

Clinical Relevance of a Raised Plasma N-Terminal Pro-Brain Natriuretic Peptide Level in a Population-Based Cohort of Nonagenarians

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OBJECTIVES: To investigate whether plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) remains a specific marker of cardiac illness in very old age and can be used to identify very elderly people at high risk for death independent of 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: Two hundred seventy-four participants were followed up from age 90 onward (median follow-up 42.3 months, interquartile range 20.2–50.2 months).

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

RESULTS: Plasma levels of NT-proBNP were not correlated with indicators of poor health or poor functioning, but the level of NT-proBNP increased significantly with increasing numbers of cardiac diagnoses ($P < .001$). High NT-proBNP was associated with overall mortality in participants with (hazard ratio (HR) = 2.8, 95% confidence interval (CI) = 1.5–5.2) and without (HR = 3.5, 95% CI = 1.6–7.5) specific cardiac diagnoses. This was also found for cardiovascular mortality risks (with specific cardiac diagnoses HR = 4.1, 95% CI = 1.5–11 vs 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 vs without HR = 3.4, 95% CI = 1.3–8.6).

CONCLUSION: Plasma NT-proBNP is a disease-specific marker of cardiac illness in nonagenarians and can possibly be used as a predictor of mortality in elderly people with and without specific cardiac diagnoses. *J Am Geriatr Soc* 57:823–829, 2009.

Key words: natriuretic peptides; morbidity; mortality; prognosis

In our aging society, chronic heart failure is becoming more frequent. The prevalence increases with age, from 2.7% in people aged 65 to 74 to 13.0% in those aged 75 to 84.¹ 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 underdiagnosis of heart failure.^{2,3} This emphasizes the need for a simple, easily applicable test to identify patients at risk. N-terminal pro-brain natriuretic peptide (NT-proBNP) is gaining recognition as a diagnostic marker for heart failure⁴ and a determinant of prognosis,⁵ but most studies have investigated the relationship between NT-proBNP and cardiac dysfunction and prognosis in younger populations and were hospital based. Some population-based studies performed in elderly (sub)populations^{6–9} found limited evidence of these associations in patients aged 75 and older.

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 although as the prevalence of possible determinants increases, especially in very elderly people, the usefulness of NT-proBNP may be limited. The high prevalence of comorbidities such as renal failure and chronic obstructive pulmonary disease may blur the interpretation of high plasma levels of NT-proBNP in very old age. Moreover, 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 occurs in very elderly people. It is possible that NT-proBNP in very old age is more a marker of failing general homeostasis, an aspecific indicator of poor health status and poor functioning, than a specific marker of cardiac morbidity.

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Therefore this study was designed 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 cohort, 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 have been 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, and participants were followed for mortality from age 90 onward.

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 (400–13,500 pg/mL). Levels of NT-proBNP for men and women were ranked into tertiles separately. Sex-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 electrocardiogram at age 90 revealing a prior myocardial infarction (Minnesota Code 1-1 or 1-2, excluding 1-2-8), atrial fibrillation (Minnesota Code 8-3-1), or 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 lipid levels.

Diabetes mellitus was considered present in cases of diagnosis in the medical record, a nonfasting glucose level greater than 11 mmol/L, or the use of antidiabetic medication. Blood samples were taken for measurement of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. The cutoff level for high total cholesterol was set at 5.0 mmol/L, for high LDL-C 2.5 mmol/L, for low HDL-C 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, 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 according to Mini-Mental State Examination (MMSE) score (range 0–30).¹⁴ A MMSE score less than 19 points was considered to indicate poor cognitive functioning. Subjective well-being was tested using a visual analog scale (Cantril) in subjects with a MMSE score greater than 18 points (range 0–10).¹⁴ A Cantril score less than 7 points was considered to be poor. Disability was assessed on the Groningen Activity Restriction Scale, which is a combination of nine items relating to activities of daily living and nine items relating to instrumental activities of daily living (range 18–72).¹⁴ A Groningen Activity Restriction Scale score greater than 55 points was considered to represent poor functioning. Depressive symptoms were measured in subjects with a MMSE score greater than 18 points using the 15-item Geriatric Depression Scale (GDS-15) (range 0–15).¹⁴ A GDS-15 score above 4 was considered to be poor.

C-reactive protein (CRP), hemoglobin levels, and renal function were measured as parameters reflecting general health status. Renal function was assessed according to renal clearance (glomerular filtration rate, GFR) estimated according to the Modification of Diet in Renal Disease Study.¹⁵ CRP levels greater than 4 mg/L, GFR less than 60 mL/min/1.73 m², and hemoglobin levels less than 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 until the census date (February 11, 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 (all other ICD-10 codes) causes. The assignment of cause of death was made independently of any study results.

Possible Confounding Variables

Possible confounding variables were body mass index, renal dysfunction, hemoglobin levels, and heart failure medication.^{17–20} Body mass index at age 90 was assessed by measuring height and weight. Data on relevant cardiovascular

medication including diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and digitalis were included in the analysis.

Data Analysis

Odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) were calculated using 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 sex and number of cardiac diagnoses.

After stratification for presence of specific cardiac diagnoses, sex-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% CIs, stratified according to presence of specific cardiac diagnoses, were calculated in a Cox proportional hazards 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).

RESULTS

Three hundred twenty-three individuals of the initial cohort of 599 who participated at age 85 had died by age 90. 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 strongly dependent on others in activities of daily living (74.9%). There was a high burden of cardiovascular (65.7%) and noncardiovascular

Table 1. Sociodemographic Data, Functional Status, and Clinical Characteristics of Participants at Age 90 (N = 274)

Characteristic	n (%)
Sociodemographic data	
Male	76 (27.7)
Institutionalized	104 (38.1)
Education, ≤6 years primary school	170 (62.0)
Income < €750/month	139 (51.1)
Functional status	
Cognitive impairment (Mini-Mental State Examination score ≤18)	72 (26.6)
Poor well-being (Cantril score <7)	51 (25.8)
Dependent in daily living (Groningen Activity Restriction Scale score ≥56)	68 (25.1)
Depression (Geriatric Depression Scale-15 score ≥5)	48 (24.0)
Clinical characteristics	
Cardiovascular morbidity	180 (65.7)
Specific cardiac diagnoses*	167 (60.9)
Other vascular morbidity†	44 (16.4)
Noncardiovascular morbidity‡	175 (63.9)
Anemia	62 (23.9)
C-reactive protein > 4 mg/mL	110 (40.9)
Glomerular filtration rate < 60 mL/min per 1.73 m ²	143 (52.2)

* Including history of myocardial infarction (clinical or according to electrocardiogram (ECG)), angina pectoris, arrhythmia, heart failure, or atrial fibrillation or left ventricular hypertrophy on ECG.

† Including history of stroke and peripheral vascular disease.

‡ Including history of Parkinson’s disease, chronic obstructive pulmonary disease, arthritis (including arthrosis, rheumatoid arthritis, and polymyalgia rheumatica), malignancies, and hip fracture.

(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 (interquartile range (IQR) = 236.35–

Table 2. Correlation Between Levels of Plasma N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) and Indicators of Poor Health and Poor Functioning in Participants Aged 90 (N = 274)

Indicators of Poor Health and Poor Functioning	Sex-Specific Tertiles of NT-proBNP			P for Trend
	T1 (n = 91)	T2 (n = 92)	T3 (n = 91)	
	Odds Ratio (95% Confidence Interval)*			
Noncardiovascular morbidity†	1	1.4 (0.71–2.8)	1.2 (0.59–2.6)	.54
Anemia‡	1	1.5 (0.60–3.6)	2.1 (0.84–5.2)	.11
C-reactive protein > 4 mg/L	1	1.6 (0.82–3.3)	2.0 (0.94–4.2)	.07
Glomerular filtration rate < 60 mL/min per 1.73 m ^{2s}	1	1.6 (0.81–3.0)	3.3 (1.6–7.0)	.002
Institutionalized	1	0.86 (0.43–1.7)	1.2 (0.59–2.6)	.62
Cognitive impairment (Mini-Mental State Examination score ≤18)	1	1.2 (0.54–2.8)	1.2 (0.48–2.9)	.70
Poor well-being (Cantril score <7)	1	1.4 (0.62–3.4)	1.3 (0.47–3.4)	.59
Dependent in daily living (Groningen Activity Restriction Scale score ≥56)	1	1.0 (0.41–2.4)	1.0 (0.39–2.8)	.94
Depression (Geriatric Depression Scale-15 score ≥5)	1	0.98 (0.40–2.4)	1.7 (0.64–4.7)	.32

* Adjusted for height, weight, renal function (Modification of Diet in Renal Disease Study; MDRD), hemoglobin, and cardiovascular medication. T1 was used as reference. Second and highest tertile cutoff values: 347.5 and 1,771.0 pg/mL in men and 284.0 and 675.3 pg/mL in women.

† Including history of Parkinson’s disease, chronic obstructive pulmonary disease, arthritis (including arthrosis, rheumatoid arthritis, and polymyalgia rheumatica), malignancies, and hip fracture.

‡ Hemoglobin < 7.5 mmol/L for women, < 8.1 mmol/L for men, adjusted for height, weight, renal function (MDRD), and cardiovascular medication.

§ Adjusted for height, weight, hemoglobin, and cardiovascular medication.

Table 3. Association Between Plasma N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) and Cardiovascular Characteristics in Participants Aged 90 (N = 274)

Characteristic	n (%)	Sex-Specific Tertiles of NT-proBNP			P for Trend
		T1 (n = 91)	T2 (n = 92)	T3 (n = 91)	
		Odds Ratio (95% Confidence Interval)			
Cardiovascular morbidity	180 (65.7)	1	1.3 (0.67–2.4)	9.7 (3.6–26)	<.001
Specific cardiac diagnosis*	167 (60.9)	1	1.4 (0.75–2.7)	9.7 (3.8–25)	<.001
Myocardial infarction (clinical and ECG)	57 (20.8)	1	0.89 (0.33–2.4)	3.4 (1.3–8.4)	.007
Angina pectoris	58 (21.6)	1	0.90 (0.38–2.1)	1.9 (0.8–4.4)	.14
Arrhythmia	77 (28.6)	1	0.83 (0.39–1.8)	2.2 (1.0–4.7)	.045
Diagnosis of heart failure	59 (21.9)	1	1.5 (0.63–3.5)	2.7 (1.1–6.5)	.030
ECG findings					
Atrial fibrillation on ECG	33 (12.1)	1	0.69 (0.11–4.5)	20 (4.8–83)	<.001
Left ventricular hypertrophy	30 (10.9)	1	2.4 (0.71–8.5)	3.7 (1.0–13)	.04
Normal ECG	44 (16.1)	1	0.60 (0.27–1.3)	0.09 (0.02–0.36)	<.001
Other vascular morbidity†	44 (16.4)	1	1.3 (0.50–3.5)	1.4 (0.48–4.0)	.55
Stroke	21 (7.8)	1	0.72 (0.16–3.3)	0.96 (0.19–4.9)	.91
Peripheral arterial disease	29 (10.8)	1	2.2 (0.70–7.1)	2.3 (0.67–7.9)	.20
Cardiovascular risk profile					
Diabetes mellitus‡	45 (18.4)	1	1.8 (0.76–4.1)	1.0 (0.39–2.8)	.88
Hypertension§	151 (56.1)	1	1.2 (0.59–2.3)	1.8 (0.85–3.9)	.14
Cholesterol ≥5 mmol/L	164 (59.9)	1	0.99 (0.48–2.0)	0.56 (0.26–1.2)	.15
Low-density lipoprotein cholesterol ≥2.5 mmol/L	193 (70.7)	1	0.64 (0.29–1.4)	0.48 (0.21–1.1)	.083
High-density lipoprotein cholesterol <1 mmol/L	19 (6.9)	1	0.34 (0.057–2.0)	0.96 (0.21–4.3)	.96
Triglycerides ≥2 mmol/L	50 (18.2)	1	1.1 (0.47–2.4)	0.40 (0.13–1.2)	.14
Body mass index > 25 kg/m ²	151 (64.3)	1	0.52 (0.26–1.0)	0.29 (0.14–0.62)	.001

Data are adjusted for height, weight, renal function (Modification of Diet in Renal Disease (MDRD)), hemoglobin, and cardiovascular medication. T1 was used as reference category.

* Including history of myocardial infarction (clinical or electrocardiogram (ECG)), angina pectoris, arrhythmia, heart failure, and ECG with atrial fibrillation or left ventricular hypertrophy.

† Including history of stroke and peripheral vascular disease.

‡ According to general practitioner or (nonfasting) glycemia > 11 mmol/L or medication for diabetes mellitus.

§ History of hypertension according to general practitioner.

|| Adjusted for renal function (MDRD), hemoglobin, and cardiovascular medication.

2,017.5 pg/mL) vs 405.9 pg/mL (IQR = 235.7–882.35 pg/mL), Mann–Whitney $P = .02$), also after adjustment for weight, height, GFR, hemoglobin, cardiovascular medication, and presence of cardiovascular morbidity ($P = .003$). Plasma levels of NT-proBNP were not correlated with indicators of poor health or poor functioning, except for a higher risk of renal impairment in participants in the highest tertile than in 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 a greater 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 a greater risk of having a history of myocardial infarction (OR = 3.4, 95% CI = 1.3–8.4) and arrhythmias (OR = 2.2, 95% CI = 1.0–4.7) and a significantly higher prevalence of heart failure (OR = 2.7, 95% CI = 1.1–6.5). In terms of specific cardiac diagnoses, as investigated using an electrocardio-

gram (ECG), there was a higher prevalence of atrial fibrillation (OR = 20, 95% CI = 4.8–83) and left ventricular hypertrophy (OR = 3.7, 95% CI = 1.0–13) for participants in the highest tertile. The prevalence of a normal ECG at the age of 90 was 16.1%. The OR for a normal 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 was higher with greater numbers of specific cardiac diagnoses (Jonckheere–Terpstra, $P < .001$): 306.7 pg/mL (IQR = 172.2–507.0 pg/mL) for no diagnoses, 447.8 pg/mL (IQR = 239.5–1,249.3 pg/mL) for one diagnosis, 748.8 pg/mL (IQR = 348.9–1,934.8 pg/mL) for two diagnoses, 982.9 pg/mL (IQR = 368.0–2,293.0 pg/mL) for three diagnoses, and 1,779.5 pg/mL (IQR = 510.4–5,258.0 pg/mL) for four or more diagnoses. The association between NT-proBNP and number of cardiac diagnoses remained significant after adjustment for sex, weight, height, GFR, hemoglobin, and cardiovascular medication ($P < .001$).

The median follow-up was 42.3 months (IQR = 20.2–50.2 months). During follow-up, 170 deaths (62.0%) occurred; 58 participants (34.1%) died from cardiovascular causes and 107 (62.9%) from noncardiovascular causes.

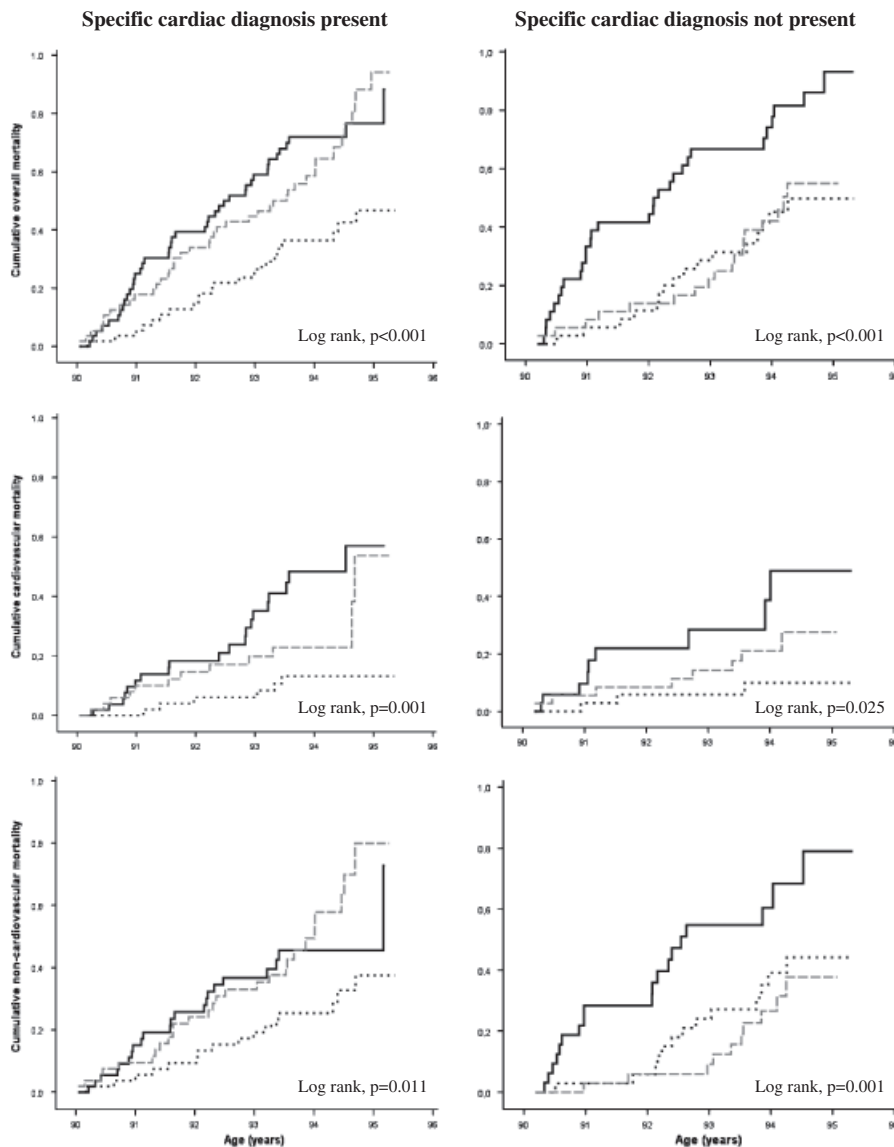


Figure 1. Cumulative overall, cardiovascular, and noncardiovascular mortality based on sex-specific tertiles of N-terminal pro-brain natriuretic peptide (NT-proBNP) stratified for presence of specific cardiac diagnoses. Second and highest tertile cutoff values: 912.8 and 2,348.0 pg/mL in men and 326.2 and 876.3 pg/mL in women with specific cardiac diagnoses. Second and highest tertile cutoff values: 211.1 and 460.7 pg/mL in men and 209.7 and 408.4 pg/mL in women without specific cardiac diagnoses. Sex-specific tertiles of NT-proBNP:

————— Tertile 1
 Tertile 2
 ————— Tertile 3

The specific cause of five deaths (3%) was unknown. Figure 1 presents the cumulative mortality for sex-specific tertiles of NT-proBNP from age 90 onward stratified according to the presence of specific cardiac diagnoses. Higher plasma levels of NT-proBNP were associated with greater cumulative mortality in both strata (log-rank test, $P < .001$). This association was present not only for overall mortality, but also for cardiovascular and noncardiovascular mortality, independent of the presence of specific cardiac diagnoses (Figure 1). After adjustment for known confounding vari-

ables, 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

Table 4. Overall and Cause-Specific Mortality Risks Depending on Plasma N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) from Age 90 and Older, Stratified According to Presence of Specific Cardiac Disorders

Mortality	Sex-Specific Tertiles of NT-proBNP			P for Trend
	T1	T2	T3	
	HR (95% CI)			
Specific cardiac diagnosis				
Observed number of deaths, n/N	23/55	41/56	42/56	
Overall mortality, HR (95% CI)	1	2.5 (1.4–4.4)	2.8 (1.5–5.2)	.001
Cardiovascular mortality, HR (95% CI)	1	2.3 (0.8–6.5)	4.1 (1.5–11.0)	.005
Noncardiovascular mortality, HR (95% CI)	1	2.7 (1.3–5.5)	1.9 (0.8–4.5)	.09
No specific cardiac diagnosis				
Observed number of deaths, n/N	16/35	18/36	30/36	
Overall mortality, HR (95% CI)	1	1.1 (0.50–2.5)	3.5 (1.6–7.5)	.003
Cardiovascular mortality, HR (95% CI)	1	4.2 (0.8–21.0)	5.6 (1.0–30.0)	.03
Noncardiovascular mortality, HR (95% CI)	1	0.6 (0.2–1.6)	3.4 (1.3–8.6)	.04

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazard models adjusted for weight, height, renal function (Modification of Diet in Renal Disease), hemoglobin, and cardiovascular medication.

HR = 3.4, 95% CI = 1.3–8.6, for the group with and without specific cardiac diagnoses, respectively) (Table 4).

DISCUSSION

A large population-based sample of 90-year-old participants 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. NT-proBNP was found to be a good predictor for cardiovascular and noncardiovascular mortality in individuals aged 90 and older, in elderly people with and without specific cardiac diagnoses.

There are few published data on the relationship between natriuretic peptides, morbidity, and mortality in very elderly people. It was shown that high BNP concentrations were predictive of 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 (aged 45–91), it was shown that left ventricular hypertrophy, ischemic heart disease, atrial fibrillation, valvular heart disease, and peripheral vascular disease were independent predictors of high NT-proBNP concentrations.²² Some studies have reported the association between high plasma levels of natriuretic peptides and high total and cardiovascular mortality not only in elderly people from the general population,^{7,23} but also in selected elderly populations such as healthy community-dwelling elderly people,²⁴ patients in nursing homes,⁶ and elderly patients in general practice with heart failure.²⁵ The current results are in line with the results of these studies.

Although in the current study high levels of NT-proBNP were specifically correlated with presence of specific cardiac diagnoses, plasma NT-proBNP was associated with cardiovascular and noncardiovascular mortality and was

able to predict mortality in participants with and without specific cardiac diagnoses. How can the prognostic characteristics for mortality of NT-proBNP that were found in this study population be explained? Participants in the highest tertiles were not functionally more disabled, did not have more noncardiovascular or other vascular morbidities, and did not have a higher cardiovascular risk profile than participants in the lower tertiles. Concentrations of natriuretic peptides are related to left ventricular filling pressures²⁶ and wall stress.²⁷ The data from the current study showed that a higher level of NT-proBNP might indicate the severity of cardiac illness. In participants without known cardiac morbidity, it is possible that high levels of NT-proBNP 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 cardiac dysfunction indicates a low cardiac reserve, and the pneumonia could have more-serious consequences, including death.

This study is the first to investigate the predictive value of NT-proBNP in a population-based sample of the very old independent of 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. The current 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 very elderly people with a high burden of comorbidity. It could be seen as a limitation that there were not data to correlate plasma levels of NT-proBNP with objective echocardiographic measurements, but because it was decided to perform all data collection of the Leiden 85-plus Study during home visits to improve participation rates and reduce dropouts, this was not technically feasible. Comorbidities may have been underdiagnosed, because they were not assessed but were reported by the general practitioner. Because any underreporting was independent of plasma levels of NT-proBNP, this is not underlying the

results. There might have been a nondifferential misclassification of cause of death, but the assignment of cause of death was made independent 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 of the presence of known cardiac diagnoses, although further research is needed to investigate the diagnostic accuracy of NT-proBNP for cardiac dysfunction in very elderly people, as well as the possibilities and effect of NT-proBNP-guided treatment for people 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.

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