FVC: forced vital capacity; ISO: International Organization for Standardization; FDA: Food and Drug Administration; BIA: bioelectrical impedance analysis; FFM: fat-free mass; SMM: skeletal muscle mass; eNO: exhaled nitric oxide; 2D: two-dimensional; LV: left ventricular; TSH: thyroid stimulating hormone; HDL: high-density lipoprotein; LDL: low-density lipoprotein; usCRP: ultrasensitive C-reactive protein; CMV IgG: cytomegalovirus-specific immunoglobulin G; IGF: insulin-like growth factor; CC16: Clara cell protein 16; SPD: surfactant protein D; CV: coefficient of variation; LOD: limit of detection; STROBE: Strengthening The Reporting of OBservational studies in Epidemiology.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

BV, principal investigator, drafted the manuscript. JD and BV initiated the BELFRAIL study, and are responsible for its design, conduct and analysis. As members of the BELFRAIL study committee, AP and PW are involved in the development of the study and obtaining research funding. NR performed all echocardiography, and NR and AP are responsible for the analyses of the echocardiography. PW, HM and PAO are responsible for the laboratory analyses. All authors participated in the critical revision of the manuscript.

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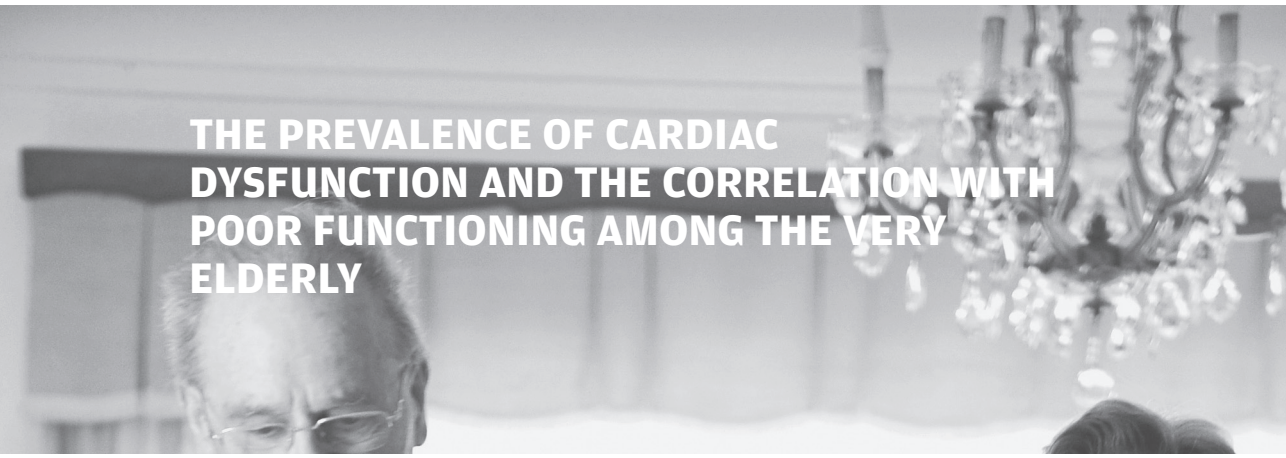
CHAPTER 5



THE PREVALENCE OF CARDIAC DYSFUNCTION AND THE CORRELATION WITH POOR FUNCTIONING AMONG THE VERY ELDERLY

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ABSTRACT

Background: Little is known about the relationship between cardiac dysfunction and poor functioning in the elderly. This study sought to describe the prevalence of cardiac dysfunction in the very elderly and to investigate the correlation between echocardiographic abnormalities and indicators of poor functioning.

Methods: A cross-sectional analysis within the BELFRAIL (BF_{C80+}) study of 567 subjects aged 80 years and older. The clinical research assistant performed an extensive examination including performance testing, questionnaires and technical examinations. Echocardiography was performed at the subject's home by a cardiologist using a portable system.

Results: The mean age of the participants was 84.7 years and 62.9% were women. Severe cardiac dysfunction was found in 19.3% and was defined as systolic dysfunction (5.8%), valvular heart disease (10.4%) or isolated severe diastolic dysfunction (3.1%). Severe cardiac dysfunction showed to be an independent identifier of poor performance (OR 1.8 (95% CI 1.1 – 3.2)), a low LAPAQ (LASA Physical Activity Questionnaire) score (OR 1.9 (95% CI 1.2 – 3.3)) and a high GDS-15 (Geriatric Depression Scale) score (OR 1.7 (95% CI 1.0 – 2.9)). This relationship was mainly explained by the strong independent correlation between aortic stenosis and poor functioning. Classic indicators of systolic and diastolic dysfunction were not able to identify participants with poor functioning.

Conclusion: This study shows the very elderly represent a very heterogeneous group of subjects with a high prevalence of comorbidities, among whom poor functioning might be triggered by multiple causes. Severe cardiac dysfunction, and more specifically aortic stenosis, showed an independent relationship with poor functioning.

INTRODUCTION

In the coming decades, the proportion of elderly people living in western society will increase dramatically. By 2050, 10% of people living in Belgium will have reached the age of 80 or older[1]. This forthcoming "grey epidemic" will lead to an explosion of chronic diseases and generate numerous complicated cases with multiple comorbid conditions. Comorbidities are known to have a detrimental impact on physical and cognitive functioning[2]. Moreover, elderly patients are often excluded from randomized trials, resulting in important implications for clinical management.

In this ageing society, the burden of chronic heart failure is rising. Prevalence increases with age, from 0.7% in people aged 55–64 years, to 2.7% in those aged 65–74 years and 13.0% in those aged 75–84 years[3]. Heart failure not only leads to increased mortality but also has negative consequences for functional status and well-being[3]. Previous research has shown a relationship between cardiac dysfunction and limited physical capacity, depression and cognitive impairment[4-8]. However, little is known about this relationship in the very elderly. Furthermore, elderly patients present as a very heterogeneous population, with the active independent community-dwelling elder at the one end and the bedridden geriatric patient at the other end of the spectrum, where poor functioning is possibly the result of an interaction of multiple causes.

The BELFRAIL study ($BF_{C80+)}$ was designed to acquire a better understanding of the epidemiology and pathophysiology of chronic diseases in the very elderly and to study the dynamic interaction between health, frailty and disability in a multi-system approach[9]. This cross-sectional analysis describes in detail the echocardiographic findings and prevalence of cardiac dysfunction in a large population-based sample of elderly patients. Furthermore, the correlation between structural and functional echocardiographic abnormalities and indicators of poor physical and cognitive functioning will be explored to determine the independent contribution of cardiac dysfunction to poor functioning in this population, which exhibits a high prevalence of comorbidities.

METHODS

Study population

The BF_{C80+} study is a prospective, observational, population-based cohort study of subjects aged 80 years and older in three well-circumscribed areas of Belgium. The study design and characteristics of the cohort have been described in detail[9]. In brief, 29 general practitioner (GP) centres were asked to include patients aged 80 and older. Only three exclusion criteria were used: severe dementia (mini-mental state examination (MMSE) <15), in palliative care and medical emergency. Between November 2, 2008 and September 15, 2009, 567 subjects were included in the BF_{C80+} study. Every study participant was invited to attend four study visits. The GP recorded background variables and medical history and performed a detailed anamnesis. The clinical research assistant (CRA) performed an extensive examination including performance testing, questionnaires and technical examinations. Echocardiography was performed at the subject's home by a cardiologist. A blood sample was collected in the morning. All participants in the study gave informed consent and the Biomedical Ethics Committee of the Medical School of the Université Catholique de Louvain (UCL) of Brussels approved the study.

Clinical characteristics

Symptoms of dyspnoea (according to the MRC (Medical Research Council) dyspnoea scale[10]), fatigue and ankle swelling were registered.

Active non-cardiovascular morbidities were defined as a positive response from the GP regarding the presence of thyroid problems, asthma, COPD, Parkinson's disease, arthritis, osteoarthritis, documented osteoporosis, malignancies and depression. Active status was defined as being present or having occurred less than six months ago. The GP was asked whether the subject had had a knee or hip replacement. The total number of non-cardiovascular morbidities (range 0 – 11) was calculated for every subject.

Indicators of the cardiovascular risk profile were presence of hypertension, diabetes mellitus and hyperlipidaemia, as determined by the GP. Smoking status was registered, and the Body Mass Index (BMI) was calculated based on a standardised measurement of weight and height by the CRA.

Cardiovascular morbidities were defined as a positive response for the history of angor pectoris or myocardial infarction, transient ischemic attack (TIA) or cerebro-vascular accident (CVA), peripheral arterial disease, decompensated heart failure, and important cardiovascular interventions or surgery (percutaneous transluminal coronary angioplasty (PTCA) or stenting, coronary or arterial surgery).

Data on relevant cardiovascular medication including diuretics, potassium-sparing agents, ß-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium antagonists, cardiac glycosides and lipid-modifying agents were registered. The total number of cardiovascular medications was calculated for every participant.

A 12-lead ECG was recorded on a QRS Universal ECG device (QRS Diagnostic, Plymouth, USA, www.qrsdiagnostics.com). Each ECG was digitally stored and analysed off-line by an experienced cardiologist according to the Minnesota Code Classification System for Electrocardiographic Findings. A prior myocardial infarction (Code 1-1 or 1-2, excluding 1-2-8), atrial fibrillation (Code 8-3-1), presence of artificial pacemaker (Code 6-8), LV hypertrophy (Code 3-1, 3-2 or 3-3) or left bundle branch block (LBBB) (Code 7-1-1) were retained. The investigator was asked at the end of the protocol to indicate whether the ECG was completely normal.

Laboratory tests

Plasma (EDTA) and serum samples were stored frozen at -80°C until analysis. Haemoglobin concentrations were measured on whole blood using the Sysmex XE-2100 automated haematology analyser (Milton Keynes, UK). Anaemia was defined as haemoglobin levels <12g/dL for women and <13g/dL for men[11]. Creatinine and usCRP were measured on serum using the UniCel® DxC

800 Synchron (Beckman-Coulter, Brea, USA). Renal function was estimated using the MDRD formula[12]. Plasma levels of BNP were measured using the Biosite® kit on a UniCel® DxI 800 Immunoassay System (Beckman-Coulter, Brea, USA). The coefficient of variation (CV) ranged from 5.4 to 6.7%. Serum NT-proBNP levels were measured using the Dade-Dimension® Xpand (Siemens, Deerfield, USA). The CV ranged from 3.9 to 4.3%.

Indicators of poor functioning

Functioning was assessed with standardised and validated self-reported and objective measures of physical activity and cognitive functioning. For further analysis these outcome variables were dichotomized, because most of them do not present a normal distribution.

- Activities of daily living (ADL)[13]: functional limitations were assessed by asking the respondent to describe the degree of difficulty they had with six activities of daily living. Response categories ranged from (1) "No I cannot" to (5) "Yes without difficulty." The total score was calculated by summing the scores of all activities and ranged between 6 and 30. Poor functioning was defined as the lowest gender-specific quintile.
- Performance testing[14]: the Short Physical Performance Battery (SPPB) is a reliable measure able to predict adverse outcomes, including mortality and the onset of new disability and is appropriate for research settings[14]. The SPPB included timed measures of walking speed, rising from a chair, putting on and taking off a cardigan and maintaining balance in a tandem stand. Categories of performance were created for each set of performance measures to permit analyses that included those unable to perform a task. For the walking test, chair-stand test and cardigan test, those who could not complete the task were assigned a score of 0. Those completing the task were assigned scores of 1 to 4, corresponding to the quartiles of time needed to complete the task, with the fastest time scored as 4. For the balance in tandem stand, a score of 0 was assigned to those who were unable to perform the test or who maintained the tandem stand for less than 3 seconds. For

those maintaining a tandem stand for more than 3 seconds but less than 10 seconds, a score of 1 was assigned; those maintaining the tandem stand for 10 seconds or more were awarded a score of 2. A summary performance scale, ranging from 0 to 14, was created by summing the category scores. Poor functioning was defined as the lowest gender-specific quintile of the total score.

- Longitudinal Aging Study Amsterdam (LASA) Physical Activity Questionnaire (LAPAQ)[15]: the LAPAQ covers the frequency and duration of walking outside, bicycling, gardening, light household activities, heavy household activities, and a maximum of two sport activities during the previous two weeks. The duration of the activities assessed with the LAPAQ was categorised in six groups. The duration of the activities, 0, 1–15, 16–30, 31–60, 61–120 and >120 min per day, were assigned scores of 0, 1, 2, 3, 4 and 5, respectively. The total score of the LAPAQ for each activity in two weeks was calculated by multiplying the frequency of the activity by the duration score. The total activity was calculated by summing the scores of the individual activities over two weeks. Poor functioning was defined as a score of 0 or the lowest gender and season-specific quartile of the remaining scores.
- MMSE[16]: cognitive function was assessed by the MMSE, with scores ranging from 0 to 30 points (optimal). The test evaluates cognitive efficiency by examining orientation in time and space, short- and middle-term memory, calculation, comprehension and constructive praxis. Poor cognitive functioning was defined as a score ≤24 points.
- Geriatric Depression Scale (GDS-15)[17]: the GDS-15 is the shortened, less time-consuming version of the 30-item GDS, which has been especially designed to screen for depression in the elderly. Scores range from 0 (optimal) to 15 points. Poor functioning was defined as a score ≥5.
- Muscle strength: grip strength was measured in the dominant hand using a JAMAR® Plus digital handheld dynamometer. Three attempts at maximal squeeze were recorded. Poor performance was defined as the lowest gender-specific quintile of the best attempt.

Echocardiography

Echocardiograms were performed at the subject's home using a commercially available portable system (CX50, Philips, Andover, Massachusetts, USA) with M-mode, 2-dimensional, and pulsed, continuous-wave and color-flow Doppler capabilities. Echocardiograms were performed by a cardiologist. All patients were examined in left lateral decubitus. A complete examination comprising standard parasternal short- and long-axis, apical and subcostal 2D views was performed according to the recommendations of the American and European Society of Echocardiography[18]. Still frames for M-Mode, continuous and pulsed Doppler and cineloops for assessment of left ventricular (LV) function were digitally stored on DVD and later transferred to a workstation. All the measurements were performed off-line using Xcelera software (Philips, Andover, Massachusetts, USA).

LV function was calculated by the Simpson biplane method[18]. Echo image quality was assessed semiquantitatively on a 5-point scale: A = complete endocardial definition; B = visualization of all segments, but not as adequate as A; C = inadequate visualization of 1 or 2 segments, but adequate visualization of adjacent segments within the same coronary territory; D = inadequate visualization of ≥3 segments, but adequate visualization of adjacent segments of the same territory; E = inadequate visualization of ≥1 whole territory[19]. In case of poor quality of the images (score E) the LV function was independently re-evaluated by a second cardiologist. Subjects were evaluated as having a poor LV function if both cardiologists visually estimated the ejection fraction (EF) was ≤50%. LA (left atrial) volume was measured using the biplane area-length formula[18].

The function of the mitral, aortic and tricuspid valves were evaluated with color Doppler echocardiography after optimizing gain and Nyquist limit. Standard continuous and pulsed-wave Doppler recordings were acquired. Stenotic and regurgitant valve diseases were evaluated according to semiquantitative and quantitative methods recommended by the American Society of Echocardiography[20, 21]. Clinically relevant valvular heart disease was defined as any mitral stenosis severity, severe aortic stenosis

(aortic valve area <1cm^2), moderate or severe mitral regurgitation, and moderate or severe aortic regurgitation. When tricuspid regurgitation was present, pulmonary artery pressure was estimated using the modified Bernoulli equation[20].

Diastolic function was assessed using mitral flow velocities obtained by pulsed Doppler and pulsed tissue Doppler at the level of the mitral annulus[22]. Additional apical and parasternal views for assessment of tissue velocity (color tissue Doppler) were also recorded. Tissue velocity was analysed using Q lab software (Philips, Andover, Massachusetts, USA). The ASA-EAE guidelines were used to assess the presence of diastolic dysfunction[22].

Echocardiographic abnormalities were defined using previously published cut-off values[18, 22, 23].

Data analysis

Continuous data are presented as the median and inter-quartile range (IQR). Categorical data are presented as numbers and frequencies. Comparisons between categories of cardiac dysfunction were performed using analysis of variance (ANOVA) testing or the Kruskal-Wallis test (nonparametric data) for unpaired data. Echocardiographic parameters of diastolic function were compared between categories of diastolic dysfunction using the Jonckheere–Terpstra test (*P* for trend). The relation between structural and functional echocardiographic abnormalities and indicators of poor functioning was explored by calculating odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) using bivariate logistic regression analysis. Afterwards, multivariable regression analysis adjustments for known confounders including age, gender, institutionalisation, BMI, anaemia, creatinine, log-transformed levels of usCRP (LogusCRP) and the number of non-cardiovascular morbidities were performed with echocardiographic parameters that showed a significant bivariate relationship ($P \leq 0.10$). Because diastolic function and pulmonary artery pressure (PAP) was not available for all participants, three models were used for multivariable regression analysis: one for the entire population (model 1, n=556) using LV and LA dimensions, systolic function and

valvular function, one for subjects in whom diastolic function was also determined (model 2, n=458) and one for those in whom also PAP was estimated (model 3, n=358). Data analysis was performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Echocardiography was performed in 556 participants (98.1%) including 350 women (62.9%) and 206 men (37.1%). The mean age of the participants was 84.7 ± 3.6 years with 41.1% older than 85 and 9% older than 90 years. A total of 55 participants (10%) were institutionalised. The median time between the CRA visit and echocardiography was 7 days (IQR 3–15 days); the median time between the GP visit and the echocardiography was 29 days (IQR 14–43 days). Echo image quality was scored A in 284 subjects (51.1%), B in 142 (25.5%), C in 68 (12.2%), D in 45 (8.1%) and E in 17 subjects (3.1%).

Prevalence of cardiac dysfunction

Table 1 shows the echocardiographic characteristics for the population under study. Most participants showed normal LV end-diastolic and end-systolic internal dimensions and had a preserved left ventricular ejection fraction (EF>50%) (n = 524, 94.2%). The prevalence of left ventricular hypertrophy was significantly different between men and women (3.4% vs. 17.7%, $P<0.001$) when using the moderately abnormal cut-off values[18]. When indexing the LV mass for Body Surface Area (BSA) and choosing the highly abnormal cut-off values (≥149g/m² for men and ≥122g/m² for women), the differences remained (2.9% (n=6) vs. 9.5%

Table 1. Echocardiographic characteristics in the BELFRAIL population (n = 567).				
	N	Median [IQR]	Cut-off value	Prevalence abnormal values, n (%)
LV and LA dimensions and systolic function (n = 556)				
LVIDd (mm)	556	50 [46 – 52]	>55	15 (2.7)
LVIDs (mm)	556	34 [31 – 36]	>45	8 (1.4)
PWTd (mm)	556	9 [8 – 10]	>10	82 (14.7)
SWTd (mm)	556	9 [8 – 10]	>10	44 (7.9)
LV Mass* (g) Men	204	160.0 [133.2 – 193.2]	≥259	7 (3.4)
Women	352	147.0 [126.1 – 174.0]	≥187	62 (17.7)
Left atrial volume (mL)	556	54 [44 – 67]		
LV ejection fraction (%)	556	55.0 [53.5 – 57.0]$	≤50	32 (5.8)
Stroke volume (mL)	556	68.0 [58.9 – 78.5]		
LV diastolic function (n = 458)				
Septal E' (cm/s)	456	6.6 [5.5 – 7.6]	<8	364 (79.8)
Lateral E' (cm/s)	456	7.0 [5.9 – 8.4]	<10	418 (91.7)
E/A	457	0.76 [0.66 – 0.93]	≤0.80	266 (58.2)
			0.80 – 1.5	166 (36.3)
			≥1.5	25 (5.5)
Average E/E'	456	11.0 [8.9 – 13.7]	≤8	66 (14.5)
			8 – 13	251 (55.0)
			≥13	139 (30.5)
Deceleration time (ms)	455	180 [144 – 210]	>200	134 (29.5)
			160 – 200	170 (37.4)

Isovolumic relaxation time (ms)	455	78 [72 – 90]	≥100	41 (9.0)
			60 – 100	321 (70.5)
			<60	93 (20.4)
Vp (cm/s)	453	57 [43 – 67]	<45	118 (26.0)
			≥45	335 (74.0)
Estimated PAP (mmHg)	358	27 [21 – 33]	>30	144 (40.2)
	Degree			n (%)
Valvular function (n=556)				
Mitral stenosis	Mild, mean PG <5mmHg			9 (1.6)
	Moderate, mean PG 5–10mmHg			9 (1.6)
	Severe, mean PG >10mmHg			1 (0.2)
Mitral regurgitation	Mild			411 (73.9)
	Moderate			4 (0.7)
	Severe			0 (0)
Aortic stenosis	Mild, AVA >1.5cm²			37 (6.7)
	Moderate, AVA 1–1.5cm²			57 (10.3)
	Severe, AVA <1cm²			33 (5.9)
Aortic regurgitation	Mild			206 (36.4)
	Moderate			9 (1.6)
	Severe			0 (0)

IQR: inter-quartile range; LVIDd: left ventricular internal dimension at end diastole; LVIDs: left ventricular internal dimension at end systole; PWTd: posterior wall thickness at end diastole; SWTd: septal wall thickness at end diastole; LV: left ventricle; E': peak velocity of mitral annulus motion during early diastole; E: early transmitral inflow wave peak velocity; A: atrial transmitral inflow wave peak velocity; Vp: flow propagation parameter of diastolic function; PAP: pulmonary arterial pressure; PG: peak gradient; AVA: aortic valve area. *, was calculated as $(0.8X\{1.04X[(LVIDd+PWTd+SWTd)^3-(LVIDd)^3]\}+0.6)$; $, IQR of LV ejection fraction in subjects with an echo of acceptable quality (n=539) .

(n=33) for men and women respectively, *P*=0.001). An enlarged indexed LA volume (>40mL/m²) was found in 122 participants (22.1%). A high prevalence of clinically relevant valvular heart disease (VHD) was found, including: any mitral stenosis (n=19, 3.4%), mitral regurgitation (≥moderate, n=4 (0.7%)), severe aortic stenosis (n=33, 5.9%) and aortic regurgitation (≥moderate, n=9 (1.6%)). Increased PAP (≥30mmHg) was found in 40.2% (n=144) of participants, 70 (48.6%) of whom had PAP above 35mmHg.

Diastolic function was determined in subjects without mitral stenosis (any) or mitral regurgitation (≥moderate) and atrial fibrillation (n=53, 9.7%) or artificial pacemaker rhythm (n=31, 5.7%) on the ECG. In eight subjects, no diastolic function could be determined, due to technical issues. The distribution of the diastolic parameters in 458 subjects is shown in Table 1.

In Figure 1 an algorithm to categorise study participants according to the presence of cardiac dysfunction is presented. In total, seven categories of cardiac dysfunction were created based on a discussion of existing guidelines and a consensus procedure launched by the research team. Among the 32 subjects with low EF, 25 had regional wall motion abnormalities (RWMA) and two had VHD. In two participants with RWMA and a normal EF (n=38), VHD was also found. In the remaining participants, VHD was found in 57 subjects (10.4%). Diastolic function was evaluated in 377 of the remaining subjects based on the ASA-EAE guidelines[22]. A first selection was made based on the values of the septal and lateral E', with 96 participants having a normal septal (≥8cm/s) or lateral E' (≥10cm/s). These subjects were categorised as having no cardiac dysfunction. The next selection was made on the E/A ratio, generating three classes of diastolic dysfunction (DD): mild (n=173, 31.6%), moderate (n=91, 16.6%) and severe (n=17, 3.1%). Table 2 shows the distribution of the other diastolic parameters among these three classes. A significant trend was found for the median values of these parameters from mild to moderate to severe DD.

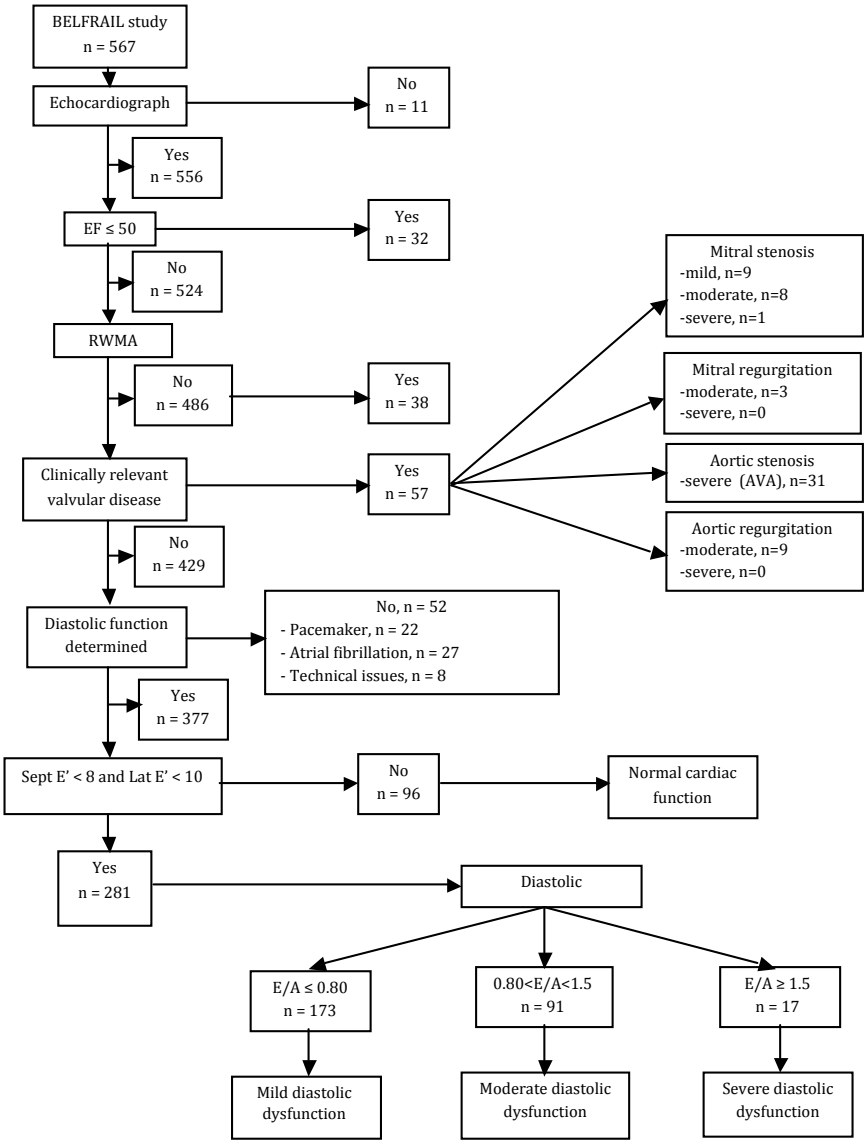

Figure 1. Classification of cardiac dysfunction

Table 2. Diastolic parameters in subjects with diastolic dysfunction (n=281).				
	Mild DD E/A ≤ 0.8 (n = 173)	**Moderate DD 0.8<E/A<1.5 (n = 91)**	**Severe DD E/A≥1.5 (n = 17)**	***P* for trend**
Average E/E', median [IQR]		11.5 [9.8 – 14.4]		
	10.7 [9.1 – 12.6]	13.3 [10.9 – 16.2]	17.8 [16.0 – 21.3]	<0.001
≤8	18 (10.4)	1 (1.1)	0 (0)	
8 – 13	117 (67.6)	41 (45.1)	1 (5.9)	
≥13	38 (22.0)	49 (53.8)	16 (94.1)	
DT (ms), median [IQR]		178 [140 – 210]		
	180 [150 - 218]	176 [145 – 202]	122 [114 – 133]	0.001
>200	58 (33.5)	22 (24.4)	1 (5.9)	
160 - 200	64 (37.0)	38 (42.2)	1 (5.9)	
<160	51 (29.5)	30 (33.3)	15 (88.2)	
IVRT (ms), median [IQR]		80 [75 – 90]		
	85 [76 – 90]	77 [67 – 87]	48 [44 – 68]	<0.001
≥100	20 (11.6)	5 (5.6)	1 (5.9)	
60 - 100	133 (76.9)	66 (73.3)	3 (17.6)	
≤60	20 (11.6)	19 (21.1)	13 (76.5)	
Vp (cm/s), median [IQR]		57 [44 – 68]		
	60 [50 – 70]	56 [41 – 65]	37 [33 – 43]	<0.001
≥45	140 (82.4)	63 (70.0)	3 (17.6)	
<45	30 (17.6)	27 (30.0)	14 (82.4)	

DD: diastolic dysfunction; E: early transmitral inflow wave peak velocity; A: atrial transmitral inflow wave peak velocity; E': peak velocity of mitral annulus motion during early diastole; IQR: inter-quartile range; DT: deceleration time; IVRT: isovolumic relaxation time; Vp: flow propagation parameter of diastolic function.

Table 3 shows the differences in socio-demographic and clinical characteristics among subjects in the different categories of cardiac dysfunction. Participants with systolic dysfunction (SD) were mainly male, current or past smokers and were more likely to have experienced a myocardial infarction, episode of decompensated heart failure or coronary surgery in their medical history. Subjects with SD or severe DD showed a higher prevalence of anaemia, had a lower level of renal function, low prevalence of normal ECG and showed the highest levels of NT-proBNP and BNP. Participants with VHD were older, showed the highest prevalence of dyspnoea, more often had a CVA in their medical history and took the highest number of cardiac medications.

Table 3. Differences in sociodemographic data, clinical characteristics and indicators of poor performance among subjects, based on cardiac function.

	Total population (n=548)	No cardiac dysfunction (n=96)	Systolic dysfunction (n=32)	RWMA (n=38)	Valvular dysfunction (n=57)	Atrial fibrillation or pacemaker (n=44)	Mild diastolic dysfunction (n=173)	Moderate diastolic dysfunction (n=91)	Severe diastolic dysfunction (n=17)	*P* value
Sociodemographic data										
Male, n (%)	204 (37.2)	41 (42.7)	25 (78.1)	19 (50.0)	17 (29.8)	18 (40.9)	60 (34.7)	21 (23.1)	3 (17.6)	<0.001
Age, mean±SD (years)	84.7 ± 3.6	83.8 ± 3.0	84.2 ± 2.7	83.9 ± 3.0	86.3 ± 4.4	84.2 ± 2.5	84.8 ± 3.8	85.2 ± 3.9	85.0 ± 3.4	0.002
Institutionalised, n (%)	55 (10.0)	4 (4.2)	2 (6.3)	3 (7.9)	9 (15.8)	3 (6.8)	21 (12.1)	10 (11.0)	3 (17.6)	0.26
Symptoms										
Dyspnoea ≥ 3*, n (%)	163 (29.9)	22 (23.2)	9 (28.1)	14 (36.8)	26 (45.6)	18 (40.9)	42 (24.3)	27 (29.7)	5 (31.3)	0.037
Fatigue, n (%)	112 (20.7)	13 (13.8)	11 (34.4)	8 (21.1)	16 (28.1)	12 (27.3)	30 (17.5)	18 (20.0)	4 (25.0)	0.16
Ankle swelling, n (%)	185 (33.9)	22 (23.2)	7 (21.9)	15 (39.5)	24 (42.1)	23 (52.3)	57 (32.9)	31 (34.1)	6 (37.5)	0.025
Non-cardiovascular morbidity										
Number of morbidities, median [IQR]	1 [1 – 2]	1 [0 – 3]	1 [1 – 2]	1 [1 – 2]	1 [1 – 2]	1 [1 – 3]	1 [1 – 2]	1 [1 – 2]	1 [0 – 3]	0.99
Anaemia, n (%)	107 (19.8)	16 (16.8)	12 (37.5)	10 (27.0)	16 (28.1)	7 (15.9)	27 (15.9)	13 (14.6)	6 (37.5)	0.015
Creatinine (mg/dL), median [IQR]	0.95 [0.78 – 1.19]	0.91 [0.77 – 1.16]	1.22 [0.97 – 1.68]	0.96 [0.85 – 1.12]	0.93 [0.79 – 1.23]	1.02 [0.75 – 1.32]	0.90 [0.73 – 1.14]	0.95 [0.80 – 1.22]	1.07 [0.88 – 1.31]	0.005
eGFR (mL/min/1.73m²), median [IQR]	66.8 [51.8 – 81.8]	68.5 [54.8 – 86.9]	55.1 [38.9 – 76.8]	67.2 [60.9 – 74.9]	67.1 [51.3 – 78.3]	66.9 [50.0 – 81.4]	70.8 [53.5 – 89.0]	65.6 [48.9 – 78.9]	55.0 [41.6 – 66.3]	0.013
usCRP (mg/dL), median [IQR]	0.18 [0.08 – 0.41]	0.15 [0.08 – 0.46]	0.38 [0.20 – 0.72]	0.22 [0.07 – 0.40]	0.16 [0.08 – 0.41]	0.22 [0.09 – 0.38]	0.17 [0.08 – 0.35]	0.18 [0.09 – 0.44]	0.14 [0.05 – 0.30]	0.090

Cardiovascular risk profile										
Hypertension, n (%)	384 (70.3)	61 (64.2)	21 (65.6)	27 (71.1)	40 (70.2)	31 (70.5)	133 (76.9)	57 (62.6)	14 (87.5)	0.17
Hyperlipidaemia, n (%)	240 (44.6)	45 (47.9)	12 (38.7)	17 (47.2)	22 (38.6)	21 (47.7)	85 (50.0)	32 (35.2)	6 (40.0)	0.40
DM type II, n (%)	102 (18.7)	13 (13.7)	8 (25.0)	4 (10.5)	12 (21.1)	9 (20.5)	40 (23.1)	14 (15.4)	2 (12.5)	0.37
Smoking *, n (%)	174 (32.9)	38 (41.8)	20 (66.7)	16 (42.1)	7 (13.0)	16 (38.1)	49 (29.2)	24 (26.7)	4 (25.0)	<0.001
BMI>25, n (%)	159 (29.2)	30 (31.6)	9 (28.1)	12 (31.6)	16 (28.6)	13 (29.5)	46 (26.6)	28 (31.1)	5 (29.4)	0.99
Cardiovascular morbidity										
Angina pectoris, n (%)	89 (16.3)	15 (15.8)	5 (15.6)	10 (26.3)	10 (17.5)	11 (25.6)	25 (14.5)	10 (11.0)	3 (18.8)	0.34
MI, n (%)	59 (10.8)	8 (8.4)	9 (28.1)	6 (15.8)	5 (8.8)	7 (15.9)	13 (7.5)	9 (10.0)	2 (12.5)	0.036
TIA, n (%)	54 (10.1)	12 (12.9)	1 (3.1)	9 (23.7)	8 (14.5)	4 (9.1)	13 (7.7)	5 (5.6)	2 (12.5)	0.040
CVA, n (%)	45 (8.3)	7 (7.4)	1 (3.1)	4 (10.5)	11 (20.0)	4 (9.1)	13 (7.6)	3 (3.4)	2 (12.5)	0.040
PAD, n (%)	49 (9.0)	8 (8.4)	6 (19.4)	1 (2.6)	9 (15.8)	3 (6.8)	15 (8.7)	6 (6.6)	1 (6.3)	0.18
Episode of DHF, n (%)	58 (10.6)	3 (3.2)	9 (28.1)	2 (5.3)	10 (17.5)	11 (25.0)	13 (7.6)	8 (8.8)	2 (12.5)	<0.001
PTCA-stent, n (%)	47 (8.6)	7 (7.4)	3 (9.4)	4 (10.8)	2 (3.5)	6 (13.6)	13 (7.5)	9 (9.9)	3 (20.0)	0.47
Coronary surgery, n (%)	36 (6.6)	4 (4.2)	6 (18.8)	5 (13.2)	4 (7.0)	7 (15.9)	5 (2.9)	3 (3.3)	2 (14.3)	0.001
Arterial surgery, n (%)	27 (5.0)	4 (4.2)	3 (9.4)	0 (0)	5 (8.8)	2 (4.5)	10 (5.8)	3 (3.3)	0 (0)	0.47
Number of cardiac medications, median [IQR]	2 [1 – 3]	1 [1 – 3]	3 [1 – 3]	2 [1 – 3]	3 [2 – 4]	2 [2 – 4]	2 [1 – 3]	2 [1 – 3]	2 [1 – 4]	0.002
ECG Findings										
MI on ECG, n (%)	76 (15.0)	13 (14.3)	9 (31.0)	5 (15.2)	5 (9.1)	8 (25.0)	22 (13.3)	10 (12.2)	4 (23.5)	0.11
LVH, n (%)	44 (8.7)	7 (7.7)	4 (13.8)	3 (8.8)	11 (20.0)	2 (6.3)	11 (6.7)	3 (3.6)	3 (17.6)	0.030
LBBB, n (%)	23 (4.5)	1 (1.1)	4 (13.8)	4 (11.8)	2 (3.6)	1 (3.0)	6 (3.6)	4 (4.8)	1 (5.9)	0.067
Normal ECG, n (%)	179 (34.3)	44 (48.4)	4 (13.3)	10 (27.8)	16 (29.1)	0 (0)	71 (42.5)	33 (40.2)	1 (5.9)	<0.001
Natriuretic peptides										
NT-proBNP (pg/mL), median [IQR]	187.9 [93.0 – 510.1]	133.4 [82.2 – 247.0]	811.1 [224.6 – 2989.9]	180.3 [92.6 – 412.4]	522.8 [178.3 – 1072.5]	710.9 [239.9 – 972.7]	125.6 [71.5 – 250.0]	153.3 [100.4 – 320.4]	652.6 [215.7 – 1178.3]	<0.001

BNP (pg/mL), median [IQR]	92.6 [53.6 – 182.7]	75.9 [48.7 – 131.5]	226.8 [79.0 – 544.5]	117.0 [56.2 – 164.1]	195.2 [109.7 – 295.0]	179.3 [99.2 – 238.6]	65.9 [42.0 – 105.9]	92.3 [64.3 – 159.1]	235.4 [126.2 – 360.1]	<0.001
Functional status										
ADL[µ], n (%)	109 (20.0)	18 (18.9)	7 (21.9)	6 (15.8)	1 (29.8)	10 (22.7)	35 (20.3)	13 (14.3)	3 (17.6)	0.53
Performance tests[µ], n (%)	116 (22.0)	19 (20.4)	6 (21.4)	6 (16.2)	21 (39.6)	9 (21.4)	35 (20.8)	16 (17.8)	4 (25.0)	0.11
LAPAQ[£], n (%)	182 (33.3)	27 (28.4)	14 (43.8)	10 (26.3)	29 (50.9)	16 (36.4)	55 (32.0)	24 (26.4)	7 (41.2)	0.049
MMSE ≤ 24, n (%)	111 (20.4)	13 (13.7)	9 (29.0)	8 (21.1)	15 (26.8)	6 (13.6)	39 (22.7)	18 (19.8)	3 (17.6)	0.39
GDS-15 ≥ 5, n (%)	113 (20.8)	8 (8.4)	6 (19.4)	6 (15.8)	23 (40.4)	14 (31.8)	28 (16.3)	23 (25.6)	5 (29.4)	<0.001
Muscle strength[µ], n (%)	105 (19.7)	18 (18.9)	8 (28.6)	8 (21.6)	11 (19.6)	9 (20.9)	35 (20.7)	13 (14.4)	3 (18.8)	0.86

RWMA: regional wall motion abnormalities; SD: standard deviation; IQR: inter-quartile range; eGFR: estimated glomerular filtration rate; usCRP: ultrasensitive C-reactive protein; DM: diabetes mellitus; MI: myocardial infarction; PAD: peripheral arterial disease; DHF: decompensated heart failure; PTCA: percutaneous transluminal coronary angioplasty; ECG: electrocardiogram; LVH: left ventricular hypertrophy; LBBB: left bundle branch block; NT-proBNP: N-terminal pro-brain natriuretic peptide; ADL: activities of daily living; LAPAQ: LASA physical activity questionnaire; MMSE: mini-mental state examination; GDS: geriatric depression scale.

[*]according to MRC (Medical Research Council) dyspnoea scale; [**]current or past; [µ]lowest gender-specific quintile; [£]0 or lowest gender-specific quartile.

Correlation of structural and functional echocardiographic abnormalities with poor functioning

Severe cardiac dysfunction was defined as the presence of SD, VHD or severe DD (n=106, 19.3%). Multivariable regression analysis, adjusting for age, gender, institutionalisation, BMI, anaemia, creatinine, LogusCRP and the number of non-cardiovascular morbidities, showed severe cardiac dysfunction to be an independent identifier of poor performance (OR 1.8 (95% CI 1.1 – 3.2), *P*=0.028), low LAPAQ score (OR 1.9 (95% CI 1.2 – 3.3), *P*=0.011) and a high GDS-15 score (OR 1.7 (95% CI 1.0 – 2.9), *P*=0.049).

Table 3 showed an abnormal LAPAQ or GDS-15 score to be more prevalent in participants with VHD. The prevalence of poor performance was also higher (39.6%) in subjects with VHD, although this trend was not significant (*P*=0.11).

In Table 4 the bivariate correlation between single echocardiographic abnormalities and poor functioning was further explored. For LA volume and stroke volume, the cut-off value of the highest quartile was used. Significant odds ratios were found for SWTd, LA volume, stroke volume and aortic stenosis to identify patients with low ADL scores. Multivariable analysis (model 1) retained increased SWTd (OR 2.0 (95% CI 0.88 – 4.7), *P*=0.095) and high stroke volume (OR 0.54 (95% CI 0.28 – 1.0), *P*=0.066) as independent identifiers of poor ADL functioning.

PWTd, SWTd, E/E', IVRT, aortic stenosis and PAP showed a significant association with poor performance testing. After multivariable analysis, model 1 retained aortic stenosis (OR 1.5 (95% CI 1.2 – 1.9), *P*<0.001), model 2 retained aortic stenosis (OR 1.5 (95% CI 1.1 – 2.1), *P*=0.007) and low IVRT (OR 2.1 (95% CI 1.1 – 4.0), *P*=0.023), and model 3 retained aortic stenosis (OR 1.9 (95% CI (1.3 – 2.7), *P*=0.001) and low IVRT (OR 3.0 (95% CI 1.3 – 6.9), *P*=0.012) as independent identifiers of poor performance.

Table 4. Correlation between structural and functional echocardiographic abnormalities and indicators of poor functioning.

	ADL[µ]	Performance Tests[µ]	LAPAQ[£]	MMSE ≤ 24	GDS-15 ≥ 5	Muscle strength[µ]
	Odds Ratio (95% Confidence Interval)[$]					
LV and LA dimensions and systolic function (n = 556)						
LVIDd >55mm	0.97 (0.27 – 3.6)	0.96 (0.26 – 3.5)	1.3 (0.47 – 3.8)	1.6 (0.49 – 5.2)	0.29 (0.037 – 2.2)	1.1 (0.31 – 4.1)
LVIDs >45mm	1.3 (0.26 – 6.6)	1.4 (0.27 – 7.4)	2.0 (0.50 – 8.1)	0.65 (0.078 – 5.5)	0.0 (0.0)	3.1 (0.69 – 14.2)
PWTd >10mm	1.6 (0.91 – 2.7)	1.8 (1.0 – 3.0)**	2.3 (1.4 – 3.6)**	1.3 (0.76 – 2.3)	1.2 (0.68 – 2.1)	1.0 (0.57 – 1.9)
SWTd >10mm	2.5 (1.3 – 4.7)**	2.2 (1.1 – 4.3)**	1.6 (0.84 – 2.9)	2.2 (1.1 – 4.2)**	0.99 (0.46 – 2.1)	1.3 (0.60 – 2.7)
LA volume >67mL	1.7 (1.0 – 2.6)**	1.5 (0.91 – 2.3)	1.8 (1.2 – 2.7)**	0.87 (0.53 – 1.4)	1.6 (1.0 – 2.6)*	1.1 (0.64 – 1.8)
EF ≤50	1.1 (0.47 – 2.6)	0.96 (0.38 – 2.4)	1.6 (0.77 – 3.3)	1.7 (0.74 – 3.7)	0.92 (0.37 – 2.3)	1.7 (0.73 – 4.0)
RWMA	1.0 (0.54 – 2.0)	0.81 (0.41 – 1.6)	1.1 (0.62 – 1.9)	1.3 (0.69 – 2.4)	0.71 (0.35 – 1.5)	1.3 (0.69 – 2.5)
Stroke volume >78.5mL	0.47 (0.27 – 0.84)**	0.83 (0.51 – 1.4)	0.72 (0.47 – 1.1)	1.2 (0.72 – 1.9)	0.77 (0.46 – 1.3)	0.51 (0.29 – 0.91)**
Diastolic function (n=458)						
Average E/E' ≥13	1.4 (0.88 – 2.4)	2.3 (1.4 – 3.7)**	1.4 (0.92 – 2.1)	1.5 (0.92 – 2.4)	1.9 (1.2 – 3.1)**	1.7 (1.0 – 2.7)**
E/A ≥1.5	0.57 (0.17 – 2.0)	1.3 (0.50 – 3.4)	1.0 (0.43 – 2.4)	0.53 (0.16 – 1.8)	2.3 (0.94 – 5.4)*	1.1 (0.40 – 3.1)
Deceleration time <160ms	0.96 (0.58 – 1.6)	0.90 (0.54 – 1.5)	1.2 (0.80 – 1.8)	1.1 (0.70 – 1.8)	1.3 (0.79 – 2.1)	1.3 (0.79 – 2.1)
Isovolumic relaxation time ≤60ms	0.94 (0.52 – 1.7)	2.1 (1.2 – 3.5)**	0.92 (0.56 – 1.5)	0.81 (0.45 – 1.5)	1.0 (0.58 – 1.9)	1.6 (0.91 – 2.7)
Vp <45cm/s	0.83 (0.48 – 1.4)	1.5 (0.90 – 2.5)	1.0 (0.67 – 1.6)	0.80 (0.46 – 1.4)	1.1 (0.67 – 2.0)	1.5 (0.90 – 2.5)
Valvular function (n=556)						
Mitral stenosis (grade)	1.1 (0.59 – 2.1)	1.3 (0.74 – 2.4)	1.2 (0.67 – 2.0)	1.5 (0.83 – 2.6)	1.5 (0.82 – 2.6)	1.0 (0.52 – 2.0)
Mitral regurgitation (grade)	1.4 (0.86 – 2.3)	1.1 (0.67 – 1.7)	1.5 (1.0 – 2.3)**	0.93 (0.59 – 1.5)	1.1 (0.71 – 1.8)	1.3 (0.77 – 2.0)
Aortic stenosis (grade)	1.3 (1.1 – 1.6)**	1.6 (1.3 – 2.0)**	1.4 (1.2 – 1.7)**	1.2 (0.93 – 1.4)	1.3 (1.0 – 1.6)**	1.1 (0.90 – 1.4)
Aortic regurgitation (grade)	0.89 (0.59 – 1.3)	0.81 (0.54 – 1.2)	1.1 (0.82 – 1.6)	1.1 (0.75 – 1.6)	1.0 (0.67 – 1.5)	1.3 (0.87 – 1.9)
PAP > 30mmHg	1.1 (0.63 – 1.8)	1.8 (1.0 – 3.0)**	1.0 (0.63 – 1.6)	0.98 (0.58 – 1.7)	1.0 (0.60 – 1.7)	1.0 (0.60 – 1.8)

ADL: activities of daily living; LAPAQ: LASA physical activity questionnaire; MMSE: mini-mental state examination; GDS: geriatric depression scale; LV: left ventricle; LA: left atrial; LVIDs: left ventricular internal dimension at end systole; LVIDd: left ventricular internal dimension at end diastole; PWTd: posterior wall thickness at end diastole; SWTd: septal wall thickness at end diastole; EF: ejection fraction; RWMA: regional wall motion abnormalities; E: early transmitral inflow wave peak velocity; E': peak velocity of mitral annulus motion during early diastole; A: atrial transmitral inflow wave peak velocity; Vp: flow propagation parameter of diastolic function; PAP: pulmonary arterial pressure.
[µ]lowest gender-specific quintile; [£]0 or lowest gender-specific quartile; [$]bivariate analysis; *P≤0.10; **P≤0.05.

Low LAPAQ score was correlated with PWTd, LA volume, mitral regurgitation and aortic stenosis. Multivariable analysis (model 1) showed increased PWTd (OR 2.2 (95% CI 1.2 – 3.9), *P*=0.010) and aortic stenosis (OR 1.4 (95% CI 1.1 – 1.8), *P*=0.002) as independent identifiers.

A low MMSE score was related to SWTd, but this relationship disappeared in the multivariable analysis. A high GDS-15 score was related to LA volume, E/E', E/A and aortic stenosis. Only model 2 retained aortic stenosis (OR 1.4 (95% CI 1.0 – 1.9), *P*=0.033) as an independent identifier.

Poor muscle strength showed a good correlation with stroke volume. High stroke volume remained an independent identifier in model 1 (OR 0.46 (95% CI 0.25 – 0.86), *P*=0.014) and model 2 (OR 0.44 (95% CI 0.22 – 0.86), *P*=0.016).

DISCUSSION

Prevalence of cardiac dysfunction

In a large population-based sample of elderly patients, we found a high prevalence of severe cardiac dysfunction (19.3%). Only 17.5% were diagnosed as having normal cardiac function. Valvular heart disease (10.4%) and isolated diastolic dysfunction (any grade, 51.3%) were found to be most prevalent. Systolic dysfunction (EF≤50%) however, was found in 5.8% of participants and an EF≤40% was found in only 1.6% (n=9) of participants.

Other studies reported similar findings with low prevalences of systolic dysfunction and increasing prevalences of diastolic dysfunction in very old subjects. In a large community-based survey, Redfield et al. found a low prevalence of systolic dysfunction (EF≤40%, 4.4%) and a high prevalence of diastolic dysfunction (mild 52.8%, moderate 14.6% and severe 3.4%) in participants aged 75 or older[24]. The Canberra Heart Study showed a prevalence of 4.2% of systolic dysfunction (EF≤40%) and a prevalence of diastolic dysfunction of 46.6% (mild 35.6% and moderate or severe 11%) in subjects aged 80 to 86[25, 26].

As previously described, the aged-related changes in cardiac structure comprise a progressive increase in LV wall thickness, whereas LV diameters and systolic LV function remain unchanged. In addition, the increasing LV stiffness and collagen deposition that accompany the patient's aging result in delayed LV relaxation and impairment of early LV diastolic filling[27]. The low prevalence of systolic dysfunction may also reflect a survival effect, as patients with severe systolic dysfunction tended to die at an earlier age.

Data on the prevalence of valvular dysfunction in the very elderly are scarce and based mostly on in-hospital series, generating an important selection bias[28, 29]. Nkomo et al. demonstrated, in a community study that included 3851 individuals older than 75 years, high absolute rates of significant VHD (11.7%), with mitral regurgitation and aortic stenosis being the most frequent valve diseases (7.1% and 4.6%, respectively)[29]. Our findings are in line with these results. Recently, however, Van Bemmel et al. showed a high prevalence of significant VHD (70%) in a population-based sample of well-functioning nonagenarians[30]. Compared with the nonagenarians of the BF_{C80+} study (n=51), study participants exhibited a lower prevalence of mitral stenosis (0% vs. 6%) and aortic stenosis (1% vs. 18%) and a higher prevalence of mitral regurgitation (≥moderate, 49% vs. 0%) and aortic regurgitation (≥moderate, 28% vs. 2%). A possible explanation for this discrepancy could be the use of a different definition of aortic stenosis, based on peak pressure gradient (Leiden) or aortic valve area (BF_{C80+}). Moreover, the difference in prevalence of mitral and aortic regurgitation is mainly explained as a difference in grade, with a high prevalence of mild regurgitation in the BF_{C80+} study (78% for mitral and 48% for aortic regurgitation) but the same prevalence of absence of regurgitation in both populations.

Correlation of structural and functional echocardiographic abnormalities with poor functioning

The current study identified severe cardiac dysfunction as an independent identifier of poor performance, low LAPAQ score and a high GDS-15 score in a very old population with a high prevalence

of comorbidities. Mainly VHD was retained as the primary identifier of poor functioning. More specifically, aortic stenosis was a strong independent correlate of poor performance, a low LAPAQ score or a high GDS-15 score. Classic indicators of systolic dysfunction were not able to identify participants with poor functioning; only stroke volume independently identified a low ADL score and poor muscle strength. As for diastolic dysfunction, only low IVRT was an independent correlate of poor performance. An increased LV wall thickness identified a low ADL and LAPAQ score, although LV mass was not an independent correlate (data not shown).

Recently, Grewal et al. reported resting diastolic function to be the strongest echocardiographic correlate of exercise tolerance in a large (young) population referred for exercise echocardiography[5]. Among the elderly, the relationship between poor functioning and indicators of cardiac dysfunction has not been extensively studied. Maugeri et al. demonstrated the existence of a correlation between decreased EF and impaired global psychocognitive performance (MMSE, GDS, ADL and IADL) in ultraseptagenarians[6]. Van Bemmel, however, did not find a relation between activities of daily living and the presence of significant valvular heart disease[29].

Our study clearly showed that the very elderly represent a very heterogeneous group of subjects with a high prevalence of comorbidities, among whom poor functioning might be triggered by multiple causes. The high prevalence of cardiac dysfunction, however, did not show a strong relationship with poor functioning. This may indicate that the ageing body is able to adapt and find a new homeostasis despite the high burden of comorbid conditions. On the other hand, this could also mean frailty in the very elderly exists as a separate entity independent of cardiac dysfunction or comorbidity. But above all, this should encourage clinicians not to be blinded by a disease-oriented approach but rather to focus on functional repercussions of cardiac dysfunction and comorbidities in the very elderly.

Strengths and limitations

This is the first large study to examine the relationship of a wide spectrum of echocardiographic parameters with standardised self-reported and objective measures of physical activity in a large community-based sample representative of very elderly patients. Although these data require confirmation in prospective studies, they point to potential modifiable factors that might be a target for interventions that could maintain normal functioning with aging.

A few limitations must be considered. First of all, this is a cross-sectional study; therefore, caution must be taken in making temporal inferences. Second, although many factors potentially associated with poor functioning were considered, confounding remains possible. Third, comorbidities may have been underdiagnosed, because they were not assessed but were reported by the general practitioner. Because any underreporting was independent of the echocardiographic measurements, this factor should not have affected the results. In addition, the applicability of current echocardiographic cut-off values to subjects aged 80 and over may be debatable, because the thresholds for normal values are usually derived from younger subpopulations.

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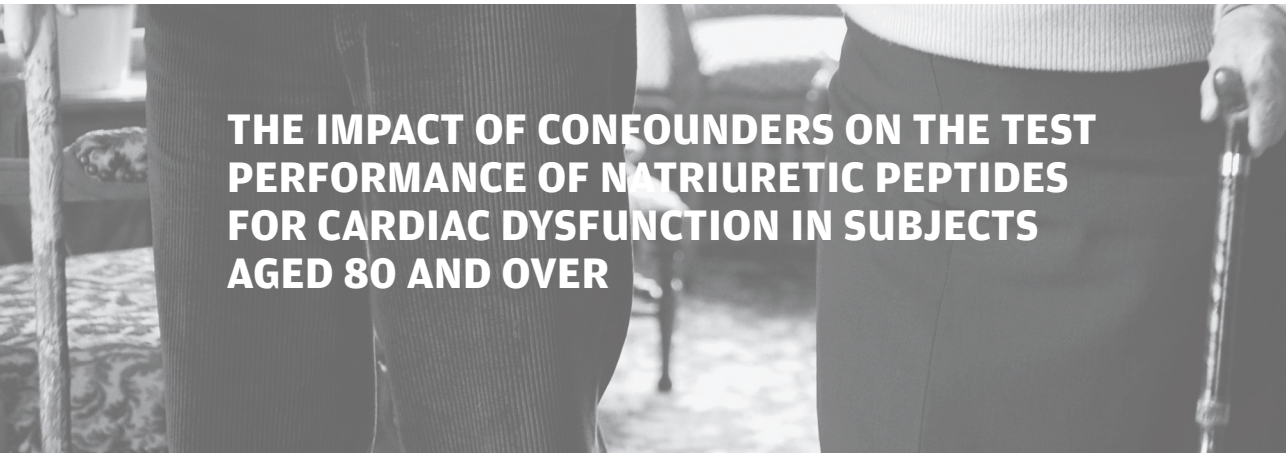
THE REFERENCE STANDARD

The target condition in the following two chapters is the presence of a left ventricular ejection fraction (LVEF) ≤ 50%, clinically relevant valvular heart disease (VHD) or severe diastolic dysfunction. Because of difficulties in interpreting diastolic parameters in subjects with chronic atrial fibrillation (CAF) or pace-maker (PM), the population under study was split in two for analysis:

- In subjects without CAF or PM, the target condition was the presence of LVEF≤50%, VHD or severe DD.
- In subjects with CAF or PM, the target condition was LVEF≤50% or VHD.

CHAPTER 6



THE IMPACT OF CONFOUNDERS ON THE TEST PERFORMANCE OF NATRIURETIC PEPTIDES FOR CARDIAC DYSFUNCTION IN SUBJECTS AGED 80 AND OVER

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Submitted

ABSTRACT

Background: The hypothesis that natriuretic peptides could be used to identify 'pancardiac' damage, even when it is silent, has been proposed. However, multiple factors are known to influence circulating levels of natriuretic peptides, especially in the elderly. Therefore, the impact of confounders on the association between natriuretic peptide levels and cardiac dysfunction was further explored.

Methods and Results: A diagnostic cross-sectional study embedded within the BELFRAIL (BF_{C80+}) study of 567 subjects aged 80 years and older in Belgium. Natriuretic peptide levels were measured and echocardiograms were performed at the subject's home. Aortic stenosis, LA volume, LVIDs, E/A, E' and DT, were independently related to circulating levels of natriuretic peptides. Cystatin C, BMI, ß blockers, diabetes, heart frequency, usCRP, age and sex were identified as confounders. The prevalence of severe cardiac dysfunction (CD) was 17.1% in the subjects without and 30.8% in the subjects with chronic atrial fibrillation (CAF) or pacemaker (PM). Only in subjects with CAF or PM the C statistic for severe CD improved after correcting for confounders. The negative predictive value for severe CD ranged from 85.1% to 96.8% and the positive predictive value ranged from 19.0% to 64.3% in different strata of confounders.

Conclusions: Several functional and structural echocardiographic parameters were independently related to circulating levels of natriuretic peptides. Adjusting for identified confounders did not improve the diagnostic accuracy of the natriuretic peptides for severe cardiac dysfunction, except in subjects with CAF or PM. Stratifying for individual confounders showed that different cut-off values could be used to optimize the diagnostic characteristics of natriuretic peptides.

INTRODUCTION

Aging populations and improved survival following acute cardiac events have led to an increased prevalence of cardiac dysfunction and heart failure, especially in the elderly[1]. Asymptomatic structural and functional abnormalities of the heart are considered to be precursors of symptomatic heart failure and are associated with high mortality[2, 3]. Therefore, timely and adequate diagnoses of cardiac dysfunction are important because treatment can delay the progression to overt heart failure[4].

A cardiac dysfunction diagnosis is often challenging when multiple comorbidities are present. The accuracy of a clinical diagnosis based on signs and symptoms is often limited in elderly patients[5]. Echocardiography is currently the diagnostic test of choice for identifying structural and functional cardiac abnormalities. However, its availability to elderly patients can be limited, so there is the possibility of considerable over- and under-diagnosis of cardiac dysfunction[6, 7]. This possibility emphasizes the need for a simple test to identify at risk patients. Measuring natriuretic peptides has been proposed as a screening method for left ventricular (LV) dysfunction in high-risk patients, such as the elderly[8, 9].

The Leiden 85 Plus Study showed natriuretic peptides to be good predictors of both cardiovascular and noncardiovascular mortality in elderly subjects with and without specific cardiac diagnoses. This result suggested that elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) levels may reflect unknown cardiac morbidity or imminent heart failure[10]. Furthermore, natriuretic peptides have been shown to identify both increased intracardiac volume/pressure and any form of asymptomatic cardiac damage, such as silent ischemia, left ventricular hypertrophy and atrial fibrillation[11-14]. The hypothesis that natriuretic peptides could be used to identify 'pancardiac' damage, even when it is silent, has been proposed[15]. However, multiple factors are known to influence circulating levels of natriuretic peptides, especially in the elderly. The prevalence of possible influencing factors, such as renal dysfunction and diabetes, increases with age[9]. Understanding these factors is a

prerequisite for optimally using these peptides to diagnose cardiac dysfunction in the community[16].

Therefore, a cross-sectional analysis within the BELFRAIL cohort (BF_{C80+}) was performed to determine the prevalence of unknown and silent cardiac dysfunction in subjects aged 80 and older. The correlations between the natriuretic peptides and various echocardiographic abnormalities of the heart and the influence of possible confounders were also investigated. In addition, the impact of identified confounders on the association between natriuretic peptide levels and cardiac dysfunction was further explored.

METHODS

Study population

The BF_{C80+} study is a prospective, observational, population-based cohort study of subjects aged 80 years and older in three well-circumscribed areas of Belgium. The study design and characteristics of the cohort have been described in detail[17]. In brief, 29 general practitioner (GP) centers were asked to enroll patients aged 80 and older. Only three exclusion criteria were used: severe known dementia (mini-mental state examination [MMSE] score <15), undergoing palliative care and experiencing medical emergencies. A total of 567 subjects were included in the BF_{C80+} study between November 2, 2008 and September 15, 2009. Each study participant was invited to attend four study visits. The GP recorded the background variables and a medical history and gathered a detailed anamnesis. A clinical research assistant (CRA) performed an extensive examination, including an electrocardiogram (ECG). The echocardiography was performed at the subject's home by a cardiologist. A blood sample was collected in the morning. All of the participants in the study gave informed consent and the Biomedical Ethics Committee of the Medical School of the Université Catholique de Louvain (UCL) of Brussels approved the study.

Clinical characteristics

The dyspnea symptoms (according to the Medical Research Council [MRC] dyspnea scale[18]), fatigue and ankle swelling were registered.

Indicators of the cardiovascular risk profile were presence of hypertension and diabetes mellitus, as determined by the GP. The patient's smoking status was registered, and the Body Mass Index (BMI) was calculated by the CRA based on a standardized measurement of weight and height.

Cardiac morbidities were defined by positive responses to a history of angina pectoris or myocardial infarction, decompensated heart failure, chronic atrial fibrillation (CAF), pacemaker (PM) implantation and important cardiac interventions or surgery (percutaneous transluminal coronary angioplasty [PTCA] or stenting and coronary or valvular surgery). A 12-lead ECG was recorded on a QRS Universal ECG device (QRS Diagnostic, Plymouth, Minnesota, USA, www.qrsdiagnostic.com)[17]. Prior histories of myocardial infarction (Minnesota Code 1-1 or 1-2, excluding 1-2-8), atrial fibrillation (Minnesota Code 8-3-1), an artificial PM (Minnesota Code 6-8), LV hypertrophy (Minnesota Code 3-1, 3-2 or 3-3) or a left bundle branch block (LBBB) (Minnesota Code 7-1-1) were noted. Myocardial infarction, CAF or PM were defined as reported by the GP or identified by the ECG.

The other cardiovascular morbidities were defined as positive responses to a history of transient ischemic attack (TIA), cerebrovascular accident (CVA), peripheral arterial disease or arterial surgery.

Data on the relevant cardiovascular medications including diuretics, potassium-sparing agents, ß-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium antagonists and cardiac glycosides were also registered.

Laboratory tests

The plasma (EDTA) and serum samples were stored at -80°C until the analysis. The hemoglobin concentrations were measured from whole blood using a Sysmex XE-2100 automated hematology

analyzer (Milton Keynes, UK). Anemia was defined as a hemoglobin level of <12g/dL for women or <13g/dL for men[19]. The serum creatinine (IDMS Jaffé method), cystatin C and ultra-sensitive C-reactive protein (usCRP) were measured using a UniCel® DxC 800 Synchron (Beckman-Coulter, Brea, USA). The plasma BNP levels were measured using the Biosite® kit on a UniCel® DxI 800 Immunoassay System (Beckman-Coulter, Brea, USA). The coefficient of variation (CV) ranged from 5.4 to 6.7%. The serum NT-proBNP levels were measured using a Dade-Dimension® Xpand (Siemens, Deerfield, USA). The CV ranged from 3.9 to 4.3%.

Echocardiography

The echocardiograms were performed using a commercially available portable system (CX50, Philips, Andover, Massachusetts, USA) with M-mode, 2-dimensional and pulsed, continuous-wave and color-flow Doppler capabilities. The echocardiograms were performed by a single cardiologist who was blinded to the clinical characteristics and laboratory test results. All of the patients were examined in left lateral decubitus position. A complete examination, consisting of standard parasternal short- and long-axis, apical and subcostal 2D views, was performed according to the recommendations of the American Society of Echocardiography and the European Society of Echocardiography[20]. Still frames for the M-Mode, continuous and pulsed Doppler and cineloops for assessing left ventricular (LV) function were digitally stored on a DVD and later transferred to a workstation. All of the measurements were performed off-line using the Xcelera software (Philips, Andover, Massachusetts, USA).

The LV function was calculated using the Simpson biplane method[20]. The echo image quality was semiquantitatively assessed on a 5-point scale[21]. In subjects with poor-quality images, the LV function was independently re-evaluated by a second cardiologist[22]. The subjects were determined to have poor LV function if both cardiologists visually estimated the ejection fraction (EF) to be ≤50%[22]. The left atrial (LA) volume was measured using the biplane area-length formula[20].

The mitral, aortic and tricuspid valves were evaluated with color Doppler echocardiography after optimizing the gain and Nyquist limit. Standard, continuous and pulsed-wave Doppler recordings were acquired. Stenotic and regurgitant valve diseases were evaluated, according to the semiquantitative and quantitative methods recommended by the American Society of Echocardiography[23, 24]. Clinically relevant valvular heart disease (VHD) was defined as mitral stenosis of any severity, severe aortic stenosis (aortic valve area <1cm²), moderate or severe mitral regurgitation, and moderate or severe aortic regurgitation. The subjects with prosthetic valves were evaluated separately[23].

The diastolic function was assessed using mitral flow velocities obtained by pulsed Doppler and pulsed tissue Doppler at the level of the mitral annulus[25]. Additional apical and parasternal views for assessing tissue velocity (color tissue Doppler) were also recorded. The tissue velocity was analyzed using the Q lab software (Philips, Andover, Massachusetts, USA). The ASA-EAE guidelines were used to assess the presence of diastolic dysfunction[25].

Echocardiographic abnormalities were defined using previously published cut-off values[20, 22, 25, 26]. The target condition was severe cardiac dysfunction (CD), including the presence of systolic dysfunction (LVEF≤50%), VHD or severe diastolic dysfunction. Because of the difficulty of interpreting diastolic parameters in subjects with CAF or PM, the population was split into two groups for the analysis: subjects with and without CAF or PM. In the subjects with CAF or PM, the target condition was LVEF≤50% or VHD.

Data analysis

The continuous data are presented as medians and inter-quartile ranges (IQR). The categorical data are presented as numbers and frequencies. Categories, based on presence of cardiac morbidity and symptoms, were compared using the Chi-Square test with linear-by-linear association.

Due to their skewed distributions, the BNP and NT-proBNP levels and the NT-proBNP/BNP ratio were log transformed.

The relationships among the natriuretic peptides, structural and functional echocardiographic abnormalities and possible confounders were explored using a stepwise multivariate linear regression analysis with LogBNP or LogNT-proBNP as the dependent variable. Two models were used for the multivariate regression analysis: one for the entire population (model 1, n=556) and one for the subjects whose diastolic function was determined (model 2, n=440).

The diagnostic accuracy of the natriuretic peptides for severe CD was calculated in the subjects with and without CAF or PM. The C statistic was calculated using the probabilities from the logistic regression analyses with and without correction for the identified confounders. In addition, receiver operating characteristic (ROC) curves analysis were constructed, and the areas under the curve (AUC), ideal cut-off values (the values that maximized sensitivity + specificity) and post-test probabilities for positive (PTP+) and negative tests (PTP-) were calculated for different strata of the identified confounders. The AUCs were compared by taking into account the correlation between the areas that is induced by the paired nature of the data[27].

The data analysis was performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, Illinois, USA) and MedCalc® 11.6.0.0 (Mariakerke, Belgium).

RESULTS

The BF_{C80+} study enrolled 567 subjects aged 80 and older. Women represented 63.1% (n=358) of the study population and had a mean age of 85.0 ± 3.9 years old. The male participants had a mean age of 84.3 ± 3.3 years old. A high prevalence of cardiac morbidity was found (n=297, 52.4%). Table 1 describes the differences between the subjects with and without cardiac morbidities. The patients with cardiac morbidities were more likely to be male, older, symptomatic and smokers or ex-smokers and to have poorer renal function and a higher prevalence of other

cardiovascular morbidities. They were also more likely to be using ACE inhibitors, ß ßblockers and cardiac glycosides. In addition, a large number of subjects without cardiac morbidity had one or more symptoms (n=129, 47.8%). Together with a high prevalence of hypertension (68.4%), numerous subjects without cardiac morbidity were found to be taking one or more cardiac medications (n=185, 68.8%).

Table 1. Description of the study population (n=567)			
Presence of cardiac morbidity			
Angina pectoris, n (%)	93 (16.5)		
Myocardial infarction*, n (%)	126 (22.2)		
Episode of DHF, n (%)	60 (10.6)		
Chronic atrial fibrillation*, n (%)	74 (13.1)		
Pacemaker*, n (%)	35 (6.2)		
PTCA or stent, n (%)	49 (8.7)		
Coronary surgery, n (%)	37 (6.6)		
Valvular surgery, n (%)	20 (3.6)		
LVH on ECG, n (%)	46 (8.9)		
LBBB on ECG, n (%)	24 (4.6)		
	No cardiac morbidity (n = 270)	Cardiac morbidity (n = 297)	P value†
Socio-demographic characteristics			
Male, n (%)	75 (27.8)	136 (45.8)	<0.001
Age (years), mean ± SD	84.3 ± 3.5	85.1 ± 3.7	0.014
Symptoms			
Dyspnea ≥3‡, n (%)	54 (20.1)	115 (38.9)	<0.001
Edema, n (%)	81 (30.1)	111 (37.5)	0.001
Fatigue, n (%)	40 (14.9)	77 (26.3)	0.064
Non-cardiovascular morbidity			
Anemia§, n (%)	44 (16.7)	67 (23.3)	0.050
usCRP, median (IQR)	0.16 (0.08 – 0.40)	0.21 (0.08 – 0.44)	0.069
Creatinine, median (IQR)	0.89 (0.73 – 1.1)	1.0 (0.81 – 1.3)	<0.001
Cystatin C, median (IQR)	1.1 (0.91 – 1.4)	1.2 (1.0 – 1.6)	<0.001
Cardiovascular risk profile			
Hypertension, n (%)	184 (68.4)	212 (71.6)	0.41
Diabetes mellitus type II, n (%)	42 (15.6)	65 (22.0)	0.053
Smoking (current or ex), n (%)	67 (25.9)	1121 (38.8)	0.001
BMI (kg/m²), mean ± SD	27.6 ± 5.3	27.2 ± 4.4	0.30
Other cardiovascular morbidity			
TIA, n (%)	19 (7.3)	39 (13.3)	0.019
CVA, n (%)	17 (6.5)	29 (9.8)	0.15
Peripheral arterial disease, n (%)	13 (4.9)	39 (13.2)	<0.001
ACE inhibitors, n (%)	53 (19.7)	100 (33.8)	<0.001
Angiotensin II RB, n (%)	42 (15.6)	45 (15.2)	0.89
β blockers, n (%)	92 (34.2)	146 (49.3)	<0.001
Cardiac glycosides, n (%)	2 (0.7)	20 (6.8)	<0.001

*: as reported by the general practitioner or on the ECG; †: independent-samples Student's T-test; ‡: according to the MRC (Medical Research Council) dyspnea scale; §, hemoglobin levels <12g/dL for women and <13g/dL for men.
DHF: decompensated heart failure; LVH: left ventricular hypertrophy; LBBB: left bundle branch block; PTCA: percutaneous transluminal coronary angioplasty; ECG: electrocardiogram; SD: standard deviation; usCRP: ultra-sensitive C-reactive protein; BMI: body mass index; TIA: transient ischemic attack; CVA: cerebrovascular accident; ACE: angiotensin converting enzyme; RB: receptor blocker.

Echocardiography was performed in 556 participants (98.1%). The diastolic parameters were determined in the subjects without (any) mitral stenosis, without (≥moderate) mitral regurgitation and without CAF or PM (n=440, 78%). Table 2 shows the prevalence of echocardiographic abnormalities by the different categories of subjects and by the presence of cardiac morbidity and symptoms. A positive trend toward subjects with cardiac morbidity, with or without symptoms, was seen for aortic stenosis, an elevated LVIDs, LVIDd or LA volume index, decreased LVEF and stroke volume, RWMA, an elevated E/A and E/E' and decreased IVRT and Vp. In the subjects without cardiac morbidity, the prevalence of aortic stenosis was 3.0%, the prevalence of an elevated LA volume index was 14.0%, the prevalence of decreased LVEF was 1.9%, the prevalence of RWMA was 6.8% and the prevalences of an elevated E/A and E/E' were 3.2% and 24.1%, respectively. The prevalence of LV hypertrophy was 9.4% in women without known cardiac diseases.

BNP levels were measured in 548 subjects (96.6%), and NT-proBNP levels were measured in 546 (96.3%). Combined echocardiographic and natriuretic peptide data were available for 541 subjects (95.4%). The median time between the blood test and echocardiography was three days (IQR 1–13 days). Figure 1 shows the distribution of LogBNP and LogNT-proBNP by category, presence of cardiac morbidities and symptoms. The mean LogBNP and mean LogNT-proBNP were highest for the subjects with cardiac morbidities and symptoms (P<0.001 in the ANOVA). Back-transformation yielded a BNP level of 136.8pg/mL and a NT-proBNP level of 396.6pg/mL for those subjects.

Table 2. Description of echocardiographic parameters by cardiac morbidity and heart failure symptoms.

	Total population	Cut-off value	No cardiac morbidity		Cardiac morbidity		P for trend*
			No symptoms (n = 141)	Symptoms (n = 129)	No symptoms (n = 114)	Symptoms (n = 183)	
	Median (IQR)		n (%)				
LV and LA dimensions and systolic function (n = 556)							
LVIDs (mm)	34 (31 – 36)	>45	0 (0)	0 (0)	4 (3.6)	4 (2.2)	0.029
LVIDd (mm)	50 (46 – 52)	>55	0 (0)	1 (0.8)	8 (7.3)	6 (3.3)	0.014
PWTd (mm)	9 (8 – 10)	>10	14 (10.0)	21 (16.7)	16 (14.5)	31 (17.2)	0.12
SWTd (mm)	9 (8 – 10)	>10	9 (6.4)	12 (9.5)	5 (4.5)	18 (10.0)	0.43
LVMI (g/m²) Women	90 (75 – 107)	>122	8 (8.6)	10 (10.2)	3 (6.0)	12 (11.3)	0.65
Men	89 (73 – 103)	>149	0 (0)	0 (0)	3 (5.0)	3 (4.1)	0.12
LA volume index (mL/m²)	31 (25 – 39)	>40	16 (11.5)	21 (16.8)	20 (18.2)	65 (36.3)	<0.001
LV ejection fraction (%)	55 (54 – 57)	≤50	2 (1.4)	3 (2.4)	13 (11.8)	14 (7.8)	0.002
Stroke volume (mL)	68 (59 – 79)	<59	29 (20.7)	30 (23.8)	25 (22.7)	57 (31.8)	0.028
RWMA, n (%)	63 (11.3)	-	8 (5.7)	10 (7.9)	18 (16.4)	27 (15.0)	0.003
LV diastolic function (n = 440)							
Septal E' (cm/s)	6.6 (5.6 – 7.6)	<8	100 (76.3)	100 (82.0)	68 (82.9)	84 (81.6)	0.30
Lateral E' (cm/s)	7.0 (5.9 – 8.4)	<10	120 (91.6)	111 (91.0)	72 (87.8)	97 (94.2)	0.70
E/A	0.76 (0.66 – 0.92)	≥1.5	4 (3.1)	4 (3.3)	3 (3.7)	10 (9.7)	0.025
Average E/E'	11.0 (8.9 – 13.6)	≥13	23 (17.6)	38 (31.1)	22 (26.8)	46 (44.7)	<0.001
DT (ms)	178 (144 – 210)	<160	38 (29.2)	40 (33.1)	24 (29.3)	42 (40.8)	0.11
IVRT (ms)	78 (72 – 90)	<60	21 (16.2)	22 (18.2)	16 (19.5)	30 (29.1)	0.018
Vp (cm/s)	57 (44 – 67)	<45	26 (20.2)	26 (21.5)	19 (23.5)	38 (36.9)	0.004
Valvular dysfunction (n=556), n (%)							
Mitral stenosis (any grade)	19 (3.4)	any grade	6 (4.3)	1 (0.8)	2 (1.8)	10 (5.6)	0.35
Mitral regurgitation (any grade)	415 (74.6)	≥moderate	0 (0)	1 (0.8)	1 (0.9)	2 (1.1)	0.27
Aortic stenosis (any grade)	115 (20.7)	severe	3 (2.1)	5 (4.0)	3 (2.7)	21 (11.7)	<0.001
Aortic regurgitation (any grade)	215 (39.0)	≥moderate	2 (1.4)	5 (4.0)	1 (0.9)	1 (0.6)	0.22

*: Chi-square test with linear-by-linear association

IQR: inter-quartile range; LV: left ventricle; LA: left atrial; LVIDs: left ventricular internal dimension at end systole; LVIDd: left ventricular internal dimension at end diastole; PWTd: posterior wall thickness at end diastole; SWTd: septal wall thickness at end diastole; LVMI: left ventricle mass index; RWMA: regional wall motion abnormalities; E': peak velocity of mitral annulus motion during early diastole; E: early transmitral inflow wave peak velocity; A: atrial transmitral inflow wave peak velocity; DT: deceleration time; IVRT: isovolumic relaxation time; Vp: flow propagation parameter of diastolic function.

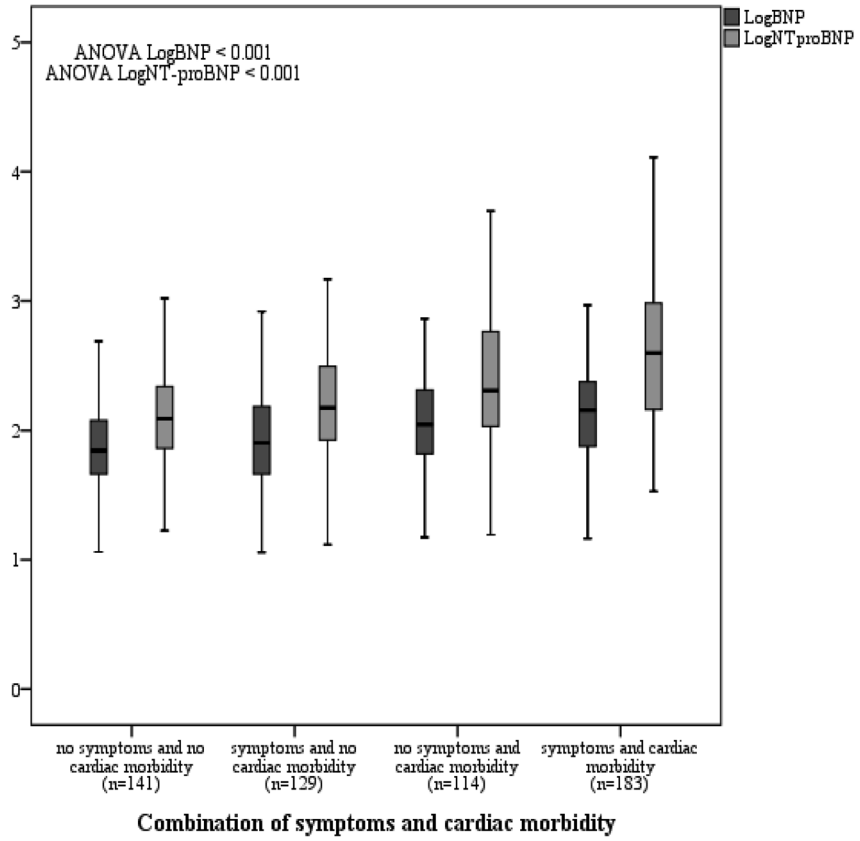

Figure 1. The relationships among LogBNP, LogNT-proBNP, the presence of cardiac morbidity and heart failure symptoms. ANOVA: analysis of variance; BNP: brain natriuretic peptide; NT-proBNP: NT-proBNP: N-terminal pro-brain natriuretic peptide

The independent correlates of BNP and NT-proBNP are presented in Table 3. All of the variables described in Table 1 and Table 2 were used in the multivariate regression analysis. Model 1 and model 2 accounted for more of the variation in NT-proBNP than the variation in BNP (53% vs. 37% and 51% vs. 39%, respectively). In both model 1 and model 2, the LA volume, aortic stenosis and LVIDs were prominent correlates of both BNP and NT-proBNP. When the diastolic parameters were included in the model (model 2), E/A, septal E' and DT were strong independent correlates of both BNP and NT-proBNP, and Vp and IVRT were strong correlates of BNP and NT-proBNP, respectively. Cystatin C, BMI, ß blockers, diabetes and heart frequency were found to be potent correlates of BNP in both models. Cystatin C, BMI, usCRP, fatigue, age, sex and heart frequency were independently related to the NT-proBNP levels in both models. Coronary surgery and CAF were the only cardiac morbidities found to be independent correlates of BNP and NT-proBNP in model 1, and angina pectoris was the only correlate of NT-proBNP in model 2.

Figure 2 shows the classification of subjects according to the presence of cardiac dysfunction. The prevalence of severe cardiac dysfunction was 17.1% (n=78) in the subjects without and 30.8% (n=28) in the subjects with CAF or PM. The prevalence of severe cardiac dysfunction in subjects without known cardiac morbidity was 12.5% (n=33), in 48.5% (n=16) of whom the cardiac dysfunction was silent.

Table 4 shows the C statistics for LogBNP, LogNT-proBNP, Log(NT-proBNP/BNP) and the combination of LogBNP and LogNT-proBNP for the presence of severe cardiac dysfunction. When corrected for the presence of cardiac morbidity and symptoms, the C statistic did not improve. The diagnostic accuracy of BNP and NT-proBNP in the subjects without CAF or PM did not change when adjusting for identified confounders. Only in subjects with CAF or PM did the C statistic improve after correcting for the confounders. In these subjects, age was the only confounder that was independently correlated with the target condition in all four models (ß = 1.2 [95% CI 1.0 – 1.4], $P<0.10$). In the LogBNP model

the presence of CAF was also an independent correlate (ß = 8.5 [95% CI 0.86–85.1], *P* = 0.068). No differences in the C statistics were seen among the four models, independent of CAF or PM.

Table 5 shows the diagnostic accuracy of BNP and NT-proBNP for different strata of the identified confounders in the subjects without CAF or PM. The negative predictive value (NPV=100 – PTP-) ranged from 85.1% to 96.1% for BNP and from 87.1% to 96.8% for NT-proBNP in the different strata. The positive predictive value (PPV=PTP+) ranged from 28.3% to 62.2% for BNP and from 19.0% to 64.3% for NT-proBNP. The AUCs for BNP and NT-proBNP were larger (*P*<0.10) in subjects with a BMI <25kg/m² and those with a heart rate <70/min. The ideal BNP cut-off value was higher (range 148.8 – 220.5pg/mL) for women, for the subjects ≥85 years old, for those with cardiac morbidity, for those with cystatin C in the highest tertile, for those with BMI <25kg/m², for those not taking ß blockers, for those with diabetes, for those with LogusCRP in the highest tertile and for those with a heart rate <70/min. The ideal NT-proBNP cut-off value was lower (range 124.2 – 164.4pg/mL) for women, for the subjects with no cardiac morbidity, for those with cystatin C in the lowest tertiles, for those with BMI ≥25kg/m², for those with LogusCRP in the low tertiles and for those with a heart rate ≥70/min. No diagnostic accuracy differences were found between BNP and NT-proBNP in the different strata.

The ROC curves for natriuretic peptides as indicators of severe cardiac dysfunction in the subjects with CAF or PM had AUCs of 0.65 (95% CI 0.55–0.75) and 0.71 (95% CI 0.61–0.80), PTP-s of 21.0% (95% CI 11.6–33.3) and 18.6% (95% CI 9.6–31.0), and PTP+s of 53.6% (95% CI 33.9–72.5) and 53.1% (95% CI 34.7–70.9) for BNP and NT-proBNP, respectively. There were no significant differences in diagnostic accuracy between BNP and NT-proBNP (*P* = 0.18). The ideal cut-off values were 245.9 pg/mL for BNP and 920 pg/mL for NT-proBNP. Due to the low number of patients, stratified analyses for the identified confounders were not performed for those with CAF or PM.

Table 3. The independent correlates of BNP and NT-proBNP in the multivariate regression analysis

	Correlate	LogBNP		LogNT-proBNP	
		β (95% CI)*	P value	β (95% CI)*	P value
Model 1		**Adjusted R^2 = 0.37**		**Adjusted R^2 = 0.53**	
	LA volume	0.004 (0.002 – 0.006)	<0.001	0.004 (0.002 – 0.007)	<0.001
	Cystatin C	0.18 (0.12 – 0.24)	<0.001	0.40 (0.33 – 0.47)	<0.001
	β blocker	0.17 (0.11 – 0.23)	<0.001	0.18 (0.11 – 0.26)	<0.001
	BMI	-0.014 (-0.020 – -0.008)	<0.001	-0.023 (-0.031 – -0.016)	<0.001
	Aortic stenosis (grade)	0.061 (0.028 – 0.095)	<0.001	0.067 (0.026 – 0.11)	0.001
	Stroke volume	-0.002 (-0.004 – -0.001)	0.008	-0.004 (-0.006 – -0.002)	<0.001
	LVIDs	0.011 (0.003 – 0.019)	0.005	0.018 (0.009 – 0.028)	<0.001
	Diabetes	-0.095 (-0.17 – -0.021)	0.012	NS	NS
	CAF	0.13 (0.028 – 0.22)	0.012	0.32 (0.21 – 0.44)	<0.001
	Heart frequency	-0.004 (-0.006 – -0.001)	0.005	-0.005 (-0.008 – -0.002)	0.003
	Invalidating fatigue	0.083 (0.010 – 0.16)	0.027	0.16 (0.069 – 0.24)	<0.001
	Male gender	-0.075 (-0.14 – -0.010)	0.023	-0.096 (-0.17 – -0.018)	0.016
	Coronary surgery	0.17 (0.041 – 0.31)	0.010	0.23 (0.073 – 0.39)	0.004
	Age	0.009 (0.001 – 0.017)	0.026	0.014 (0.004 – 0.023)	0.005
	LogusCRP	NS	NS	0.11 (0.048 – 0.18)	0.001
Model 2		**Adjusted R^2 = 0.39**		**Adjusted R^2 = 0.51**	
	Cystatin C	0.21 (0.14 – 0.27)	<0.001	0.43 (0.35 – 0.51)	<0.001
	E/A	0.14 (0.033 – 0.25)	0.010	0.20 (0.072 – 0.32)	0.002
	LA volume	0.004 (0.001 – 0.006)	0.003	0.005 (0.002 – 0.007)	0.001
	BMI	-0.019 (-0.026 – -0.012)	<0.001	-0.024 (-0.033 – -0.016)	<0.001
	β blocker	0.12 (0.053 – 0.19)	0.001	NS	NS
	Vp	-0.002 (-0.005 – -0.000)	0.034	NS	NS
	Aortic stenosis (grade)	0.069 (0.027 – 0.11)	0.002	0.066 (0.015 – 0.12)	0.012
	LVIDs	0.013 (0.005 – 0.021)	0.003	0.017 (0.006 – 0.029)	0.003

	LVIDs	0.013 (0.005 – 0.021)	0.003	0.017 (0.006 – 0.029)	0.003
	LogusCRP	0.071 (0.009 – 0.13)	0.025	0.16 (0.086 – 0.23)	<0.001
	Septal E'	-0.022 (-0.043 – -0.001)	0.038	-0.036 (-0.061 – -0.011)	0.004
	Diabetes	-0.12 (-0.20 – -0.033)	0.006	NS	NS
	Peripheral edema	0.098 (0.028 – 0.17)	0.006	NS	NS
	DT	-0.001 (-0.002 – 0.000)	0.030	-0.001 (-0.002 – 0.000)	0.015
	Heart frequency	-0.004 (-0.008 – -0.001)	0.010	-0.006 (-0.010 – -0.002)	0.003
	Invalidating fatigue	NS	NS	0.11 (0.006 – 0.21)	0.038
	Age	NS	NS	0.012 (0.002 – 0.023)	0.018
	Angina pectoris	NS	NS	0.12 (0.017 – 0.23)	0.023
	RWMA	NS	NS	0.13 (0.002 – 0.26)	0.047
	IVRT	NS	NS	-0.002 (-0.004 – 0.000)	0.074
	Male sex	NS	NS	-0.096 (-0.18 – -0.013)	0.023

*: the linear regression analysis (stepwise method) with LogBNP or LogNT-proBNP as the dependent variable; Model 1: the entire population without diastolic parameters (n=556); Model 2: the population having diastolic parameters determined (n=440); LA: left atrial; BMI: body mass index; LVIDs: left ventricular internal dimension at end systole; CAF: chronic atrial fibrillation; usCRP: ultra-sensitive C-reactive protein; E: early transmitral inflow wave peak velocity; A: atrial transmitral inflow wave peak velocity; Vp: flow propagation parameter of diastolic function; E': peak velocity of mitral annulus motion during early diastole; DT: deceleration time; RWMA: regional wall motion abnormalities; IVRT: isovolumic relaxation time.

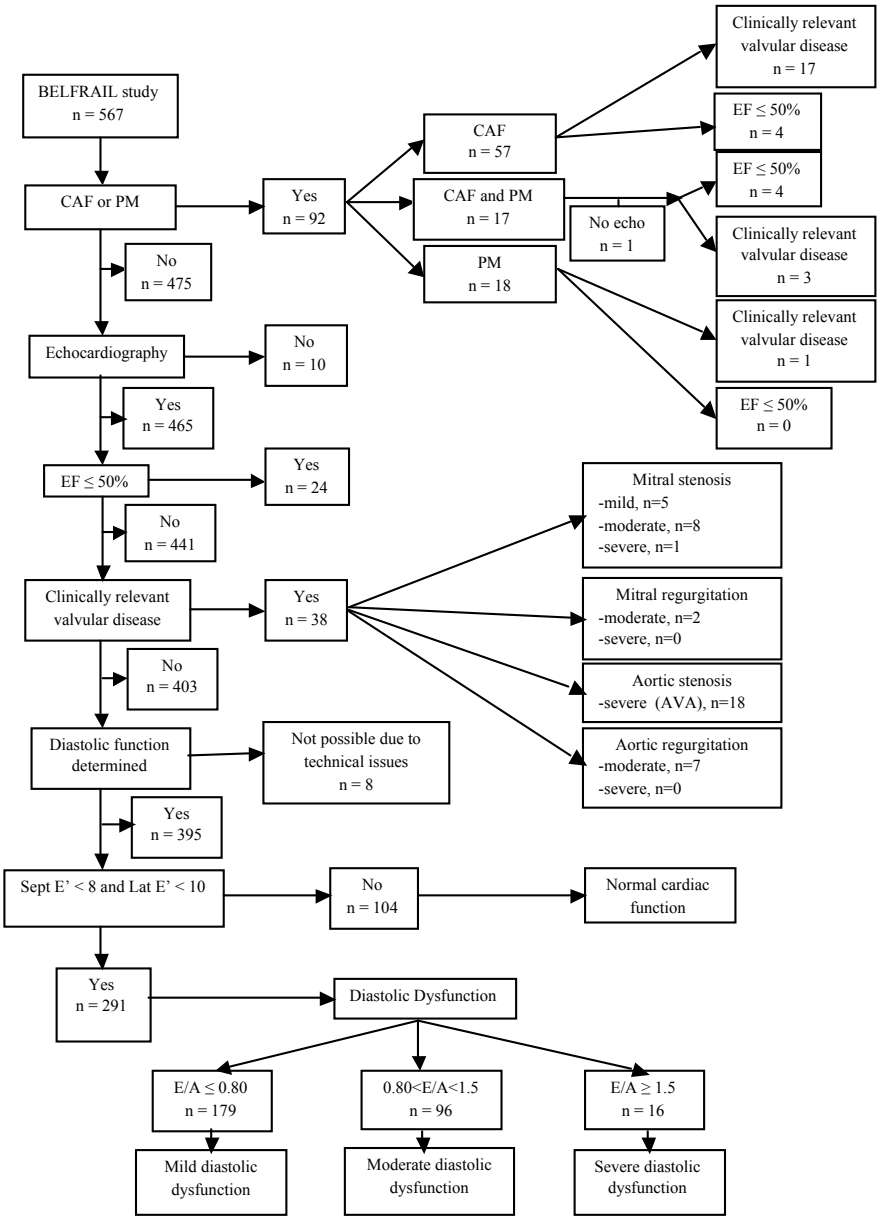

Figure 2: The classification of severe cardiac dysfunction

Table 4. The diagnostic accuracy of natriuretic peptides for severe cardiac dysfunction with and without adjustments for confounders				
	No adjustments	Model A[1]	Model B[2]	Model C[3]
	C statistic (95% CI)			
Detection of severe cardiac dysfunction in the population without CAF or PM (n=457)				
LogBNP	0.75 (0.69 – 0.82)	0.76 (0.69 – 0.83)	0.76 (0.69 – 0.82)	0.75 (0.69 – 0.82)
LogNT-proBNP	0.75 (0.69 – 0.81)	0.76 (0.69 – 0.82)	0.76 (0.69 – 0.82)	0.76 (0.70 – 0.82)
LogBNP AND LogNT-proBNP	0.76 (0.69 – 0.82)	0.76 (0.70 – 0.82)	0.76 (0.70 – 0.82)[*]	0.77 (0.70 – 0.83)[*]
Log(NT-proBNP/BNP)	0.63 (0.56 – 0.70)	0.67 (0.59 – 0.74)	0.65 (0.57 – 0.72)[*]	0.66 (0.59 – 0.73)[*]
Detection of severe cardiac dysfunction[†] in the population with CAF or PM (n=92)				
LogBNP	0.65 (0.53 – 0.78)	0.62 (0.50 – 0.75)	0.80 (0.70 – 0.91)[‡]	-
LogNT-proBNP	0.71 (0.59 – 0.83)	0.71 (0.59 – 0.83)	0.82 (0.71 – 0.93)[§]	-
LogBNP and LogNT-proBNP	0.71 (0.60 – 0.83)	0.71 (0.60 – 0.83)	0.83 (0.72 – 0.94)[ǁ]	-
Log(NT-proBNP/BNP)	0.68 (0.56 – 0.81)	0.68 (0.56 – 0.80)	0.82 (0.71 – 0.93)[#]	-

[1]: adjusted for the presence of cardiac morbidity and presence of symptoms; [2]: adjusted for the confounders retained from model 1 (no echocardiographic parameters); [3]: adjusted for the confounders retained from model 2 (no echocardiographic parameters); [*]: adjusted for the variables shown to be independent correlates of BNP and/or NT-proBNP (no echocardiographic parameters); [†]: EF≤50 or VHD; [‡]: difference compared to the AUC without adjustments (P=0.076); [§]: difference compared to the AUC without adjustments (P=0.16); [ǁ]: difference compared to the AUC without adjustments (P=0.16); [#]: difference compared to the AUC without adjustments (P=0.10); AUC: area under the curve; CI: confidence interval; CAF: chronic atrial fibrillation; PM: pacemaker.

Table 5. The diagnostic accuracy of BNP and NT-proBNP in the ROC analysis, stratified for the identified confounders

	BNP					
	Prevalence	AUC (95% CI)	Cut-off value*	PTP+ (95% CI)	PTP- (95% CI)	P value†
Total population	77/446 (17.3)	0.75 (0.71–0.79)	118.7	34.4 (27.1–42.2)	7.4 (4.7–11.1)	
Sex						
Men	31/160 (19.4)	0.71 (0.63–0.78)	107.1	33.9 (22.1–47.4)	10.9 (5.6–18.7)	**0.23**
Women	46/286 (16.1)	0.79 (0.74–0.84)	159.4	46.9 (34.3–59.8)	7.2 (4.2–11.5)	
Age						
<85	44/265 (16.6)	0.77 (0.71–0.82)	106.5	35.6 (25.7–46.4)	6.9 (3.6–11.7)	**0.72**
≥85	33/181 (18.2)	0.74 (0.67–0.80)	191.9	53.8 (37.0–70.1)	8.5 (4.4–14.3)	
Cardiac morbidity and symptoms						
No/No	16/135 (11.9)	0.76 (0.68–0.83)	107.1	28.9 (15.3–46.2)	5.2 (1.7–11.6)	
No/Yes	16/123 (13.0)	0.77 (0.69–0.84)	117.0	28.3 (16.0–43.5)	3.9 (0.8–11.0)	
Yes/No	15/81 (18.5)	0.69 (0.57–0.78)	148.8	45.5 (23.9–68.3)	8.5 (2.8–18.7)	
Yes/Yes	30/107 (28.0)	0.75 (0.66–0.83)	185.9	57.6 (38.9–74.8)	14.9 (7.7–25.0)	
Cystatin						
Tertile 1-2	47/293 (16.0)	0.74 (0.69–0.79)	106.5	32.7 (23.5–42.9)	7.7 (4.4–12.4)	**0.61**
Tertile 3	30/145 (20.7)	0.78 (0.70–0.84)	186.8	48.9 (33.5–64.4)	8.0 (3.5–15.2)	
BMI						
<25	32/142 (22.5)	0.85 (0.78–0.91)	199.8	62.2 (44.8–77.5)	8.6 (4.0–15.6)	**0.009**
≥25	45/302 (14.9)	0.68 (0.62–0.73)	118.6	29.3 (20.6–39.3)	7.9 (4.6–12.5)	
β blocker						
No	39/264 (14.8)	0.75 (0.70–0.80)	159.6	51.2 (35.5–66.7)	7.7 (4.5–12.0)	**0.66**
Yes	37/180 (20.6)	0.72 (0.65–0.79)	118.7	34.5 (24.4–45.8)	8.3 (3.7–15.8)	
Diabetes						
No	64/364 (17.6)	0.78 (0.73–0.82)	118.7	35.0 (27.1–43.5)	6.7 (3.8–10.8)	**0.16**
Yes	12/80 (15.0)	0.61 (0.50–0.72)	220.5	55.6 (21.2–86.3)	9.9 (4.1–19.3)	
LogusCRP						
Tertile 1-2	46/296 (15.5)	0.72 (0.67–0.77)	118.7	33.7 (24.2–44.3)	7.4 (4.2–11.9)	**0.28**
Tertile 3	31/148 (20.9)	0.80 (0.72–0.86)	161.9	47.8 (32.9–63.1)	8.8 (4.1–16.1)	
Heart frequency						
<70	55/319 (17.2)	0.80 (0.75–0.84)	155.2	44.2 (33.4–55.4)	7.3 (4.3–11.4)	**0.095**
≥70	22/127 (17.3)	0.66 (0.58–0.75)	125.5	34.4 (18.3–53.5)	11.6 (5.9–19.8)	

*: cut-off value that maximizes sensitivity + specificity; †: AUC compared between two different strata; ≠ : comparison between BNP and NT-proBNP AUCs within a single stratum.
BNP: brain natriuretic peptide; NT-proBNP: NT-proBNP: N-terminal pro-brain natriuretic peptide; AUC: area under the curve; CI: confidence interval; PTP+: post-test probability of positive test; PTP-: post-test probability of negative test; AF atrial fibrillation; BMI: body mass index; usCRP: ultra-sensitive C-reactive protein.

NT-proBNP						P value[‡]
Prevalence	AUC (95% CI)	Cut-off value[*]	PTP+ (95% CI)	PTP- (95% CI)	P value[†]	
76/443 (17.2)	0.75 (0.71–0.79)	432.2	46.5 (35.6–57.7)	10.1 (7.2–13.7)		0.95
30/159 (18.9)	0.73 (0.65–0.79)	426.3	48.4 (30.2–66.9)	11.7 (6.7–18.6)	**0.49**	0.37
46/284 (16.2)	0.77 (0.72–0.82)	143.6	27.5 (20.5–35.4)	3.7 (1.2–8.5)		0.47
44/263 (16.7)	0.74 (0.69–0.80)	421.2	50.0 (34.2–65.8)	10.4 (6.7–15.2)	**0.70**	0.40
32/180 (17.8)	0.77 (0.70–0.83)	636.1	54.8 (36.0–72.7)	10.1 (5.7–16.1)		0.22
16/134 (11.9)	0.68 (0.60–0.76)	124.2	19.0 (10.2–30.9)	5.6 (1.6–13.8)		0.13
15/122 (12.3)	0.75 (0.66–0.82)	164.4	22.0 (12.3–34.7)	3.2 (0.4–11.1)		0.77
15/80 (18.8)	0.73 (0.62–0.82)	545.6	64.3 (34.0–87.9)	9.1 (3.4–18.7)		0.20
30/107 (28.0)	0.77 (0.68–0.85)	428.0	56.8 (39.2–73.1)	12.9 (6.1–23.0)		0.54
46/292 (15.8)	0.74 (0.68–0.79)	163.3	28.2 (20.3–37.3)	7.4 (4.0–12.4)	**0.51**	0.91
30/145 (20.7)	0.78 (0.71–0.85)	432.2	44.2 (30.3–58.8)	7.5 (3.1–14.9)		0.79
32/142 (22.5)	0.84 (0.77–0.90)	245.0	49.1 (35.2–63.1)	5.7 (1.9–12.9)	**0.011**	0.72
44/299 (14.7)	0.69 (0.63–0.74)	143.7	21.9 (15.5–29.3)	7.4 (3.8–12.9)		0.71
38/261 (14.6)	0.76 (0.70–0.81)	432.2	50.0 (32.9–67.1)	8.9 (5.5–13.4)	**0.60**	0.71
37/180 (20.6)	0.72 (0.65–0.79)	431.4	42.9 (28.8–57.8)	12.2 (7.1–19.1)		0.97
63/361 (17.5)	0.76 (0.71 – 0.80)	432.2	47.1 (34.8–59.6)	10.6 (7.3–14.7)	**0.50**	0.54
12/80 (15.0)	0.69 (0.58 – 0.79)	428.0	41.2 (18.4 – 67.1)	7.9 (2.6–17.7)		0.29
45/295 (15.3)	0.73 (0.68–0.78)	163.3	28.0 (20.1–37.0)	6.8 (3.6–11.5)	**0.52**	0.48
31/148 (20.9)	0.78 (0.70–0.84)	417.9	50.0 (34.2–65.8)	9.4 (4.6–16.7)		0.61
54/317 (17.0)	0.80 (0.75–0.84)	431.4	50.0 (37.2–62.8)	8.7 (5.5–12.9)	**0.072**	0.92
22/126 (17.5)	0.66 (0.57–0.74)	130.4	26.2 (15.8–39.1)	9.2 (3.4–19.1)		0.92

DISCUSSION

A high prevalence of cardiac morbidity was found in a large population-based sample of elderly patients. A substantial number of subjects without known cardiac morbidity were shown to have severe cardiac dysfunction, with almost 50% being asymptomatic. Natriuretic peptides have been shown both to identify increased intracardiac pressure and to detect coronary artery disease[13, 14], left ventricular hypertrophy[11] and LA enlargement[12], even when these conditions are silent. Therefore, Struthers et al. have suggested that natriuretic peptides could possibly be used to detect symptomatic or asymptomatic pancardiac damage[15]. This study confirmed that natriuretic peptide levels are also associated with structural echocardiographic abnormalities, such as LA and LV enlargement, independent of aberrant cardiac function. Furthermore, systolic dysfunction, diastolic dysfunction and VHD were independently associated with serum natriuretic peptide levels. Moreover, these correlations were found to be independent of known cardiac morbidity and symptoms possibly related to heart failure.

Raymond et al. have identified various confounders involved in interpreting NT-proBNP levels, such as age, sex, heart rate, diabetes and (especially) renal function, which seemed to be the most important confounder[28]. When ordering a natriuretic peptide test, physicians should realize the values can be elevated without accompanying echocardiographic evidence of abnormal cardiac structure or function[8]. This consideration is particularly important in elderly patients with multiple comorbidities. The current results are consistent with those findings, although only 37% to 53% of the variation in the natriuretic peptides could be explained, indicating the complexity of possible confounding in elderly patients. Furthermore, this study found cystatin C, rather than creatinine, to be independently related to circulating levels of natriuretic peptides. Linzbach et al. have already shown NT-proBNP to be a strong predictor of cystatin C, independent of creatinine-based estimates of renal function[29]. This finding may indicate that cystatin C reflects both renal function and cardiac stress or damage[29].

Until now, there have been little available evidence on the value of using natriuretic peptides to diagnose cardiac dysfunction or heart failure in elderly patients (aged 75 and older) from the general population[30]. The current study confirmed that natriuretic peptides are best used to exclude cardiac dysfunction, given that their NPVs ranged from 86% to 97%. The 'ruling out' cut-off value of 100pg/mL for BNP and 400pg/mL for NT-proBNP that have been proposed by the ESC[26] were confirmed in this study (with found cut-off values of >118.7pg/mL and >432.2pg/mL, respectively). Using these cut-off values, 163 of 446 and 86 of 443 subjects would have been referred for echocardiography, leading to 21 of 283 and 36 of 357 false negatives for BNP and NT-proBNP, respectively. The 'ruling in' cut-off values of 400pg/mL and 2000pg/mL[26] would still lead to 5 of 20 (PPV=75%) and 3 of 14 (PPV=79%) false positives for BNP and NT-proBNP, respectively.

Several authors have argued that in daily practice, natriuretic peptide cut-off values should be adjusted according to confounders, such as age, sex, BMI or renal function[9, 28, 31, 32]. Others have advised using multivariable diagnostic algorithms for daily practice, using natriuretic peptide levels (without cut-off points), and including age, sex or renal function to account for the influence of these items on natriuretic peptide levels[33]. This study showed that adjusting for identified confounders did not improve the diagnostic accuracy of natriuretic peptides for severe cardiac dysfunction, except in the subjects with CAF or PM. By contrast, stratifying by the individual confounders showed that different cut-off values could be used to optimize the test characteristics of BNP and NT-proBNP, possibly due to different prevalences in the different strata.

Costello-Boerrigter et al. have concluded that NT-proBNP has a test performance in a community population that is superior or equivalent to that of BNP for an LVEF≤40%[34]. Furthermore, it has been shown that NT-proBNP is more stable than BNP[35] and may have lower intra-individual and inter-individual variation[36]. However, the current study was not able to identify differences in the diagnostic abilities of BNP and NT-proBNP. Moreover, no benefits from combining BNP and NT-proBNP or from using NT-

proBNP/BNP were discovered.

This was the first large study to examine the relationships between natriuretic peptides and a wide spectrum of structural and functional echocardiographic parameters in a large representative community-based sample of elderly patients; it supported the hypothesis that natriuretic peptides are markers of pancardiac damage. This study was also the first to investigate in detail whether natriuretic peptides levels need to be adjusted for multiple confounders to improve test characteristics.

A few limitations should be considered. First, the heterogeneity of the population in question could be seen as a limitation and a possible explanation for the large percentages of variation in BNP and NT-proBNP that were not explained in the multivariate analysis. Although many factors potentially associated with circulating levels of natriuretic peptides were considered, additional confounding remains possible. However, this study reflected an unselected, 'real-life' population in general practice and was representative of individuals aged 80 and older living in Belgium[17]. Second, the comorbidities may have been underdiagnosed because they were reported by the general practitioner rather than being assessed. Third, the applicability of current echocardiographic cut-off values in subjects aged 80 and older may be debatable because the thresholds for normal values are usually derived from younger populations. Fourth, due to the lack of a gold standard for heart failure, the severe CD reference standard was chosen based on a discussion of existing guidelines and a consensus procedure launched by the research team[22].

CONCLUSION

A high prevalence of cardiac morbidity was found in this large, population-based sample of elderly subjects. Several functional and structural echocardiographic parameters, such as aortic stenosis, LA volume, LVIDs, E/A, E' and DT, were independently related to circulating levels of natriuretic peptides, confirming their ability

to detect pancardiac damage, even when it is silent. Adjusting for identified confounders did not improve the diagnostic accuracy of the natriuretic peptides for severe cardiac dysfunction, except in those subjects with CAF or PM. Stratifying for individual confounders showed that different cut-off values could be used to optimize the diagnostic characteristics of BNP and NT-proBNP.

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DISCLOSURES

None.

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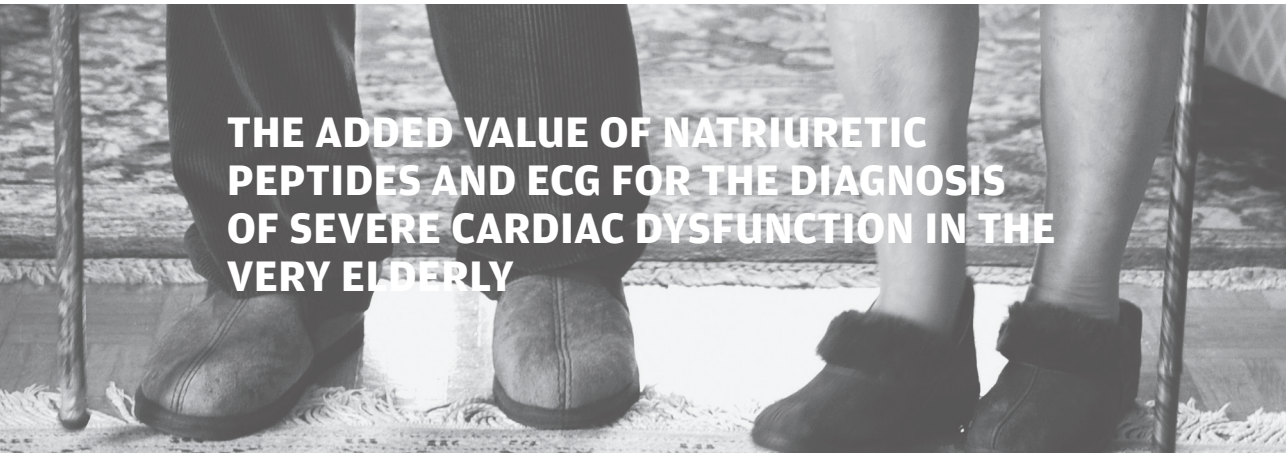
CHAPTER 7



THE ADDED VALUE OF NATRIURETIC PEPTIDES AND ECG FOR THE DIAGNOSIS OF SEVERE CARDIAC DYSFUNCTION IN THE VERY ELDERLY

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Submitted

ABSTRACT

Background: Natriuretic peptides (NP) and electrocardiograms (ECG) have been generally accepted as valuable tools for the diagnosis of cardiac dysfunction (CD). However, previous studies primarily utilised the diagnostic characteristics of a single NP or ECG test and did not integrate any previous clinical knowledge. Therefore, studies reflecting routine clinical practice remain scarce.

Methods: A cross-sectional analysis within the BELFRAIL (BF_{C80+}) study including 567 subjects aged 80 years and older was conducted to determine the added diagnostic value of NP and ECG beyond previous medical history, anamnesis, physical examination and routine laboratory tests for patients with severe CD. Logistic regression analysis and Classification and Regression Trees (CART) analysis were used as analytical tools.

Results: Severe CD was present in 17.1% (n=78) of subjects without and 30.8% (n=28) of subjects with chronic atrial fibrillation (CAF) or pace-makers (PM). In subjects without CAF or PM, the clinical model showed a C statistic of 0.79 (95% CI 0.74–0.85). The combination of NP with a negative ECG increased the C statistic to 0.82 (95% CI 0.76–0.88) (P=0.50). In subjects with CAF or PM, the clinical model showed a very high C statistic of 0.90 (95% CI 0.82–0.98). No other tests were independently correlated with severe CD. CART analysis showed that an additional 58 subjects (13%) were correctly classified using NP and ECG in subjects without CAF or PM. In participants with CAF or PM, more than 90% was correctly classified, but no difference was observed between the two models.

Conclusion: In a large population-based sample of unselected, very elderly patients, there was little added value in implementing NP or ECG for diagnosing severe CD in daily practice. In subjects without CAF or PM, a higher number of participants were correctly classified by integrating NP and ECG in the diagnostic process. In participants with CAF or PM, the clinical model showed very high

accuracy and no added value of NP was found.

INTRODUCTION

In the next several decades, the proportion of very elderly people living in industrialised countries will increase dramatically[1]. People aged 80 and older are the fastest growing age segment in the Western world, and their numbers will peak by 2050[2]. Furthermore, improved survival following acute cardiac events has led to an increased prevalence of cardiac dysfunction (CD), especially in the elderly[3]. Currently, there is growing evidence of the progression from risk factors to asymptomatic cardiac dysfunction and eventually symptomatic heart failure and death[4-8]. Therefore, timely identification of severe cardiac dysfunction is important because early treatment could delay the onset of overt heart failure[9;10].

As multiple comorbidities are present, typical symptoms of heart failure, such as dyspnoea, fatigue or peripheral oedema, are very prevalent in elderly patients[11] and show little specificity for cardiac dysfunction[12]. The recognition of cardiac dysfunction and heart failure, particularly in the early stages, may be hindered by the lack of diagnostically accurate signs and symptoms[13]. Furthermore, the limited availability of echocardiography outside of hospitals increases the likelihood of a considerable number of misdiagnoses[14;15].

Natriuretic peptides (NP) and electrocardiograms (ECG) have been generally accepted as valuable tools for the diagnosis of heart failure[9]. Moreover, their mainly exclusionary characteristics have also been demonstrated in unselected, elderly populations for detecting cardiac dysfunction[16;17]. However, previous studies calculated the diagnostic characteristics of a single NP or ECG test as though the diagnostic procedure was a univariable activity and previous clinical knowledge had no clinical impact[18]. Studies that estimate the added value of NP and ECG in addition to medical history and clinical examination, which is representative of current clinical practice, remain scarce[19].

Therefore, a cross-sectional, "intention to diagnose"[20] analysis

was performed within the BELFRAIL cohort (BF_{C80+}) to determine the added diagnostic value of NP and ECG beyond previous medical history, anamnesis, physical examination and routine laboratory tests for severe cardiac dysfunction. Thus, the goal of this study was not to develop a new diagnostic algorithm for clinical practice but to investigate the possible diagnostic gain of implementing NP and ECG in a case-finding strategy for cardiac dysfunction in an unselected population of subjects aged 80 and older.

METHODS

Study population

The BF_{C80+} study is a prospective, observational, population-based cohort study of subjects aged 80 years and older in three well-circumscribed areas of Belgium. All participants in the study gave informed consent, and the Biomedical Ethics Committee of the Medical School of the Université Catholique de Louvain (UCL) of Brussels approved the study. The study design, methods and characteristics of the cohort were previously described in detail[21]. Briefly, 29 general practitioner (GP) centres were asked to include patients aged 80 and older. No other inclusion criteria were specified, and only three exclusion criteria were used: known severe dementia (mini-mental state examination<15), in palliative care and medical emergency. Two sampling methods for the recruitment of patients were used. Two GP centres were asked to include all eligible patients. The remaining 27 centres were asked to include a maximum of three consecutive patients during a three-week interval, which was repeated five times, with each interval beginning on a different day. Every study participant was invited to attend four study visits.

Study visits

Visit by the general practitioner

The GP was asked to record known non-cardiovascular and cardiovascular comorbidities of the study subjects and perform a

structured and standardised anamnesis and clinical examination[21]. The GP was blinded to the results of the other study visits.

Non-cardiovascular morbidities were defined as the presence of thyroid problems, asthma, COPD, osteoarthritis, documented osteoporosis and malignancies. Cardiovascular morbidities were defined as the presence of hypertension, diabetes mellitus, hyperlipidaemia, history of angina pectoris or myocardial infarction (MI), known cardiomyopathy, history of transient ischaemic attack or cerebro-vascular accident, peripheral arterial disease (PAD), history of decompensated heart failure, chronic atrial fibrillation (CAF) or valvular heart disease (VHD). The GP was asked to report important cardiovascular interventions, such as percutaneous transluminal coronary angioplasty or stenting, coronary, valvular or arterial surgery, or the placement of a pace-maker (PM).

Data on relevant cardiovascular medication, including cardiac glycosides, diuretics, ß-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers (ARB) and lipid lowering agents, were also recorded.

The anamnesis included questions about symptoms of angina pectoris, dyspnoea (Medical Research Council scale score≥3[22]), invalidating fatigue, orthopnoea, cough (nocturnal or diurnal), wheezing, oedema of the lower extremities, palpitations, loss of appetite, smoking status (ex-smoker or current smoker), alcohol intake (units per week), recent changes in symptoms, recent weight change and alteration of mental and psychological status (MPS).

The clinical examination consisted of resting heart rate, blood pressure and breathing rate measurements. Heart auscultation was performed to detect S3, S4 or cardiac murmurs. The apex beat was palpated and recorded when abnormal. Lung auscultation was performed to detect crepitations, wheezing and rhonchi. The carotid arteries were auscultated to detect murmurs. The jugular venous pressure was measured and noted if raised, and the presence of hepatojugular reflux (HJR) was also checked. The GP was asked to determine whether hepatomegaly or oedema of the lower extremities was present and to note whether the patient had ascites.

Visit by the clinical research assistant (CRA) and ECG

The Body Mass Index (BMI) was calculated based on a standardised measurement of weight and height. A 12-lead ECG was recorded on a QRS Universal ECG device (QRS Diagnostic, Plymouth, USA). Each ECG was digitally stored by the CRA and analysed off-line by a single, experienced cardiologist (blinded to the results of all other examinations) according to the Minnesota Code Classification System for Electrocardiographic Findings[23]. For this study, patients with prior myocardial infarction, atrial fibrillation, presence of artificial PM, LV hypertrophy, left bundle branch block, right bundle branch block, sinus tachycardia and sinus bradycardia were included. Moreover, the cardiologist was asked to report whether the ECG was completely normal.

Laboratory tests

A blood sample was collected in the morning, and plasma (EDTA) and serum samples were stored frozen at -80°C until analysis. Haemoglobin concentrations were measured on whole blood using the Sysmex XE-2100 automated haematology analyser (Milton Keynes, UK). Anaemia was defined as haemoglobin levels <12 g/dL for women and <13 g/dL for men[24]. Total cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol, triglycerides, ultra-sensitive C-Reactive Protein (usCRP) and Cystatin C in the serum were measured using the UniCel® DxC 800 Synchron (Beckman-Coulter, Brea, USA). The glomerular filtration rate was estimated (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration Cystatin C 2 formula[25]. Plasma levels of Brain Natriuretic Peptide (BNP) were measured using the Biosite® kit on a UniCel® DxI 800 Immunoassay System (Beckman-Coulter, Brea, USA). The coefficient of variation (CV) ranged from 5.4 to 6.7%. Serum N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) levels were measured using the Dade-Dimension® Xpand (Siemens, Deerfield, USA). The CV ranged from 3.9 to 4.3%.

Echocardiography

Echocardiograms were performed at the home of each subject

by a single cardiologist (blinded to all other test results) using a commercially available portable system (CX50, Philips, Andover, Massachusetts, USA). A complete examination, in accordance with the recommendations of the American and European Society of Echocardiography, was performed[26]. The methodology, prevalence of echocardiographic abnormalities and classification of subjects according the presence of cardiac dysfunction were previously described in detail[11]. Briefly, LV function was calculated by the Simpson biplane method[26]. Systolic dysfunction was defined as a LV ejection fraction (EF) ≤50%. The function of the mitral and aortic valves was evaluated with colour Doppler echocardiography after optimising the gain and Nyquist limit. Stenotic and regurgitant valve diseases were evaluated according to semiquantitative and quantitative methods recommended by the American Society of Echocardiography[27;28]. Subjects with a prosthetic valve were evaluated separately[27]. Clinically relevant VHD was defined as any mitral stenosis severity, severe aortic stenosis, moderate or severe mitral regurgitation, and moderate or severe aortic regurgitation.

Diastolic function was assessed using mitral flow velocities obtained using pulsed Doppler and pulsed tissue Doppler at the level of the mitral annulus[29]. Additional apical and parasternal views for the assessment of tissue velocity (colour tissue Doppler) were also recorded. The ASA-EAE guidelines were used to assess the presence of diastolic dysfunction (DD)[29].

Because of difficulties in interpreting diastolic parameters in subjects with CAF or PM, the population under study was split in two for analysis. In subjects without CAF or PM (on ECG or by GP), the target condition was severe cardiac dysfunction, including LVEF≤50%, VHD or severe DD. In subjects with CAF or PM, the target condition was LVEF≤50% or VHD.

Data analysis

Continuous variables are presented as the mean and standard deviation (SD) or median and inter-quartile range (IQR). Categorical variables are presented as numbers and frequencies. Comparisons between different categories of subjects were performed using

Student's t test or the Mann-Whitney U test (nonparametric data) for unpaired data.

The added value of natriuretic peptides (NP) and ECG was measured using logistic regression analysis and Classification and Regression Trees (CART) analysis. Two strategies were used: one used all clinical variables collected by the GP and blood analyses without NP (clinical model) and the other included NP and/or ECG (clinical+ model).

For the logistic regression analysis, BNP, NT-proBNP and usCRP were Log-transformed, anaemia was used instead of haemoglobin levels, Cystatin C instead of eGFR and BMI was dichotomised (>or≤25 kg/m²). LDL was not used because of a strong correlation with the levels of total cholesterol (Pearson correlation=0.94, $P<0.001$). First, a univariate logistic regression analysis was performed with all possible variables. Subsequently, all variables with a P-value≤0.10 were included in the multivariate analyses (stepwise, forward conditional) to determine which diagnostic items were independently related to the diagnosis of severe cardiac dysfunction. The C statistic and 95% confidence interval (CI) was calculated using the probabilities calculated from the regression analysis and compared between different models[30].

Tree-based models (such as CART) are non-linear and non-parametric alternatives to linear models for regression and classification problems[31]. CART models are fitted by binary recursive partitioning of a multidimensional covariate space, in which the dataset is successively split into increasingly homogeneous subsets until a specified criterion is reached[32;33]. The minimum diagnostic cost tree (lowest error rate), regardless of size, was selected as the best tree. A stepwise approach in tree generation was used. First, a tree with an equal cost for false negatives (FN) and false positives (FP) was calculated. Second, the cost for FN was set to three-fold that of FP[34] to generate a tree that excludes severe cardiac dysfunction. Third, a tree to identify the different subtypes of cardiac dysfunction (equal cost for FN and FP) was calculated in the remaining population. For each tree, the area under the curve (AUC) was determined, and the sensitivity, specificity and post-

test probability of a negative (PTP-) and positive (PTP+) test were calculated using 2x2 tables.

The data analysis was performed using SPSS 19.0 for Windows (SPSS Inc., Chicago, IL, USA) and the Salford Predictive Modeler Builder v6.6 (Salford Systems, San Diego, CA, USA).

RESULTS

Between November 2, 2008, and September 15, 2009, 567 subjects were included in the BF_{C80+} study. Women accounted for 63.1% (n = 358) of the study population and had a mean age of 85.0±3.9 years; the men had a mean age of 84.3±3.3 years. The majority of study participants lived at home (89.9%). The participants showed a high burden of non-cardiovascular and cardiovascular morbidity (2 [IQR 1–2] and 2 [IQR 1–4] morbidities, respectively). Symptoms of dyspnoea, fatigue or peripheral oedema were present in 312 subjects (55.2%). Only 83 subjects (14.7%) did not receive cardiovascular medication, while the others received mainly diuretics (49.0%), ß-blockers (42.1%) and ACE-I or ARB (41.8%).

Echocardiography was performed in 548 participants, of whom 91 subjects (16.6%) had CAF or PM. The target condition was present in 78 subjects (17.1%) without and 28 (30.8%) with CAF or PM. The median time between echocardiography and examination by the GP was 29 days [IQR 14–43], 7 days [IQR 3–15] between echo and ECG and 3 days [IQR 1–13] between echo and NP testing. The number of participants that underwent all index tests and echocardiography (n=509, 90%) is shown in a flow diagram (Figure 1). Some subjects failed to receive an ECG, NP testing or echocardiography as a result of technical issues, and others had inconclusive echocardiography results.

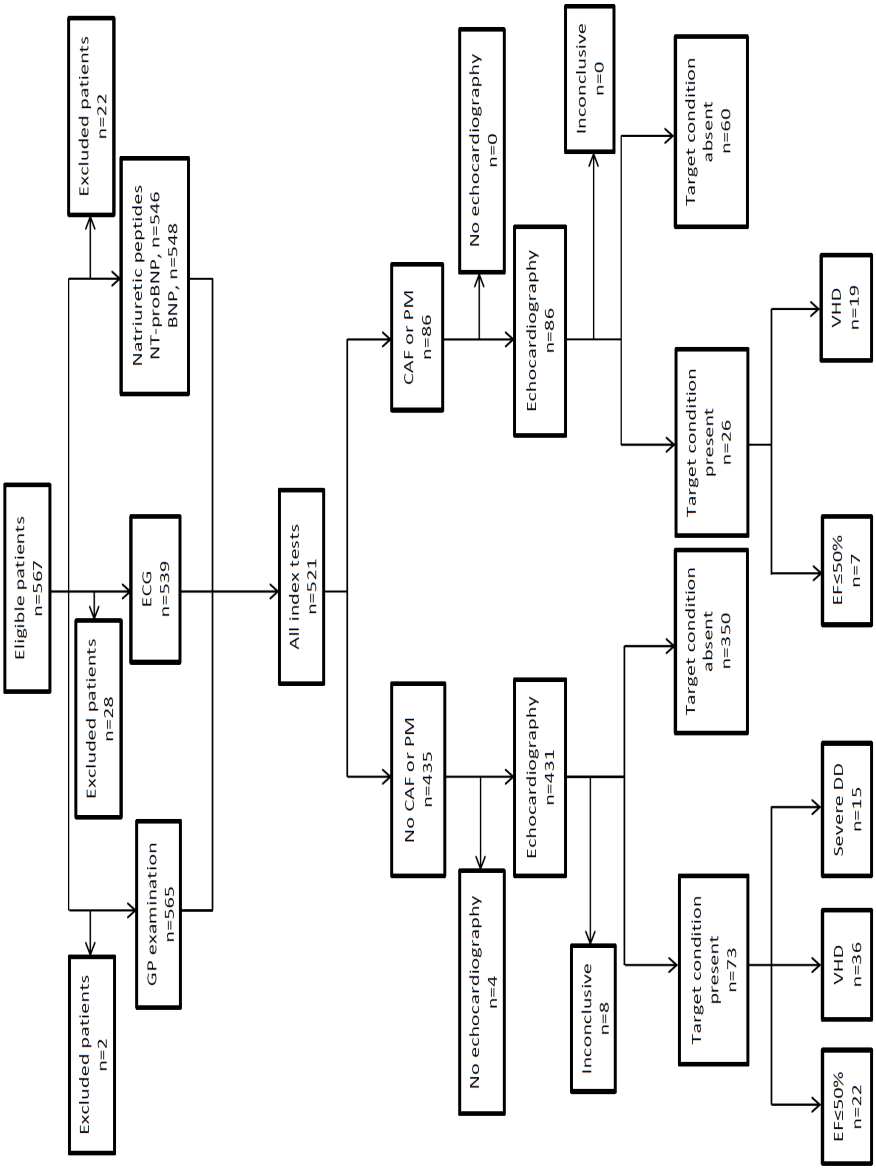

Figure 1. Study flow diagram

Table 1 presents the background variables and Table 2 shows the results of the index tests according to the presence of the target condition in the 548 participants with or without CAF or PM. In subjects without CAF or PM, the presence of thyroid dysfunction, reported VHD and coronary surgery in the medical history; alteration of MPS in the anamnesis, S3 and cardiac murmur detected by clinical examination; and the level of triglycerides, cystatin C and presence of anaemia were independent determinants of severe CD (clinical model, C statistic 0.79 (95% CI 0.74–0.85), Table 3). In subjects with CAF or PM, age and the presence of PAD, alteration of MPS, the presence of cardiac murmur and HJR and level of total cholesterol were independent identifiers of the target condition (clinical model, C statistic 0.90 (95% CI 0.82–0.98)).

Table 1. Background variables relevant to the presence of severe cardiac dysfunction in 548 subjects with or without CAF or PM.						
	No CAF or PM		P value*	CAF or PM		P value*
	No severe CD (n = 379)	Severe CD (n = 78)		No severe CD (n = 63)	Severe CD (n = 28)	
Age (years), mean ± SD	84.5 ± 3.6	84.9 ± 3.8	0.27	84.7 ± 3.0	86.8 ± 3.5	0.003
Men, n (%)	133 (35.1)	32 (41.0)	0.32	24 (38.1)	15 (53.6)	0.17
Institutionalised, n (%)	38 (10.0)	10 (12.8)	0.47	4 (6.3)	3 (10.7)	0.48
Non-cardiovascular morbidities						
Thyroid dysfunction, n (%)	26 (6.9)	11 (14.3)	0.083	7 (11.1)	4 (14.3)	0.67
Asthma, n (%)	18 (4.8)	3 (3.9)	0.74	4 (6.3)	1 (3.6)	0.60
COPD, n (%)	37 (9.8)	10 (13.0)	0.40	12 (19.0)	2 (7.1)	0.095
Osteoarthritis, n (%)	220 (58.8)	42 (54.5)	0.49	35 (57.4)	16 (57.1)	0.98
Osteoporosis, n (%)	86 (23.1)	18 (24.0)	0.87	14 (22.6)	3 (11.1)	0.17
Malignancies, n (%)	77 (20.4)	16 (20.8)	0.94	12 (19.0)	7 (25.0)	0.52
Cardiovascular morbidities						
Hypertension, n (%)	262 (69.3)	56 (72.7)	0.55	47 (74.6)	19 (67.9)	0.51
Hyperlipidaemia, n (%)	173 (46.4)	31 (40.8)	0.37	28 (45.2)	8 (29.6)	0.16
Diabetes, n (%)	70 (18.5)	12 (15.6)	0.54	12 (19.0)	8 (28.6)	0.32
Angina pectoris, n (%)	56 (14.8)	13 (16.9)	0.65	14 (22.6)	6 (21.4)	0.90
Myocardial infarction, n (%)	35 (9.3)	12 (15.6)	0.16	9 (14.3)	3 (10.7)	0.65
Cardiomyopathy, n (%)	24 (6.4)	10 (13.0)	0.11	11 (18.3)	8 (29.6)	0.28
Transient ischaemic attack, n (%)	37 (10.0)	4 (5.3)	0.12	8 (12.7)	5 (18.5)	0.48
CVA, n (%)	27 (7.2)	8 (10.7)	0.37	5 (7.9)	5 (17.9)	0.23
Peripheral arterial disease, n (%)	28 (7.4)	8 (10.4)	0.38	5 (7.9)	8 (29.6)	0.030
Episode of decompensated HF, n (%)	22 (5.8)	15 (19.5)	0.005	17 (27.0)	4 (14.3)	0.15
Reported valvular heart disease, n (%)	62 (16.5)	32 (41.6)	<0.001	25 (39.7)	17 (60.7)	0.064
PTCA or stent, n (%)	31 (8.2)	8 (10.5)	0.52	7 (11.1)	1 (3.6)	0.16
Coronary surgery, n (%)	16 (4.2)	9 (12.0)	0.051	8 (12.7)	3 (10.7)	0.79

Valvular surgery, n (%)	8 (2.1)	3 (4.0)	0.34	6 (9.5)	2 (7.1)	0.72
Arterial surgery, n (%)	16 (4.2)	4 (5.3)	0.68	3 (4.8)	4 (14.3)	0.20
Cardiovascular medication						
Cardiac glycosides, n (%)	4 (1.1)	1 (1.3)	0.37	9 (14.3)	9 (32.1)	0.082
Diuretics, n (%)	170 (45.0)	43 (55.8)	0.082	34 (54.0)	20 (71.4)	0.11
B-blockers, n (%)	146 (38.6)	37 (48.1)	0.14	33 (52.4)	16 (57.1)	0.68
Calcium antagonists, n (%)	86 (22.8)	18 (23.4)	0.91	20 (31.7)	11 (39.3)	0.49
ACE inhibitor or ARB, n (%)	143 (37.8)	39 (50.6)	0.043	32 (50.8)	16 (57.1)	0.58
Lipid modifier, n (%)	130 (34.4)	22 (28.6)	0.31	18 (28.6)	7 (25.0)	0.73

*Student's t test; ¤ haemoglobin levels <12 g/dL for women and <13 g/dL for men; &: GFR estimated using the Chronic Kidney Disease epidemiology collaboration 2 Cystatin C equation.

CAF: chronic atrial fibrillation; PM: pace-maker; CD: cardiac dysfunction; SD: standard deviation; IQR: inter-quartile range; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; CVA: cerebrovascular accident; HF: heart failure; PTCA: percutaneous transluminal coronary angioplasty; ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker.

Table 2. Clinical characteristics, ECG and laboratory tests according to the presence of severe cardiac dysfunction in 548 subjects with or without CAF or PM.

	No CAF or PM		P value*	CAF or PM		P value*
	No severe CD (n = 379)	Severe CD (n = 78)		No severe CD (n = 63)	Severe CD (n = 28)	
Anamnesis						
Symptoms of AP, n (%)	43 (11.4)	12 (15.6)	0.35	10 (15.9)	4 (14.3)	0.85
Dyspnoea, n (%)	98 (25.9)	27 (35.1)	0.13	24 (38.1)	14 (50.0)	0.29
Invalidating fatigue, n (%)	66 (17.6)	21 (27.3)	0.082	15 (23.8)	10 (35.7)	0.27
Orthopnoea, n (%)	19 (5.0)	8 (10.4)	0.15	3 (4.8)	3 (10.7)	0.37
Cough at night, n (%)	21 (5.6)	2 (2.6)	0.18	6 (9.5)	2 (7.1)	0.72
Cough during the day, n (%)	38 (10.1)	10 (13.0)	0.45	10 (15.9)	7 (25.0)	0.31
Wheezing, n (%)	40 (10.6)	10 (13.0)	0.55	6 (9.5)	2 (7.4)	0.75
Peripheral oedema, n (%)	118 (31.2)	21 (27.3)	0.50	30 (47.6)	16 (57.1)	0.41
Palpitations, n (%)	39 (10.3)	12 (15.6)	0.18	15 (23.8)	7 (25.0)	0.90
Loss of appetite, n (%)	44 (11.6)	6 (7.8)	0.27	6 (9.5)	7 (25.0)	0.098
Smoker or ex-smoker, n (%)	121 (32.0)	25 (32.5)	0.94	22 (34.9)	6 (21.4)	0.18
Alcohol (units/day), median [IQR]	1 [0 – 7]	1 [0 – 7]	0.80$	1 [0 – 7]	2 [0 – 7]	0.99$
Recent change in symptoms, n (%)	49 (13.0)	13 (16.9)	0.37	5 (7.9)	3 (11.1)	0.63
Recent weight change, n (%)	69 (18.4)	17 (22.1)	0.45	10 (15.9)	5 (17.9)	0.82
Alteration MPS, n (%)	88 (23.3)	26 (33.8)	0.078	17 (27.0)	14 (50.0)	0.045
Clinical examination						
Heart frequency (bpm), mean ± SD	68 ± 10	68 ± 10	0.72	71 ± 11	68 ± 12	0.36
Systolic BP (mmHg), mean ± SD	138 ± 19	141 ± 21	0.24	137 ± 21	137 ± 15	0.95
Diastolic BP (mmHg), mean ± SD	73 ± 9	74 ± 9	0.62	74 ± 9	73 ± 10	0.60
Breathing frequency (bpm), mean ± SD	17 ± 5	17 ± 4	0.91	18 ± 6	19 ± 6	0.69
Normal heart beats, n (%)	346 (91.5)	69 (89.6)	0.59	54 (85.7)	22 (78.6)	0.40
S3, n (%)	7 (1.9)	7 (9.1)	0.035	2 (3.2)	2 (7.1)	0.40
S4, n (%)	4 (1.1)	1 (1.3)	0.85	3 (4.8)	0 (0)	0.083

Cardiac murmur, n (%)	93 (24.6)	40 (51.9)	<0.001	23 (36.5)	19 (67.9)	0.005
Abnormal apex beat, n (%)	12 (3.2)	6 (7.8)	0.15	9 (14.3)	5 (17.9)	0.67
Normal breathing sounds, n (%)	288 (76.2)	58 (75.3)	0.87	45 (71.4)	22 (78.6)	0.48
Crepitations on auscultation, n (%)	57 (15.1)	7 (9.1)	0.12	11 (17.5)	5 (17.9)	0.96
Wheezing on auscultation, n (%)	23 (6.1)	6 (7.8)	0.58	5 (7.9)	1 (3.6)	0.44
Rhonchi on auscultation, n (%)	13 (3.4)	6 (7.8)	0.18	3 (4.8)	1 (3.6)	0.80
Murmur carotids, n (%)	36 (9.6)	15 (19.7)	0.039	2 (3.2)	6 (22.2)	0.032
Raised JVP, n (%)	22 (5.8)	10 (13.0)	0.079	11 (17.5)	8 (28.6)	0.27
HJR, n (%)	22 (5.8)	16 (20.8)	0.003	8 (12.7)	8 (28.6)	0.11
Hepatomegaly, n (%)	4 (1.1)	0 (0)	0.37	1 (1.6)	1 (3.6)	0.56
Peripheral oedema, n (%)	112 (29.6)	23 (29.9)	0.97	26 (41.3)	17 (60.7)	0.088
Suspicion ascites, n (%)	1 (0.3)	0 (0)	0.54	0 (0)	0 (0)	-
BMI (kg/m²), mean ± SD	27.6 ± 4.8	26.6 ± 5.7	0.16	27.4 ± 4.4	27.3 ± 3.7	0.96
BMI>25 kg/m², n (%)	264 (70.0)	45 (57.7)	0.046	42 (66.7)	22 (81.5)	0.13
ECG						
Heart frequency (bpm), mean ± SD	65 ± 11	65 ± 13	0.72	67 ±13	65 ±12	0.41
Prior myocardial infarction, n (%)	46 (12.9)	14 (18.4)	0.25	10 (21.3)	6 (24.0)	0.80
Atrial fibrillation, n (%)	-	-	-	28 (45.9)	20 (76.9)	0.005
Presence of artificial PM, n (%)	-	-	-	22 (36.1)	7 (26.9)	0.41
LV hypertrophy, n (%)	22 (6.1)	11 (14.5)	0.053	4 (8.7)	7 (28.0)	0.064
LBBB, n (%)	14 (3.9)	4 (5.3)	0.58	3 (6.3)	2 (8.0)	0.78
RBBB, n (%)	23 (6.4)	8 (10.5)	0.27	7 (14.0)	2 (8.0)	0.46
Sinus tachycardia, n (%)	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Sinus bradycardia, n (%)	22 (6.1)	7 (9.2)	0.32	2 (3.3)	2 (7.7)	0.38
Negative ECG, n (%)	160 (44.1)	20 (26.3)	0.002	-	-	-
Laboratory tests						
Haemoglobin (g/dL), mean ± SD	13.4 ± 1.4	13.1 ± 1.5	0.075	13.5 ±1.6	13.3 ± 1.6	0.52
Anaemia[u], n (%)	61 (16.4)	26 (33.8)	0.003	11 (17.5)	9 (32.1)	0.16
Total cholesterol (mg/dL), mean ± SD	204 ± 46	195 ± 45	0.11	205 ± 30	179 ± 32	<0.001

LDL (mg/dL), mean ± SD	124 ± 39	118 ± 36	0.20	128 ± 30	109 ± 28	0.005
HDL (mg/dL), mean ± SD	56 ± 15	57 ± 16	0.70	55 ± 15	46 ± 11	0.003
Total cholesterol/HDL, mean ± SD	3.8 ± 1.1	3.6 ± 0.84	0.019	3.9 ± 0.97	4.1 ± 1.3	0.36
Triglycerides (mg/dL), mean ± SD	123 ± 67	99 ± 39	<0.001	107 ± 41	120 ± 76	0.30
usCRP (mg/dL), median [IQR]	0.17 [0.078 – 0.40]	0.20 [0.069 – 0.41]	0.67$	0.23 [0.11 – 0.40]	0.36 [0.14 – 0.77]	0.055$
Cystatin C (mg/L), mean ± SD	1.2 ± 0.48	1.4 ± 0.65	0.037	1.3 ± 0.41	1.5 ± 0.59	0.15
eGFR (mL/min), mean ± SD	66 ± 26	58 ± 22	0.013	60 ± 23	53 ± 20	0.16
eGFR≤45 ml/min&, n (%)	73 (20.2)	22 (28.6)	0.14	17 (27.0)	10 (37.0)	0.35
BNP (pg/mL), median [IQR]	75 [47 – 130]	200 [86 – 374]	<0.001$	170 [98 – 242]	250 [171 – 328]	0.020$
NT-proBNP (pg/mL), median [IQR]	137 [79 – 255]	445 [169 – 1088]	<0.001$	607 [188 – 920]	1047 [551 – 2056]	0.002$

*, Student's t test; $, Mann-Whitney U test.

CAF: chronic atrial fibrillation; PM: pace-maker; CD: cardiac dysfunction; AP: angina pectoris: IQR: inter-quartile range; MPS: mental and psychological state; SD: standard deviation; BP: blood pressure; BMI: body mass index; JVP: jugular venous pressure; HJR: hepatojugular reflux; LV: left ventricular; LBBB: left bundle branch block; RBBB: right bundle branch block; ECG: electrocardiogram; LDL: low density lipoprotein; HDL: high density lipoprotein; usCRP: ultra-sensitive C-reactive protein; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Table 3. Determinants of the presence of severe cardiac dysfunction in subjects with or without CAF or PM from background variables, anamnesis, clinical examination, ECG and natriuretic peptides with logistic regression analysis.

Model	No CAF or PM		C statistic (95% CI)	CAF or PM		C statistic (95% CI)
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)		Unadjusted OR (95% CI)	Adjusted OR (95% CI)	
Clinical model			0.79 (0.74 – 0.85)			0.90 (0.82 – 0.98)
Background variables						
Age	NS	-		1.2 (1.1 – 1.4)	1.3 (1.0 – 1.6)	
Thyroid dysfunction	2.3 (1.1 – 4.8)	2.3 (0.92 – 5.7)		NS	-	
Cardiomyopathy	2.2 (1.0 – 4.8)	NS		NS	-	
PAD	NS	-		4.9 (1.4 – 17)	5.7 (1.0 – 32)	
Episode DHF	3.9 (1.9 – 7.9)	NS		NS	-	
Reported VHD	3.6 (2.1 – 6.1)	2.7 (1.4 – 5.1)		2.3 (0.95 – 5.8)	NS	
Coronary surgery	3.1 (1.3 – 7.3)	2.8 (1.0 – 7.5)		NS	-	
Cardiovascular medication						
Cardiac glycosides	NS	-		2.8 (0.98 – 8.2)	NS	
Diuretics	1.5 (0.95 – 2.5)	NS		NS	-	
ACE-I or ARB	1.7 (1.0 – 2.8)	NS		NS	-	
Anamnesis						
Invalidating fatigue	1.8 (0.99 – 3.1)	NS		NS	-	
Orthopnoea	2.2 (0.92 – 5.2)	NS		NS	-	
Loss of appetite	NS	-		3.2 (0.95 – 11)	NS	
Alteration of MPS	1.7 (0.99 – 2.8)	1.8 (0.97 – 3.4)		2.7 (1.1 – 6.8)	4.2 (1.0 – 17)	
Clinical examination						
S3	5.3 (1.8 – 15)	4.5 (1.2 – 17)		NS	-	
Cardiac murmur	3.3 (2.0 – 5.9)	2.3 (1.2 – 4.2)		3.7 (1.4 – 9.4)	4.5 (1.1 – 18)	
Abnormal apex beat	2.6 (0.94 – 7.1)	NS		NS	-	
Rhonchi	2.4 (0.87 – 6.5)	NS		NS	-	

Murmur carotids	2.3 (1.2 – 4.5)	NS		8.7 (1.6 – 47)	NS	
Raised JVP	2.4 (1.1 – 5.3)	NS		NS	-	
HJR	4.2 (2.1 – 8.5)	NS		2.8 (0.91 – 8.3)	5.4 (1.2 – 25)	
Oedema LE	NS	-		2.2 (0.89 – 5.5)	NS	
BMI>25	0.58 (0.35 – 0.96)	NS		NS	-	
Laboratory results						
Anaemia	2.6 (1.5 – 4.5)	1.8 (0.90 – 3.4)		NS	-	
Total cholesterol	NS	NS		0.97 (0.96 – 0.99)	0.96 (0.94 – 0.98)	
HDL	NS	-		0.94 (0.90 – 0.98)	NS	
Total cholesterol/HDL	0.77 (0.59 – 0.99)	NS		NS	-	
Triglycerides	0.99 (0.99 – 1.0)	0.99 (0.98 – 1.0)		NS	-	
LogusCRP	NS	-		2.2 (0.97 – 5.2)	NS	
Cystatin C	1.7 (1.1 – 2.6)	1.7 (1.0 – 2.8)		2.2 (0.87 – 5.6)	NS	
Clinical+ model						
Electrocardiogram						
LV hypertrophy	2.6 (1.2 – 5.6)	1.5 (0.60 – 4.0)[$]	0.79 (0.74 – 0.85)	4.1 (1.1 – 16)	3.5 (0.24 – 52)[$]	0.91 (0.82 – 1.0)
Atrial fibrillation	-	-		3.9 (1.4 – 11)	3.5 (0.71 – 18)[$]	0.91 (0.83 – 0.99)
Negative ECG	0.45 (0.26 – 0.79)	0.46 (0.25 – 0.87)	0.80 (0.74 – 0.85)	-	-	
Natriuretic peptides						
LogBNP	16 (7.5 – 35)	8.3 (3.3 – 21)	0.81 (0.75 – 0.87)	4.2 (0.83 – 21)	0.74 (0.089 – 6.2)[$]	0.90 (0.82 – 0.98)
LogNT-proBNP	7.1 (4.1 – 12)	6.5 (3.1 – 13)	0.81 (0.75 – 0.87)	5.3 (1.7 – 16)	1.0 (0.23 – 4.7)[$]	0.90 (0.82 – 0.98)
Clinical model + LogBNP + negative ECG			0.82 (0.76 – 0.87)			-
Clinical model + LogNT-proBNP + negative ECG			0.82 (0.76 – 0.88)			-

[$], P>0.10.

CAF: chronic atrial fibrillation; PM: pace-maker; ECG: electrocardiogram; OR: odds ratio; CI: confidence interval; NS: not significant (P>0.10); DHF: decompensated heart failure; PAD: peripheral arterial disease; VHD: valvular heart disease; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; MPS; mental and psychological status; JVP: jugular venous pressure; HJR: hepatojugular reflux; LE: lower extremities; BMI: body mass index; HDL: high-density lipoprotein; usCRP: ultrasensitive C-reactive protein; LV: left ventricular; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Of the additional tests, LV hypertrophy on ECG, negative ECG, NT-proBNP and BNP were univariate determinants of severe CD in subjects without CAF or PM. Of these tests the combination NT-proBNP or BNP with a negative ECG had the largest added value, resulting in an increase (P=0.50) in the C statistic to 0.82 (95% CI 0.76–0.88). In patients with CAF or PM, no other test was an independent correlate of severe CD.

The presence of cardiac murmur emerged as the strongest discriminating factor for severe CD when building a clinical model in subjects without CAF or PM using CART analysis (Tree 1 (Table 4 and 5)). The lowest cost tree showed that cardiac murmur was the only splitter (AUC 0.63, 38 FN and 93 FP). Increasing the cost for FN yielded a 5-node tree (Tree 2 (Figure 2A)) that was able to exclude 132 participants from further analysis (AUC 0.73, 0 FN and 247 FP). Three participants could not to be classified and were kept in the group for further analysis as a result of missing discriminating factors. In the remaining 328 subjects, the lowest cost tree (relative cost = 0.770) was a single node tree in which cardiac murmur as the only splitter that was able to correctly classify 52 subjects (16%) in different categories of CD (tree not shown). A 9-node tree (Tree 3 (Figure 2B)) with an acceptable relative cost (0.785) is shown due to its clinical use. This tree was able to correctly classify 111 subjects (34%).

The CART analysis showed BNP to be the strongest discriminating factor in building a clinical+ model (Tree 4). The lowest cost tree was a single node tree using BNP with a cut-off value of 192 pg/mL (AUC 0.71, 37 FN and 42 FP). Increasing the cost for FN, a 4-node tree emerged (Tree 5 (Figure 2C)) that was able to exclude 145 participants (AUC 0.76, 2 FN and 236 FP). Four participants were not able to be classified because of missing values. In the remaining 316 subjects, the lowest cost tree (relative cost = 0.773) was also a single node tree that used the presence of cardiac murmurs and correctly categorised 50 participants (16%) (tree not shown). A 9-node tree (Tree 6 (Figure 2D)) with an acceptable relative cost (0.825) is shown because of its clinical use. This tree was able to correctly classify 160 subjects (51%).

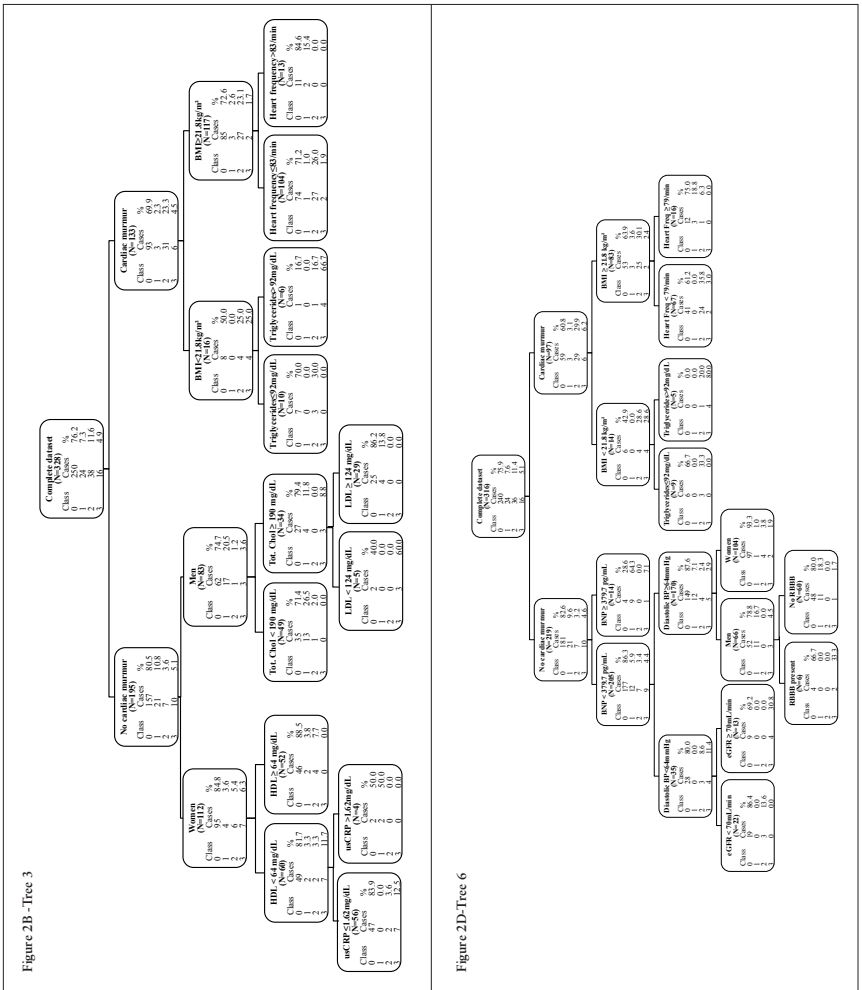

Figure 2. CART trees in subjects without CAF or PM

Table 4. Ranking of variables used in the CART analysis by overall discriminatory power in subjects without CAF or PM.

Tree 1		Tree 2		Tree 3	
Variable	Power	Variable	Power	Variable	Power
Cardiac murmur	100.0	eGFR	100.0	Total cholesterol/HDL	100.0
Reported VHD	96.4	Cystatin C	99.9	BMI	90.5
JVP	19.1	Age	90.3	LDL	74.7
Abnormal apex beat	13.0	Cardiac murmur	52.4	Total cholesterol	73.3
Age	7.6	Reported VHD	47.8	HDL	71.8
Normal heart beats	1.4	Haemoglobin	45.0	Cardiac murmur	71.6
		Triglycerides	44.4	Men	63.5
		Anaemia	33.3	Age	63.4
		Valvular surgery	19.5	Diastolic BP	57.7
		BMI	14.0	Smoker or ex-smoker	53.8
		Orthopnoea	12.5	Triglycerides	51.8
		Alcohol	10.9	eGFR	39.1
		Total cholesterol	10.7	usCRP	32.5
		JVP	9.0	Heart frequency	25.2
		Abnormal apex beat	6.0	Breathing frequency	19.7
		Systolic BP	3.5	Alcohol	18.8
		HDL	1.1	Diuretics	18.4
		Heart frequency	0.94	COPD	16.6
		usCRP	0.82	S3	16.1
		Normal heart beats	0.72	S4	15.4
		Total cholesterol/HDL	0.04	Institutionalised	14.8
				Reported VHD	13.9
				Cystatin C	12.9
				Dyspnoea	10.5
				JVP	7.8

				Calcium blocker	4.9
				Systolic BP	3.1
				Suspicion of ascites	0.99
Tree 4		Tree 5		Tree 6	
Variable	Power	Variable	Power	Variable	Power
BNP	100.0	BNP	100.0	BNP	100.0
NT-proBNP	81.0	NT-proBNP	58.0	Cardiac murmur	99.5
Episode DHF	20.7	Heart frequency ECG	52.3	Age	89.4
S3	12.5	BMI	33.1	Heart frequency ECG	84.2
Heart frequency ECG	9.4	Negative ECG	27.0	BMI	78.5
eGFR	7.8	Triglycerides	24.5	Diastolic BP	77.3
		Total cholesterol	19.8	eGFR	73.2
		Age	15.2	Men	71.2
		eGFR	10.4	Triglycerides	64.7
		Bradycardia ECG	8.8	NT-proBNP	59.6
		usCRP	5.4	Smoker or ex-smoker	53.2
		Diastolic BP	3.6	Cystatin C	51.9
		Cystatin C	1.5	RBBB	45.0
		LDL	0.71	HDL	38.8
		Heart frequency (CE)	0.31	HJR	37.0
		Total cholesterol/HDL	0.14	Heart frequency	35.3
				Total cholesterol/HDL	26.0
				Total cholesterol	25.8
				Reported valvular disease	23.9
				Abnormal apex beat	23.4
				Haemoglobin	22.9
				Diuretics	22.5
				Alcohol	21.0
				Orthopnoea	20.7

				Palpitations	19.2
				S3	19.1
				Dyspnoea	15.8
				usCRP	10.3
				Systolic BP	8.9
				JVP	8.7
				LDL	7.2

CART: classification and regression trees; CAF: chronic atrial fibrillation; PM: pace-maker; VHD: valvular heart disease; HJR: hepatojugular reflux; JVP: jugular venous pressure; eGFR: estimated glomerular filtration rate; BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; usCRP: ultrasensitive C-reactive protein; LDL: low-density lipoprotein; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide; DHF: decompensated heart failure; RBBB: right bundle branch block; ECG: electrocardiogram.

Table 5. Accuracy of different diagnostic algorithms for the presence of severe cardiac dysfunction as determined with the CART analysis.

Model*	Target condition	Prevalence n (%)	AUC	Sensitivity (95% CI)	Specificity (95% CI)	PTP- (95% CI)	PTP+ (95% CI)
No CAF or PM							
Clinical model (Tree 1)	Severe CD	78/457 (17.1)	0.63	51 (40 – 63)	75 (71 – 80)	12 (8.4 – 16)	30 (22 – 39)
Clinical model with low FN (Tree 2)	Severe CD	78/457 (17.1)	0.73	100 (95 – 100)	35 (30 – 40)	0.0 (0.0 – 2.8)	24 (19 – 29)
Clinical model after	LVEF≤50%	24/328 (7.3)	0.87	88 (68 – 97)	76 (70 – 80)	1.3 (0.3 – 3.7)	22 (14 – 32)
algorithm with low FN (Tree 3)	VHD	38/328 (11.6)	0.79	79 (63 – 90)	71 (65 – 76)	3.7 (1.6 – 7.2)	26 (19 – 35)
	Severe DD	16/328 (4.9)	0.92	88 (62 – 98)	83 (78 – 87)	0.8 (0.1 – 2.7)	21 (12 – 33)
Clinical+ model (Tree 4)	Severe CD	78/457 (17.1)	0.71	53 (41 – 64)	89 (85 – 92)	10 (7.1 – 13)	49 (38 – 61)
Clinical+ model with low FN (Tree 5)	Severe CD	78/457 (17.1)	0.76	97 (91 – 100)	38 (33 – 43)	1.4 (0.2 – 4.9)	24 (20 – 30)
Clinical+ model after	LVEF≤50%	23/316 (7.6)	0.91	96 (79 – 100)	77 (72 – 82)	0.4 (0.0 – 2.4)	26 (17 – 36)
algorithm with low FN (Tree 6)	VHD	36/316 (11.4)	0.85	83 (67 – 94)	76 (70 – 81)	2.8 (1.0 – 5.9)	31 (22 – 41)
	Severe DD	16/316 (5.1)	0.86	63 (35 – 85)	95 (92 – 97)	2.0 (0.8 – 4.4)	42 (22 – 63)
CAF or PM							
Clinical model (Tree 7)	Severe CD	28/91 (30.8)	0.95	93 (77 – 99)	94 (85 – 98)	3.3 (0.4 – 11)	87 (69 – 96)
Clinical+ model (Tree 8)	Severe CD	28/91 (30.8)	0.95	93 (77 – 99)	92 (82 – 97)	3.3 (0.41 – 12)	84 (66 – 95)

*, tree with the lowest cost was selected. Only for tree 3 and 6, trees with a higher relative cost were selected because of the clinical interpretation (tree 3: relative cost 0.785 instead of 0.770; tree 6: relative cost 0.825 instead of 0.773).

CART: classification and regression trees; AUC: area under the curve; CI: confidence interval; PTP: post-test probability; CAF: chronic atrial fibrillation; PM: pace-maker; CD: cardiac dysfunction; FN: false negatives; LVEF: left ventricular ejection fraction; VHD: valvular heart disease; DD: diastolic dysfunction.

In participants with CAF or PM, a 7-node tree (Tree 7 (Figure 3A)) emerged from the CART analysis for the clinical model, and a 6-node tree emerged for the clinical+ model (Tree 8 (Figure 2B)). Both trees had a high AUC of 0.95, low PTP- and high PTP+ (Table 5). LDL and total cholesterol appeared to be the strongest discriminating factors in both models, followed by BNP in the clinical+ model (Table 6). The trees for the clinical and clinical+ models were able to correctly classify 85 (93%) and 84 (92%) participants, respectively, according to the presence of severe CD.

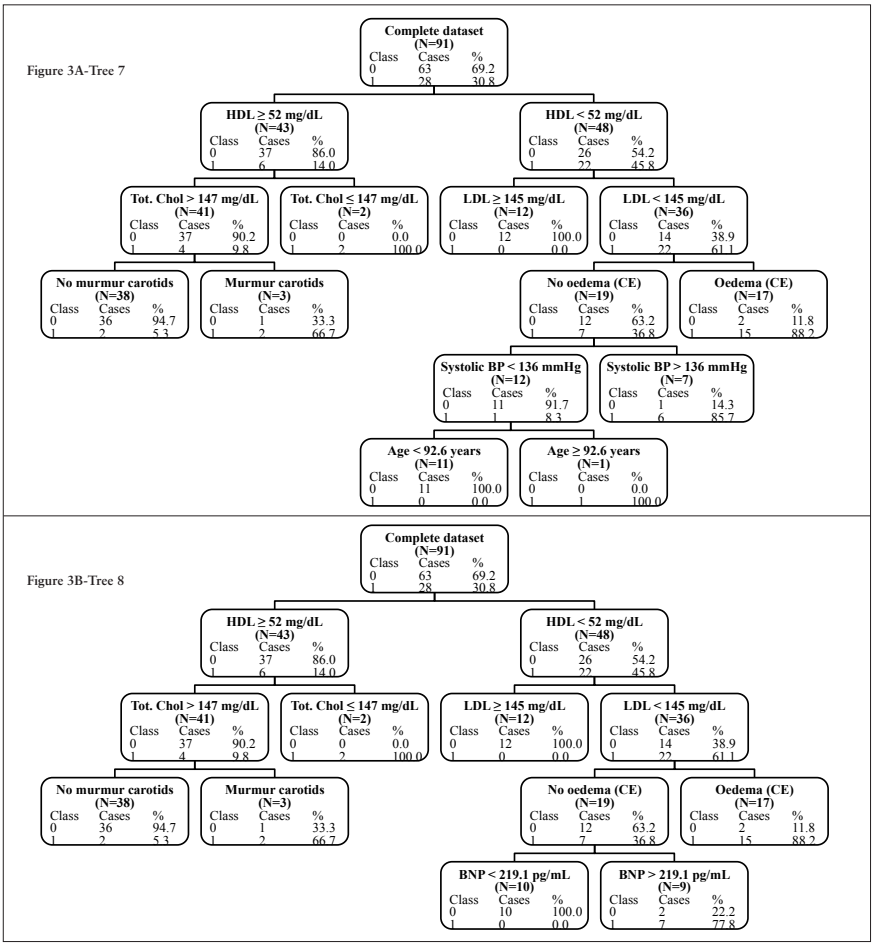

Figure 3. CART trees in subjects with CAF or PM

Table 6. Ranking of variables used in the CART analysis by overall discriminatory power in subjects with CAF or PM.

Tree 7		Tree 8	
Variable	Power	Variable	Power
LDL	100.0	LDL	100.0
Total cholesterol	68.5	Total cholesterol	77.2
HDL	56.1	BNP	71.1
Total cholesterol/HDL	47.0	HDL	63.2
usCRP	42.8	NT-proBNP	60.3
Systolic BP	38.1	BMI	32.7
Age	32.6	Total cholesterol/HDL	31.9
Murmur carotids	24.2	Murmur carotids	27.3
Peripheral oedema (CE)	22.2	usCRP	27.2
Triglycerides	20.8	Systolic BP	26.8
Haemoglobin	20.0	Peripheral oedema (CE)	25.0
Orthopnoea	12.7	Triglycerides	23.4
eGFR	12.0	Alcohol	23.3
JVP	11.8	Heart frequency ECG	22.2
Alcohol	11.2	Age	15.6
HJR	9.9	Orthopnoea	14.3
Peripheral oedema (A)	9.4	Peripheral oedema (A)	10.6
Heart frequency	8.6	Heart frequency	9.7
Cardiomyopathy	7.0	Haemoglobin	9.3
Hepatomegaly	6.3	Hepatomegaly	7.1
Crepitations	5.3	eGFR	6.5
Cystatin C	4.4	Cystatin C	4.9
BMI	4.4	Diuretics	3.8
Breathing frequency	4.2	Diastolic BP	0.44
Diuretics	3.4		
Normal breathing sounds	2.3		
Diastolic BP	0.39		

CART: classification and regression trees; CAF: chronic atrial fibrillation; PM: pace-maker; LDL: low-density lipoprotein; HDL: high-density lipoprotein; usCRP: ultrasensitive C-reactive protein; BP: blood pressure; CE: clinical examination; eGFR: estimated glomerular filtration rate; JVP: jugular venous pressure; HJR: hepatojugular reflux; A: anamnesis; BMI: body mass index; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide; ECG: electrocardiogram.

DISCUSSION

In a large population-based sample of unselected, very elderly patients, many of whom receive medication that can potentially alter the symptoms of clinical heart failure, logistic regression analysis was not able to show an added value of implementing NP or ECG in a case-finding strategy for cardiac dysfunction in daily practice. CART analysis confirmed these results when looking at the reported estimates of the diagnostic accuracy of different strategies. However, 58 subjects (13%) more were correctly classified according to the presence of severe CD with the clinical+ model in subjects without CAF or PM. In participants with CAF or PM, a high C statistic was found in both models. Furthermore, CART analysis yielded a correct classification for more than 90% for both models.

Previous studies investigating the added value of NP and ECG were conducted in selected populations of patients suspected of heart failure[35;36] or stable COPD patients[19]. These studies showed a benefit in including NP in a diagnostic model for heart failure. The C statistic increased from 0.75 to 0.92 with NT-proBNP[36] and from 0.79 to 0.92 after implementing BNP in the model[35]. The ECG contributed less to the estimated accuracy. The reference standard was the diagnosis of heart failure by a panel of experts. This, however, significantly increases the likelihood of an incorporation bias. Although panels were blinded to the value of NP, they had full access to all other relevant data that were included in the analyses.

Aside from risk scores, which were generated based on previous studies[19;36], algorithms for the diagnosis of heart failure that utilise clinical information have also been suggested[37;38]. The NICE guidelines recommend only using NP in patients with a previous MI as a diagnostic characteristic[37]. Mant et al. made a distinction between men and women regarding NP cut-off values[38]. In women, the presence of ankle oedema was further used to specify the NP cut-off value. The present study also tried to determine the place of NP and ECG in a possible diagnostic pathway. CART analysis found BNP to be a good first-line triage test for excluding severe CD and a negative ECG to further rule out the target condition

in those with a BNP < 119 pg/mL and a heart rate frequency > 57 beats/min. Furthermore, in the remaining patients who did not have cardiac murmurs, a high plasma level of BNP > 380 pg/mL was able to identify 43% (9/21) of subjects with systolic dysfunction. This confirms the exclusionary characteristics and cut-off values previously reported[9].

Studies investigating the test performance of NP in selected patients with AF are scarce[39]. In dyspnoeic patients, BNP levels were higher in those with AF, suggesting that a higher diagnostic threshold should be used in subjects with AF for acute congestive heart failure[39]. The current findings are in line with these results but are the first to show that there is no added value of using NP for the case-finding of severe CD in patients with CAF or PM.

One limitation in the current study is that an unselected population of very elderly patients was used, which can potentially decrease its clinical relevance. However, with more than 90% of participants having cardiovascular morbidity, 55% presenting with at least one cardinal symptom of heart failure and 85% taking potentially symptom-reducing medication, this representative population-based sample of very elderly patients can clearly be considered an at-risk population. Moreover, choosing severe CD as a reference standard completely precluded any possible incorporation bias. The clinical relevance of identifying elderly subjects with systolic dysfunction, VHD or severe DD is evidenced by numerous epidemiological studies showing an increased mortality in these patients[5-8]. Because such patients are often excluded from clinical trials[40], one could argue that the management of severe CD in elderly patients with a wide range of comorbidities is hampered by the lack of evidence-based guidelines. The therapeutic management of elderly patients with systolic dysfunction is mainly based on extrapolating results of studies with younger populations, although some have shown the benefit of beta-blockers and ACE-I in the elderly[41;42]. No therapeutic interventions have been proven to improve outcomes in heart failure with preserved EF; therefore, interventions are mainly directed towards monitoring the risk factors of severe DD, such as diabetes, hypertension and atrial

fibrillation[9]. However, above all, establishing diagnostic criteria for severe CD in very elderly patients remains essential, not only to optimise the monitoring of identified cases but also to prevent potential side effects of medication in those being excluded with severe CD.

This study is the first to examine the added value of NP and ECG in a case-finding strategy for severe CD in a large population-based sample of very elderly patients. As all relevant and known clinical data were used, this "intention to diagnose" study accurately reflects the impact of implementing these tests in an unselected, heterogeneous population in routine clinical practice. However, a few limitations should be considered. First, comorbidities may have been underdiagnosed because they were not assessed but instead reported by a general practitioner. Second, although there are multiple advantages to using CART analysis (interactions are automatically taken into account, the possibility of generating trees with more than two diagnostic outcomes, and weights can be attributed to FN and FP, procedures to deal with missing data and indicators of diagnostic accuracy that can be easily calculated from the output), the most important disadvantage remains its variability. Different datasets from the same setting can lead to quite different final trees. However, a reproducibility test of the present analyses was not performed because no external dataset was available and alternative methods that average different trees based on bootstrap samples lose their interpretability[43].

CONCLUSION

In a large population-based sample of unselected very elderly patients, implementing NP or ECG added little value to a case-finding strategy for severe CD in daily practice. In subjects without CAF or PM, a larger number of participants were correctly classified by integrating NP and ECG into the diagnostic process. In participants with CAF or PM, the clinical model showed a very high accuracy, and no added value of NP or ECG was found.

ACKNOWLEDGEMENTS

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GENERAL DISCUSSION

CARDIAC DYSFUNCTION IN THE VERY ELDERLY: THE RELEVANCE OF CASE-FINDING AND THE PLACE OF NATRIURETIC PEPTIDES

1.

THE GREY EPIDEMIC REVISITED

1.1 Leiden 85-plus and BELFRAIL: partnership in ageing research

In this thesis, data from two large population-based cohorts were analysed. The demographic characteristics of the participants, from both the Leiden 85-plus Study and the BELFRAIL (BF_{C80+}) study, were representative of the general Dutch and Belgian populations of the oldest old, respectively[1;2].

In Leiden all the inhabitants born between September 1, 1912, and September 1, 1914, were invited to participate shortly after their 85th birthday without exclusion on grounds of health, cognitive function or living situation. A response rate of 87% was reached. The proportion of women was 66%, more than half of the participants (58%) were widowed, and 18% of all participants were institutionalized[3]. At age 90, women represented 72% of the population under study and 38% of all study subjects in this group were institutionalized[4].

Subjects from the BF_{C80+} study were representative in gender and age of the very elderly living in Belgium[5]. The study participants were included by their general practitioner (GP), using two different sampling methods[2]. The participating GP centres included subjects aged 80 and older except for patients with a known severe dementia, patients in palliative care and patients needing urgent medical care. Women represented 63% of the study population, the mean age was 84.7 ± 3.7 years, 50% of the participants were widowed and the majority of study participants lived at home (89.9%)[2].

In addition to the methodology of the Leiden 85-plus Study, all participants of the BF_{C80+} study also underwent an intensive examination by their GP, who performed a standardised anamnesis and clinical examination. Furthermore, all participants had a series of technical investigations at home, such as echocardiography, spirometry and bio-electrical impedance measurement[2]. In Leiden

only a convenience sample of well-functioning nonagenarians underwent an echocardiography at the research centre[6].

1.2 Ageing = adaptation?

Both cohorts showed a high level of morbidity. In Leiden, a high burden of cardiovascular (65.7%) and non-cardiovascular (63.9%) morbidity was found at age 90[4]. In the BF_{C80+} population only 1% was free of any pathology; non-cardiovascular morbidity was reported in 81.2% and cardiovascular morbidity in 92.7%[2]. Moreover, there was a high prevalence of multimorbidity, with half of the BF_{C80+} population presenting with two or more non-cardiovascular morbidities and 30% suffering from more than three cardiovascular morbidities[2].

In both the Leiden 85-plus Study and the BF_{C80+} study, the physical and the psychocognitive functioning of the study participants were extensively assessed. Elderly patients present as a very heterogeneous population, with the active independent community-dwelling senior at the one end of the spectrum and the bedridden geriatric patient at the other. When applying cut-off values for poor physical and cognitive functioning on six different indicators of functioning, the BF_{C80+} study showed that 61% of all participants scored poorly on at least one parameter tested[7]. Thus, 39% had an acceptable or better score on all six parameters, in comparison to other study subjects of the same gender.

In earlier research the meaning of successful ageing was explored in the Leiden 85-plus Study[3]. Successful ageing from a public health perspective was defined as a state of being, and the classification of participants was based on scores for physical, social, and psychocognitive functioning and on feelings of well-being. Although 45% had optimal scores for well-being, only 13% had optimal scores for overall functioning. In total, only 10% of the participants could be classified as successfully aged. On the other hand, qualitative indepth interviews showed that most elderly people viewed success as a process of adaptation rather than a state

of being, so that many more probably could be considered to be successfully aged[3].

The hypothesis of adaptation could also be an explanation of successful ageing on the physiological level. In many ways very elderly could be seen as survivors. This is perhaps not just a story of genetics, but probably also a story of adaptation with a series of subtle homeostatic processes in the ageing body that causes a delicate equilibrium in many elderly.

1.3 From a disease-oriented approach towards horizontal comprehensive care

With regard to the previous section, frailty is considered as a multidimensional geriatric syndrome with biological, physiological and psychosocial components, and as a state of increasing vulnerability and loss of adaptability to stress[8;9]. Furthermore, frailty has been described as a condition or syndrome which results from a multi-system reduction in reserve capacity to the extent that a number of physiological systems are close to, or past, the threshold of symptomatic clinical failure[10]. It has been clearly shown that there is an overlap between chronic diseases, frailty and disability[11]. A better understanding of the dynamic process leading from health to frailty and eventually disability is of primary interest if preventive interventions are planned.

As an example, within the Leiden 85-plus Study it was found that general impairments, such as cognitive impairment, depressive symptoms or dizziness upon rising, contributed more to walking disability than do common chronic diseases[12]. Furthermore, the diagnosed diseases did not explain the impairments that led to walking disability. The researchers concluded that clinicians should focus not merely on common chronic diseases but particularly on general impairments as targets for diagnostic analysis and treatment for walking disability[12].

In line with these findings, this thesis clearly showed that the very elderly represent a very heterogeneous group of subjects with

a high prevalence of comorbidities, among whom poor functioning might be triggered by multiple causes. However, apart from aortic stenosis, cardiac dysfunction did not show a strong relationship with poor functioning[7]. This may indicate that the ageing body is able to adapt and find a new homeostasis despite the heavy burden of comorbid conditions. On the other hand, this could also mean that frailty in the very elderly exists as a separate entity, independent of cardiac dysfunction or comorbidity. But above all, this should encourage clinicians not to be blinded by a disease-oriented approach, but rather to focus on functional repercussions of cardiac dysfunction and comorbidities in the very elderly[7].

In this regard, a recent article in the Lancet described the need to switch from a vertical, disease-oriented approach to more horizontal, integrated and comprehensive care to tackle the heavy burden of chronic diseases[13]. In this respect, integrated primary care is essential as chronic conditions are influenced by patients' perceptions and behavior[13]. Therefore, effective management of chronic diseases will require a paradigm shift from problem-oriented to goal-oriented care[14] that will put people and their values at the centre of the process, rather than specific diseases[13].

2.

THE PREVALENCE OF CARDIAC DYSFUNCTION AND RELEVANCE OF IDENTIFYING THIS CONDITION IN THE ELDERLY

2.1 Chronic heart failure in the elderly revisited

As already shown in the introduction, the question arises of whether the current definition of chronic heart failure still holds in the case of the very elderly. In the light of a shift towards a more horizontal and comprehensive care, especially in complex geriatric

patients with a high burden of multimorbidity and polypharmacy, perhaps the existing concept of heart failure in the elderly should be revisited.

Up to now, heart failure has been defined as the presence of symptoms and signs typical of heart failure along with the objective evidence of a structural or functional abnormality of the heart at rest[15]. However, as discussed before, the specificity of typical symptoms and signs of heart failure decreases drastically in the elderly[16]. Moreover, the prevalence of structural or functional abnormalities of the heart increases with age[17]. In view of evidence emerging from this thesis, chronic heart failure should be evaluated using a multi-system approach, as the manifestation of severe cardiac dysfunction, taking full account of the interaction with concomitant, chronic conditions. Furthermore, the use of the NYHA (New York Heart Association) classification to monitor the severity of heart failure and functional limitations due to heart failure, is probably too limited in complex geriatric patients, as it mainly focusses on the presence of "typical" symptoms when making physical efforts. Therefore, the evaluation of functional impairments due to heart failure should be reconsidered in the elderly, putting the patients' perceptions and values at the centre of this assessment. As an alternative for the NYHA classification the Short Physical Performance Battery (SPPB) could be considered. These performance-based tests of physical function include timed measures of walking speed, rising from a chair, putting on and taking off a cardigan, and maintaining balance in a tandem stand[2]. The SPPB has been shown to be a reliable and valid measure of physical functioning and demonstrated to be an indicator of quality of life and a predictor of mortality[18].

2.2 The clinical relevance of severe cardiac dysfunction

In this thesis the presence of severe cardiac dysfunction was put forward as the target condition. The definition of this condition emerged from a discussion of existing guidelines and a

consensus procedure launched by the research team[7]. Severe cardiac dysfunction was defined in the BF_{C80+} study as the presence of systolic dysfunction, clinically relevant valvular heart disease and severe diastolic dysfunction and was found to be highly prevalent (19%)[7]. A trend towards high prevalences of valvular heart disease and isolated diastolic dysfunction and low prevalences of systolic dysfunction in the elderly had already been reported by previous studies[17,19-21].

However, as the applicability of current echocardiographic cut-off values to subjects aged 80 and over may be debatable, seeing that the thresholds for normal values are usually derived from younger subpopulations, the clinical relevance of this target condition may be argued. The methodology of the BF_{C80+} study, however, offers the opportunity to explore the significance of this choice from a cross-sectional and longitudinal perspective[2]. The association of cardiac dysfunction with functional, physical and cognitive, impairment, and the development of disability and dependency or risk of mortality could be investigated. This research is important in order to identify potential, modifiable factors that might be a target for interventions that could maintain normal functioning with ageing and thus lower mortality.

Previous research showed a relationship between cardiac dysfunction and limited physical capacity, depression and cognitive impairment[22-26]. This thesis accordingly identified severe cardiac dysfunction as an independent identifier of poor performance, low LAPAQ score and a high GDS-15 score. Mainly valvular heart disease, and more specifically aortic stenosis, was retained as the primary identifier of poor functioning. Classic indicators of systolic dysfunction and diastolic dysfunction, however, were not able to identify participants with poor functioning.

Numerous epidemiological studies evidenced the clinical relevance of identifying subjects with systolic dysfunction, valvular heart disease or severe diastolic dysfunction and demonstrated increased mortality in these patients, and also in the elderly[21;27-29]. Figure 1 shows a preliminary Kaplan-Meier curve for overall mortality after a median follow-up time of 16.1 months [IQR

14.4 – 17.5] in the BF_{C80+} study. By that time, 52 participants had died (9.2%) and no drop-outs for the mortality analyses had been reported. This clearly demonstrates the increased risk of mortality when severe cardiac dysfunction is present in the elderly. Cox regression analyses confirmed, after correction for age, gender and renal function, severe cardiac dysfunction as an independent risk factor for mortality with a hazard ratio (HR) of 2.3 (95% CI 1.3 – 4.2). When the analyses were performed with separated categories of severe cardiac dysfunction, mainly valvular heart disease emerged as an independent risk factor (HR 2.6 95% CI 1.3 – 5.4). An estimated glomerular filtration rate <45mL/min, based on Cystatin C, had a HR of 2.9 (95% CI 1.6 – 5.2).

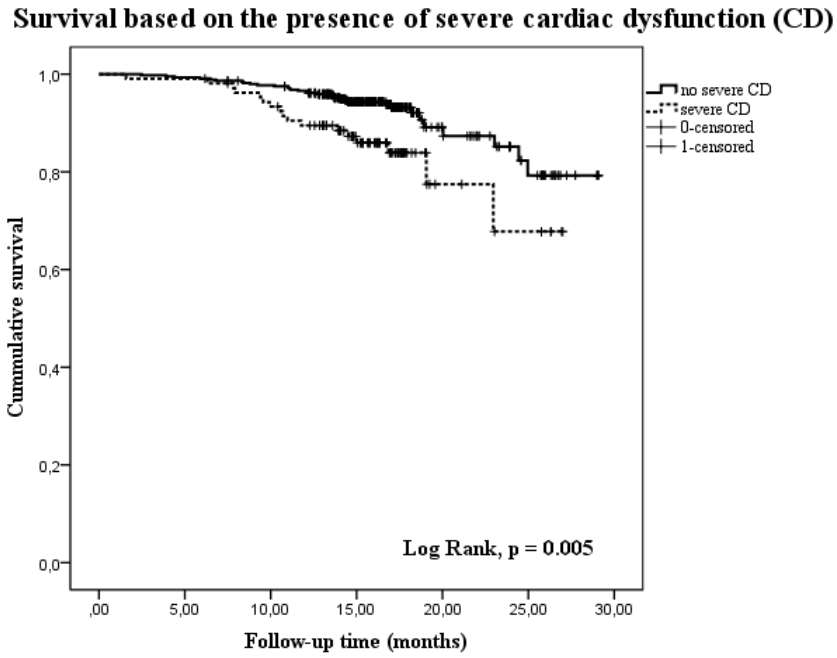

Figure 1. Survival based on the presence of severe cardiac dysfunction

Future analyses of the follow-up data of the BF_{C80+} study will be directed to identify those potential, modifiable, functional and structural echocardiographic abnormalities that contribute most to the development of disability and dependency and the risk of mortality. However, since the very elderly are often banned from clinical trials[30], one could argue that the management of severe cardiac dysfunction in elderly patients is hampered by the lack of evidence-based guidelines. Although some studies showed the benefit of beta-blockers and ACE-I in the elderly[31;32], the therapeutic management of systolic dysfunction is mainly based on extrapolating results of studies elaborated in younger populations. On the other hand, surgical intervention for aortic stenosis in the elderly showed some advantage[33]. No therapeutic interventions, however, have yet been proven to improve outcome in heart failure with preserved ejection fraction, therefore interventions are mainly directed towards monitoring risk factors of severe diastolic dysfunction like diabetes, hypertension and atrial fibrillation[15]. But above all, establishing a diagnosis of severe cardiac dysfunction in the very elderly remains essential, not only to optimise the monitoring of identified cases, but also to prevent potential side effects of medication in those without severe cardiac dysfunction.

3.

THE RELEVANCE OF NATRIURETIC PEPTIDE TESTING IN THE ELDERLY IN CLINICAL PRACTICE

3. Natriuretic peptides: still a disease specific marker in old age

Once a clinically relevant target condition has been determined, the need to identify patients that are affected is generated. However, as previously shown, the diagnosis of cardiac dysfunction, especially in old age, is not straightforward, mainly due to the heavy burden of comorbidities. This fact calls for a

simple, easily accessible test, such as natriuretic peptides, to diagnose severe cardiac dysfunction. Furthermore, the hypothesis that the interpretation of high natriuretic peptide levels in the very elderly could possibly be blurred by the presence of multimorbidity, was not confirmed by the results shown in Chapter 1 of this thesis. On the contrary, NT-proBNP remained a disease specific marker of cardiac illness in nonagenarians[4]. Moreover, the level of NT-proBNP increased significantly with the number of cardiac diagnoses, possibly indicating the severity of cardiac illness[4].

The next step was to evaluate the diagnostic accuracy of natriuretic peptides for cardiac dysfunction or chronic heart failure in community-dwelling elderly people. However, a systematic review found limited evidence of these tests being implemented in daily practice (Chapter 2). The five studies that were retrieved mainly confirmed earlier observations in other (younger) populations that natriuretic peptide levels can best be used to exclude cardiac dysfunction[34]. Several issues about the interpretation of these tests remained unanswered.

3.2 Natriuretic peptides: a marker of pancardiac disease in old age

Most studies only focussed on systolic dysfunction, expressed as a lowered ejection fraction (EF)[35-37], and ignored prognostically significant diastolic dysfunction and valvular heart disease[21;27]. Moreover, as shown, the prevalence of systolic dysfunction decreases over the age of 80 in contrast to the prevalence of valvular heart disease and diastolic dysfunction[17,19-21]. Furthermore, initial analyses of the BF_{C80+} data demonstrated that a low ejection fraction possibly contributes less to functional impairment and overall mortality than, for example, aortic stenosis. Of course, these are preliminary conclusions and need to be confirmed with longer follow-up, but they possibly indicate that other types of cardiac dysfunction are more relevant to be identified in old age, with a view to possible future treatment.

In this thesis we further explored the hypothesis that

natriuretic peptides are a marker of pancardiac disease[38]. In a convenience sample of 80 well-functioning nonagenarians of the Leiden 85-plus Study, NT-proBNP was found to be not just an indicator of increased cardiac pressure but to be related to a wide variety of functional and structural echocardiographic abnormalities (Chapter 3)[6]. The BF_{C80+} study confirmed that natriuretic peptide levels are associated with structural echocardiographic abnormalities, such as left atrial and left ventricular (LV) enlargement, independent of aberrant cardiac function (Chapter 6). Furthermore, echocardiographic indicators of systolic dysfunction (not LVEF), diastolic dysfunction and valvular heart disease were independently associated with natriuretic peptide levels.

3.3 The impact of confounding on the test performance

Multiple factors are known to influence circulating levels of natriuretic peptides, especially in the elderly. The prevalence of possible influencing factors, such as renal dysfunction and diabetes, increases with age[35]. Several authors have argued that in daily practice, natriuretic peptide cut-off values should be adjusted according to confounders, such as age, gender, BMI or renal function[35;39-41]. Others have advised using multivariable diagnostic algorithms for daily practice, using natriuretic peptide levels (without cut-off points), and including age, gender or renal function to account for the influence of these items on natriuretic peptide levels[42].

Therefore, the impact of confounders on the test performance of natriuretic peptides for severe cardiac dysfunction was further checked in the BF_{C80+} study. In chapter 6 it was shown that adjustment for identified confounders did not improve the diagnostic accuracy of natriuretic peptides for severe cardiac dysfunction, except in subjects with chronic atrial fibrillation (CAF) or pacemaker (PM). By contrast, stratifying by the individual confounders showed that different cut-off values could be used to optimise the test characteristics of BNP and NT-proBNP, possibly

due to different prevalences in the various strata.

3.4 Gender differences in the distribution of natriuretic peptide levels

Redfield et al. found BNP levels to be higher in women than in men in a subgroup of subjects without known cardiovascular disease or detectable structural heart disease (age range 44-83years)[37]. These associations were not explained by age- or gender-related changes in blood pressure, renal function, or cardiac structure. The association of female gender and BNP appeared to be in part related to oestrogen status, as BNP levels were higher in women using hormone replacement therapy (HRT)[37]. However, in this large population-based study, the proportion of very elderly was low: in the healthy subgroup the 75-83years segment was represented by only 18 women and 2 men. Furthermore, the discriminatory values, derived by ROC analysis, to detect a LVEF≤40% in subjects aged 75 and older were slightly higher in men than women[37].

In the entire Leiden 85-plus cohort NT-proBNP levels were higher for men than for women at age 90 (Mann–Whitney, P = 0.019), also after adjustment for weight, height, eGFR, hemoglobin, cardiovascular medication and presence of cardiovascular morbidity (p = 0.003)[4]. However, in the convenience sample of 80 subjects that also underwent an echocardiography, NT-proBNP levels did not differ between men and women (Mann–Whitney, P = 0.14). Furthermore, gender was no independent predictor of NT-proBNP in the linear regression analysis (P = 0.88)[6]. Therefore, no gender-specific cut-off values were used.

In the BELFRAIL cohort no gender difference was seen in the distribution of BNP and NT-proBNP levels (Mann-Whitney, P = 0.95 and P = 0.61, respectively). However, in Chapter 6 multivariable regression analysis showed gender to be an independent correlate of BNP and NT-proBNP levels. These analyses showed BNP and NT-proBNP to be higher in women (negative correlation for male gender). The ideal cut-off values (highest sum of sensitivity and specificity), derived by ROC analysis, showed a

higher discriminatory value for BNP in women and a higher cut-off value in men for NT-proBNP for the diagnosis of severe cardiac dysfunction.

3.5 The measurement of natriuretic peptides in daily practice: an added value?

Most previous studies calculated the diagnostic characteristics of a single natriuretic peptide test, as if the process of diagnosis is a univariable activity and previous clinical knowledge does not play a role[43]. Studies that estimate the added value of natriuretic peptides to data from the history taking and clinical examination that represent routine clinical practice, still remain scarce. Previous studies investigating the added value of natriuretic peptides and ECG were conducted in selected populations of patients suspected of heart failure[44;45] or stable COPD patients[46]. These studies showed a benefit in including natriuretic peptides in a diagnostic model for heart failure. Aside from risk scores, which were generated based on previous studies[45;46], algorithms for the diagnosis of heart failure that utilise clinical information and integrate natriuretic peptides have also been suggested[47;48].

In this thesis, an "intention to diagnose"[49] analysis, integrating all relevant and known clinical data, was performed within the BF_{C80+} cohort to investigate the possible diagnostic gain of implementing natriuretic peptides and ECG in a case-finding strategy for cardiac dysfunction in an unselected population of subjects aged 80 and older (Chapter 7). Logistic regression analysis showed that adding natriuretic peptides or ECG to a model with all relevant clinical data only marginally increased the C statistic. Furthermore, the C statistic of the clinical model was acceptably high in subjects without CAF or PM and very high in subjects with CAF or PM. CART analysis showed BNP could be used as a triage test to "rule out" severe cardiac dysfunction, and as a "rule in" test to further differentiate between different types of cardiac dysfunction in subjects without CAF or PM. Moreover, previously

suggested cut-off values were confirmed[15]. Although trees based on clinical data showed almost equivalent accuracies, a higher number of subjects were correctly classified by integrating natriuretic peptides and ECG into the diagnostic process. With more than 90% of subjects accurately classified without the use of natriuretic peptides, CART analysis showed that adding natriuretic peptides to the clinical model in subjects with CAF or PM had absolutely no effect.

3.6 BNP or NT-proBNP?

The biological variability of NT-proBNP and BNP in stable heart failure patients was investigated by O'Hanlon et al[50]. They concluded there is considerable intra-individual variability in these peptides. Changes of approximately 50% and 66% for NT-proBNP and BNP from week to week are needed to indicate an altered clinical status and caution should be exercised in interpreting serial changes in peptide levels when monitoring patient responses to treatment or clinical status[50].

It has been shown that NT-proBNP is more stable than BNP[51], and may have lower intra-individual and inter-individual variation[52], which may make this test more suitable for a general practice setting. Costello-Boerrigter et al. have concluded that NT-proBNP has a test performance in a community population that is superior or equivalent to that of BNP for an LVEF≤40%[53]. In the BF_{C80+} study the diagnostic accuracy of BNP and NT-proBNP was compared, but did not show any difference (Chapter 6). However, when both were added as possible variables to build a CART tree, BNP had the highest discriminatory power and was used as a splitter (Chapter 7). Additionally, no added value was found in combining BNP and NT-proBNP, nor in using the ratio NT-proBNP/BNP (Chapter 6).

3.7 The measurement of natriuretic peptides: impact on patient outcome?

A single natriuretic peptide measurement has shown to have excellent prognostic characteristics[54]. More specifically, the association between high natriuretic peptide levels and increased total and cardiovascular mortality has been shown in the elderly from the general population[55,56]. Moreover, this thesis showed a single NT-proBNP measurement at age 90 could possibly be used as a predictor of overall and cause-specific mortality independent from the presence of known cardiac diagnoses[4]. These findings indicated elevated levels of NT-proBNP possibly reflect unknown cardiac morbidity or imminent heart failure in the oldest old without known cardiac morbidity.

Although natriuretic peptide measurement helps to improve patient management and reduces the total treatment cost in patients with acute dyspnoea, the impact on patient outcome of a case-finding strategy in clinical practice for severe cardiac dysfunction that includes natriuretic peptides has not yet been studied. A previous, randomized, controlled trial demonstrated that NT-proBNP measurement significantly improved the diagnostic accuracy of heart failure by general practitioners over and above customary clinical review[57]. In this thesis CART analysis showed that an additional 58 subjects (13%) were correctly classified using natriuretic peptides and ECG in subjects without CAF or PM (Chapter 7). However, whether the introduction of natriuretic peptides in daily practice will influence patient outcome depends on a possible treatment change that the patient could benefit from. But as discussed before, a great deal of further difficult work remains to be done in this field.

In line with this, a cost-effectiveness analysis has not been performed yet for the treatment of the elderly. A cost-effectiveness analysis assesses whether the cost of using a given test is acceptable to society, related to its output parameters[58]. Hedberg et al. calculated the basic screening costs for systolic dysfunction with or without natriuretic peptides and ECG in patients of 75 years

old without taking into account relevant outcome characteristics[35]. Heidenreich et al., on the other hand, did include the lifetime cost of care and outcome in their cost-effectiveness analysis and calculated the cost per quality-adjusted life years (QALY)[59]. However, their analysis only applied to men and women of 60 years old.

4.

CONCLUSION

To conclude, this thesis found a high prevalence of severe cardiac dysfunction in an unselected population of the very elderly. The clinical relevance of choosing this condition as the reference standard for this thesis was apparent from the correlation with poor functioning and preliminary follow-up analyses for mortality. Furthermore, the evidence of the progression from asymptomatic cardiac dysfunction to symptomatic heart failure and eventually death, also in the elderly, is growing. The management of severe cardiac dysfunction in elderly patients, however, is still hampered by the low number of intervention trials, since the very elderly are often banned from clinical trials.

Despite the high burden of multimorbidity, natriuretic peptides remain disease specific markers of cardiac illness in the oldest old. These peptides are not just related to an increased intracardiac volume or pressure, but are able to identify multiple structural and functional echocardiographic abnormalities, and thus could be used as markers of pancardiac disease. Many confounders of natriuretic peptides were identified, but they had little impact on the diagnostic accuracy of these peptides for severe cardiac dysfunction, although stratifying by the individual confounders could optimize their test characteristics. Regression analysis and CART analysis showed that information from the medical history, anamnesis and clinical examination had a high diagnostic accuracy for the identification of subjects with severe cardiac dysfunction, especially in those with CAF or PM. In subjects without CAF or PM

a substantial larger number of participants was correctly classified when natriuretic peptides were integrated into the diagnostic process. Natriuretic peptides were found to be good triage tests with high negative predictive values, but also to be "rule-in" tests to further differentiate between different types of cardiac dysfunction. Furthermore, a single measurement of natriuretic peptides is able to predict cause-specific mortality in the oldest old. The impact on patient outcome and cost-effectiveness of a community screening programme for severe cardiac dysfunction in the oldest old including natriuretic peptides remains to be determined.

5.

THE BELFRAIL STUDY: FUTURE PROSPECTS

The general aim of the BF_{C80+} cohort study is to acquire a better understanding of the epidemiology and pathophysiology of chronic diseases in the very elderly and to study the dynamic interaction between health, frailty and disability in a multi-system approach. The BF_{C80+} study included 567 participants who all underwent a thorough multi-dimension investigation in order to take a detailed "medical photograph". Of these, 450 subjects (79%) were fully re-examined after 18 months. Future research within this cohort study will focus on the interaction between cardiac dysfunction and other comorbid conditions, such as renal insufficiency, chronic inflammation and lung disease. In addition, the contribution of cardiac dysfunction to the development of dependency and disability and cardiac dysfunction as a cause of mortality within a horizontal, comprehensive approach, will be further explored. The latter research area will aim mainly to identify possible modifiable factors as a target for future treatment and the accuracy of natriuretic peptides to identify these factors will be further examined.

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SUMMARY

The **introduction** provides the rationale and aim for this thesis. First, the problem of a forthcoming "grey epidemic" is outlined. In coming decades, this will lead to a heavy burden of chronic diseases and high prevalence of multimorbidity in elderly of our western society. Attention is then focussed on the problem of heart failure in this ageing society. To date, little reliable data on the prevalence and incidence of heart failure are available for Belgium. Furthermore, there is no gold standard for the diagnosis of heart failure. Moreover, the diagnosis of chronic heart failure is often challenging, particularly in the elderly. This emphasises the need for a simple test to identify patients at risk. Natriuretic peptides have been suggested as the 'ultimate' biochemical test for heart failure. However, whether this is also true in complex geriatric subjects remains to discover. Therefore, this thesis sets out to unravel unsolved issues about the implementation of natriuretic peptides in routine clinical practice for the diagnosis of severe cardiac dysfunction in the oldest old.

In **Chapter 1** we investigated whether natriuretic peptides remained a specific marker of cardiac illness and were able to predict all cause and cause specific mortality in a population-based cohort of nonagenarians from the Leiden 85-plus Study. The median follow-up for the 274 90-year-old participants was 42.3 months. We found levels of NT-proBNP increased significantly with increasing numbers of cardiac diagnoses. High NT-proBNP levels were associated with overall mortality, cardiovascular mortality and non-cardiovascular mortality, both in participants with and without specific cardiac diagnoses. The latter meaning in participants without known cardiac morbidity elevated levels of NT-proBNP possibly reflect unknown cardiac morbidity or imminent heart failure. We concluded NT-proBNP remains a disease specific marker of cardiac illness in nonagenarians and can possibly be used as a predictor of mortality independent from the presence of known cardiac diagnoses.

Chapter 2 presents a systematic review to evaluate the diagnostic accuracy of plasma natriuretic peptide measurement in elderly patients from the general population. Electronic searches of

MEDLINE and EMBASE were performed. The quality of the selected studies was assessed with the modified QUADAS tool and the data extracted by two independent reviewers. Five studies with moderate quality were included. The extracted data could not be pooled. To conclude, limited evidence was found supporting the measurement of natriuretic peptides for diagnosis of cardiac dysfunction or heart failure in the elderly of 75 years and over in the general population. Furthermore, important questions about the implementation of plasma natriuretic peptide measurement in daily practice remain unresolved.

Chapter 3 studies the relation between NT-proBNP and cardiac abnormalities and evaluates the use of NT-proBNP to exclude structural and functional cardiac abnormalities in a community-based sample of "well-functioning" nonagenarians. Therefore, a diagnostic cross-sectional study embedded within the Leiden 85-plus Study was performed in a convenience sample of 80 nonagenarians. Levels of NT-proBNP were related to a wide variety of echocardiographic abnormalities. A pre-specified cut-off level showed high negative predictive values (NPV) for left ventricular systolic dysfunction, left atrial enlargement, severe valvular heart disease and pulmonary hypertension. The test performance of NT-proBNP to exclude any echocardiographic abnormality showed a moderately high NPV. To conclude, NT-proBNP could be used to exclude echocardiographic abnormalities in well-functioning nonagenarians and might be used to indicate who needs to be referred for further cardiovascular examination.

Chapter 4 describes the methodology of the BELFRAIL cohort study (BF_{C80+}). The BF_{C80+} study is a prospective, observational, population-based cohort study of 567 subjects aged 80 years and older in three well-circumscribed areas of Belgium. The general aim of the BF_{C80+} study is to examine the dynamic interaction between health, frailty and disability in a multi-system approach focusing on cardiac dysfunction and chronic heart failure, lung function, sarcopenia, renal insufficiency and immunosenescence. Only three

exclusion criteria were used: severe dementia, in palliative care and medical emergency. Two sampling methods for the recruitment of patients were used. Every study participant was invited to undergo four study visits. The general practitioner recorded background variables and medical history and performed a detailed anamnesis and clinical examination. The clinical research assistant performed an extensive examination including performance testing, questionnaires and technical examinations. Echocardiography was performed at home by a cardiologist. A blood sample was collected in the morning. Follow-up reporting of hard outcome measures including mortality, hospitalization and morbidity was organized. A second data collection is planned after 18 months. The wide variety of dimensions investigated in the BF_{C80+} will enable us not only to investigate in depth the relationship between the different physiological systems but also to initiate new research questions based on this unique database of community-dwelling elderly.

In **Chapter 5** we sought to describe the prevalence of cardiac dysfunction in the very elderly and to investigate the correlation between echocardiographic abnormalities and indicators of poor functioning. This study was a cross-sectional analysis within the BF_{C80+} study. Severe cardiac dysfunction was found to be very prevalent and was defined as systolic dysfunction, valvular heart disease or isolated severe diastolic dysfunction. Severe cardiac dysfunction, and more specifically aortic stenosis, showed to be an independent identifier of poor performance, a low LAPAQ (LASA Physical Activity Questionnaire) score and a high GDS-15 (Geriatric Depression Scale) score. Classic indicators of systolic and diastolic dysfunction, however, were not able to identify participants with poor functioning. This study shows the very elderly represent a very heterogeneous group of subjects with a high prevalence of comorbidities, among whom poor functioning might be triggered by multiple causes. We concluded these findings should encourage clinicians not to be blinded by a disease-oriented approach but rather to focus on functional repercussions of cardiac dysfunction and comorbidities in the very elderly.

In **Chapter 6** we further investigated the hypothesis that natriuretic peptides could be used to identify 'pancardiac' damage. Furthermore, the impact of confounders on the association between natriuretic peptide levels and cardiac dysfunction was explored. This study was a diagnostic cross-sectional study embedded within the BF_{C80+} study. Circulating levels of natriuretic peptides were independently related to several functional and structural echocardiographic parameters, such as aortic stenosis, left atrial volume, left ventricular diameter, E/A, E' and deceleration time. Adjusting for identified confounders did not improve the diagnostic accuracy of the natriuretic peptides for severe cardiac dysfunction, except in subjects with chronic atrial fibrillation (CAF) or pacemaker (PM). However, stratifying for individual confounders showed that different cut-off values could be used to optimise the diagnostic characteristics of natriuretic peptides.

In **Chapter 7** a cross-sectional, "intention to diagnose", analysis within the BF_{C80+} study was conducted to determine the added diagnostic value of natriuretic peptides and electrocardiograms beyond previous medical history, anamnesis, physical examination and routine laboratory tests for patients with severe cardiac dysfunction. Two analytical tools were used: logistic regression analysis and Classification and Regression Trees (CART) analysis. In patients without CAF or PM, there was only little added value in implementing natriuretic peptides or electrocardiograms for diagnosing severe cardiac dysfunction in daily practice. However, a higher number of participants were correctly classified by integrating natriuretic peptides and electrocardiograms in the diagnostic process. In participants with CAF or PM, the clinical model showed very high accuracy and no added value of natriuretic peptides was found.

In the **general discussion** the main findings that sorted from this thesis are combined and interpreted. First, the framework in which context these results should be interpreted is discussed. The forthcoming grey epidemic and therefore booming of multimorbidity in an

ageing society, necessitates a paradigm shift from a disease-oriented approach to more horizontal, comprehensive care. In this regard, the target condition of this thesis was studied within a multi-dimensional approach. The discussion further focusses on the relevance of identifying severe cardiac dysfunction and the use of natriuretic peptides to reach this goal. Furthermore, the implementation of natriuretic peptides in routine clinical practice for the case-finding of severe cardiac dysfunction is discussed. Finally, future research topics within the BF_{C80+} study are described.

RESUMÉ

L'**introduction** présente l'analyse et les objectifs de cette thèse. En premier lieu, nous abordons le problème de la surpopulation de personnes âgées à venir. Au cours des prochaines décennies, celle-ci provoquera un nombre considérable de maladies chroniques et une forte prévalence de la multimorbidité chez les personnes âgées dans nos sociétés occidentales. Nous nous attarderons ensuite sur la problématique de l'insuffisance cardiaque dans une société vieillissante. Actuellement, nous ne possédons que très peu de données sur la prévalence et l'incidence de l'insuffisance cardiaque en Belgique. Par ailleurs, il n'existe aucune règle établie pour diagnostiquer l'insuffisance cardiaque. Enfin, le diagnostic de l'insuffisance cardiaque chronique se révèle bien souvent compliqué, particulièrement chez les personnes âgées. Cela souligne la nécessité d'un test simple destiné à identifier les patients à risque. D'aucuns considèrent que les peptides natriurétiques constituent le test biochimique «ultime» pour déceler l'insuffisance cardiaque. Il reste cependant à découvrir si cela vaut également pour les patients gériatriques complexes. Voilà pourquoi cette thèse a pour ambition d'apporter quelques éléments de réponse à des questions en suspens au sujet de l'utilisation de peptides natriurétiques dans la pratique clinique courante pour le diagnostic de la dysfonction cardiaque sévère chez les plus âgés.

Dans le **Chapitre 1**, nous avons cherché à savoir si les peptides natriurétiques constituaient des marqueurs spécifiques de maladie cardiaque. Ce faisant, nous avons pu prédire la mortalité globale et spécifique d'une cohorte de nonagénaires de l'étude Leiden 85-plus. Le suivi moyen pour les 274 nonagénaires s'est élevé à 42,3 mois. Nous avons remarqué une hausse considérable des taux de NT-proBNP à mesure de l'augmentation des diagnostics cardiaques. Des taux élevés de NT-proBNP ont été associés à la mortalité globale, cardio-vasculaire et non-cardio-vasculaire, chez les participants souffrant de maladies cardiaques spécifiques ou non. Cela implique pour les patients sans affection cardiaque connue que le taux élevé de NT-proBNP traduit potentiellement une affection cardiaque

insoupçonnée ou une insuffisance cardiaque imminente. Nous avons donc conclu que le NT-proBNP demeure un marqueur spécifique de maladie cardiaque chez les nonagénaires et qu'il peut être employé en guise de variable prédictive de mortalité, indépendamment du diagnostic avéré d'une maladie cardiaque.

Le **Chapitre 2** présente une étude systématique destinée à évaluer la précision du diagnostic des taux de peptides natriurétiques chez les personnes âgées issues de la population générale. Nous avons effectué des recherches électroniques dans les bases de données MEDLINE et EMBASE. La qualité des études retenues a été évaluée à l'aide d'une version adaptée du logiciel QUADAS, et les données extraites par deux analystes indépendants. Cinq études de qualité moyenne ont été incluses. Les données extraites n'ont pu être groupées. En conclusion, nous n'avons trouvé que peu d'éléments susceptibles d'étayer les mesures de peptides natriurétiques pour diagnostiquer da la dysfonction cardiaque ou de l'insuffisance cardiaque chez les personnes âgées de 75 ans et plus dans la population générale. En outre, plusieurs questions essentielles concernant l'utilisation des mesures de peptides natriurétiques dans la pratique courante demeurent sans réponses.

Le **Chapitre 3** étudie le lien entre le NT-proBNP et les anomalies cardiaques et évalue le recours au NT-proBNP pour exclure les anomalies cardiaques structurelles et fonctionnelles sur un échantillon de nonagénaires qui fonctionnent bien. À cet effet, une étude transversale intégrée à l'étude Leiden 85-plus a été menée sur un échantillon de commodité de 80 nonagénaires. Les taux de NT-proBNP étaient liés à de nombreuses anomalies échocardiographiques. Un seuil d'inclusion prédéfini a signalé des valeurs prédictives négatives élevées (VPN) pour des cas de dysfonction systolique du ventricule gauche, de dilatation de l'oreillette gauche, de valvulopathie sévère et d'hypertension pulmonaire. L'essai avec du NT-proBNP, afin d'exclure toute anomalie échocardiographique, a montré des VPN modérément élevées. En conclusion, le NT-proBNP pourrait être utilisé pour

exclure les anomalies échocardiographiques chez des nonagénaires qui fonctionnent bien et pour indiquer qui doit subir des examens cardiovasculaires supplémentaires.

Le **Chapitre 4** décrit la méthodologie de l'étude de cohorte BELFRAIL (BF_{C80+}). L'étude BF_{C80+} est une étude de cohorte prospective et d'observation en population générale sur 567 patients âgés de 80 ans et plus, habitant dans trois régions belges bien déterminées. L'objectif global de l'étude BF_{C80+} est d'examiner l'interaction dynamique entre la santé, la fragilité et le handicap selon une approche multisystémique qui se penche sur la dysfonction cardiaque et l'insuffisance cardiaque chronique, la fonction pulmonaire, la sarcopénie, l'insuffisance rénale et l'immunosénescence. Seuls trois critères d'exclusion ont été retenus : démence grave, soins palliatifs et urgence médicale. Deux méthodes d'échantillonnage pour le recrutement des patients ont été utilisées. Chaque participant à l'étude était invité à se soumettre à quatre examens. Le médecin enregistrait les variables de base et les antécédents médicaux, et effectuait une anamnèse détaillée, ainsi qu'un examen clinique. L'assistant de recherche clinique procédait à un examen complet, incluant notamment des tests de performance, des questionnaires et des examens techniques. Un cardiologue procédait à une échocardiographie chez le patient. Un échantillon de sang était prélevé le matin. Un rapport de suivi des résultats clairement identifiables et mesurables (mortalité, hospitalisation et morbidité) était alors établi. Une seconde collecte de données est prévue après 18 mois. La grande variété des aspects étudiés dans le cadre de BF_{C80+} nous permettra non seulement d'étudier en profondeur la relation entre les différents systèmes physiologiques, mais également de découvrir de nouveaux thèmes de recherche à partir de cette base de données unique de personnes âgées.

Dans le **Chapitre 5**, nous avons tenté de décrire la prévalence de la dysfonction cardiaque chez les personnes très âgées et d'étudier la corrélation entre les anomalies échocardiographiques et les indicateurs de mauvais fonctionnement. Il s'agissait d'une étude

transversale au sein de l'étude cBFC80+. Il a été découvert que la dysfonction cardiaque sévère était très prévalente et définie comme étant une dysfonction systolique, une valvulopathie cliniquement pertinente, ou une dysfonction diastolique sévère isolé. La dysfonction cardiaque sévère, plus particulièrement la sténose aortique, s'est avéré un identifiant indépendant de mauvaise performance, un faible score LAPAQ (activité physique générale) et un score GDS-15 (échelle de dépression gériatrique) élevé. Les indicateurs classiques de dysfonction systolique et diastolique n'ont toutefois pas permis d'identifier les participants présentant un déficit fonctionnel. Cette étude montre que les personnes très âgées représentent un groupe extrêmement hétérogène avec une forte prévalence à la comorbidité, chez lesquelles un déficit fonctionnel peut être déclenché par des causes multiples. Nos conclusions devraient encourager les médecins à ne pas se limiter à une approche orientée vers la maladie, mais à se concentrer plus sur les répercussions fonctionnelles de la dysfonction cardiaque et des comorbidités chez les personnes âgées.

Dans le **Chapitre 6**, nous avons approfondi notre étude sur le recours aux peptides natriurétiques pour identifier les dégâts «pancardiaques». En outre, nous nous sommes penchés sur l'impact des facteurs de confusion sur le lien entre le taux de peptides natriurétiques et la dysfonction cardiaque. Il s'agissait d'une étude transversale au sein de l'étude cBFC80+. Le taux de peptides natriurétiques était lié à plusieurs paramètres échocardiographiques fonctionnels et structurels, tels que la sténose aortique, le volume de l'oreillette gauche, le diamètre du ventricule gauche, le rapport E/A, E' et le temps de décélération. L'ajustement en fonction des facteurs de confusion identifiés n'a pu affiner le diagnostic de peptides natriurétiques en cas de dysfonction cardiaque sévère, sauf sur les patients atteints de fibrillation auriculaire chronique (FAC) ou portant un stimulateur cardiaque (SC). Toutefois, lorsque l'on étudie chaque facteur de confusion individuellement, nous apercevons qu'il est possible d'utiliser des seuils d'inclusion différents afin d'optimiser la performance diagnostique concernant les peptides natriurétiques.

Dans le **Chapitre 7**, une étude transversale avec « intention de diagnostiquer », intégrée au sein de l›étude cBFC80+, a été menée pour déterminer la valeur ajoutée en termes de diagnostic des peptides natriurétiques et de l'électrocardiogramme, par rapport aux antécédents médicaux, l›anamnèse, l›examen clinique et les essais de routine en laboratoire, sur des patients souffrant de dysfonction cardiaque sévère. Nous avons utilisé deux outils d›analyse : la régression logistique et les algorithmes CART (Classification and Regression Trees). Chez les patients sans FAC ou SC, l›utilisation des peptides natriurétiques et l' électrocardiogramme n›a apporté que peu de valeur ajoutée pour permettre le diagnostic de dysfonction cardiaque sévère dans la pratique courante. Toutefois, il s›est avéré possible de classer correctement davantage de participants en intégrant les peptides natriurétiques et l'électrocardiogramme dans le processus de diagnostic. Chez les participants avec FAC et SC, le modèle clinique a affiché une très grande précision, sans que les peptides natriurétiques n›apportent de valeur ajoutée.

Dans la **synthèse générale,** nous avons combiné et interprété les principaux résultats de cette thèse. Premièrement, nous abordons le contexte dans lequel ces résultats doivent être interprétés. L'accroissement de la population âgée qui s'annonce et l'explosion de la multimorbidité qui s'ensuit nécessitent de passer d'une approche orientée vers la maladie à une vision plus horizontale, plus globale des soins. Dans cette perspective, cette thèse a été étudiée selon une approche multidimensionnelle. Notre synthèse se concentre sur la pertinence d'identifier la dysfonction cardiaque sévère et de recourir aux peptides natriurétiques pour atteindre cet objectif. Ensuite, nous traitons de l'utilisation des peptides natriurétiques dans la pratique clinique courante à des fins de diagnostic de la dysfonction cardiaque sévère. Enfin, nous décrivons quelques thèmes de recherche future au sein de l'étude BF_{C80+}.

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STUDIES AND FUNCTIONS

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AWARD

2005 Encouragement Award GP in training, Eerste Lijn Symposium

PUBLICATIONS IN INTERNATIONAL SCIENTIFIC JOURNALS

1 Vaes B, de RW, Degryse J, Westendorp RG, Gussekloo J. Clinical relevance of a raised plasma N-terminal pro-brain natriuretic peptide level in a population-based cohort of nonagenarians. J Am Geriatr Soc 2009;57(5):823-829.

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1 Vaes B, de Ruijter W, Degryse J, Westendorp RGJ, Gussekloo J. Plasma NT-proBNP of the very elderly in the general population: a prospective study. ESC Heart Failure Congress, 2008, Milan. Abstract and poster presentation.

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