

BNP and NT-proBNP, Predictors of 1-Year Mortality in Nursing Home Residents

Maaïke Barents, MD, Hans H.L. Hillege, MD, PhD, MSc, Iwan C.C. van der Horst, MD, PhD, Rudolph A. de Boer, MD, PhD, J. Koster, MSc, Frits A.J. Muskiet, PhD, and Mike J.L. de Jongste, MD, PhD

Objectives: To investigate 1-year mortality prediction of B type natriuretic peptide (BNP) and N terminal-proBNP (NT-proBNP) in institutionalized elderly with multiple morbidities.

Design: Prospective cross-sectional study.

Setting: One nursing home.

Participants: Ninety-three residents (mean age 81 ± 3 years, 66% female). Residents with serious cognitive impairments, aphasia, or metastatic cancer were excluded.

Measurements: Clinical assessment, immobilization, medical history, electrocardiogram (ECG), echocardiogram, blood samples. One general geriatrician assessed noncardiovascular diseases; a cardiologist panel established the diagnosis of chronic heart failure (CHF). Subjects were tracked for 1 year as far as status of death.

Main results: Eighteen of 93 enrolled individuals died. BNP was significantly higher in nonsurvivors compared with survivors (138 [49–753] versus 87 [27–162], $P = .029$), NT-proBNP was higher but did not reach

significance 1382 (193–5683) versus 335 (175–900) pg/mL (interquartile range [IQR], $P = .059$). The adjusted value on 1-year mortality of 6 predefined chronic diseases, immobilization, age, sex, NT-proBNP, and BNP was estimated by means of Cox proportional hazard regression analyses. Finally, both for NT-proBNP and BNP, a mutually adjusted multivariate Cox proportional hazard analysis with the covariates presented that BNP and NT-proBNP predicted 1-year mortality significantly (hazard ratio [HR] 1.67 and $P = .000$, HR 0.60 and $P = .000$, respectively). The mortality risk increased at rising BNP and NT-proBNP levels.

Conclusion: BNP and NT-proBNP are predictors of 1-year mortality independently of age, gender, and morbidity. The mortality risk increases at elevating natriuretic peptide concentrations. We postulate that plasma levels of BNP and NT-proBNP are also of use to predict prognosis in institutionalized elderly with multiple morbidity. (*J Am Med Dir Assoc* 2008; 9: 580–585)

Keywords: B-type natriuretic peptides; prognosis; elderly; nursing home; comorbidity

Elderly individuals with multiple morbidities admitted to a nursing home (NH) are faced with questions concerning their health, living conditions, and social life. Information about the prognosis of their diseases is essential for them to make

decisions on these questions and therefore is of importance for the quality of their lives. Aside existing chronic diseases and their progression, body mass index (BMI), waist-hip ratio, and biomarkers such as albumin and natriuretic peptides also predict 1-year mortality.^{1–6} Natriuretic peptides (B type natriuretic peptide [BNP] and N terminal-proBNP [NT-proBNP]) have become available as tools for the diagnosis of heart failure and for prognosis.^{7–11} Their prognostic role was evaluated independently of the presence of chronic heart failure and found to be of importance. However, most of these data are obtained from specialized clinics treating relatively younger patients with heart failure without comorbidity. In addition, BNP levels also increase in noncardiac conditions such as old age, being female, pulmonary diseases (pulmonary hypertension or embolism, chronic obstructive pulmonary disease [COPD]), and renal dysfunction.^{12–15} Although nearly all NH residents suffer from multiple morbidity, data on the value of use of natriuretic peptides in them are limited. We therefore investigated whether BNP and NT-proBNP plasma

Nursing Home “het Zonnehuis,” Zuidhorn, the Netherlands (M.B.); Department of Cardiology, University Medical Center Groningen, Groningen, the Netherlands (H.H.L.H., I.C.C.v.d.H., R.A.d.B., J.K., M.J.L.d.J.); Department of Pathology and Laboratory Medicine, University Medical Center Groningen, Groningen, the Netherlands (F.A.J.M.).

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Address correspondence to Maaïke Barents, MD, Nursing Home “het Zonnehuis,” Suite 138, Hoofdstraat 2a, 9801 BW LG Zuidhorn, the Netherlands. E-mail: mbarents@planet.nl; m.j.l.de.jongste@thorax.umcg.nl

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levels remain of prognostic value in elderly patients with multiple morbidity.

METHODS

During the course of this study, there were 140 persons in the departments for residents with diseases of somatic origin in NH “het Zonnehuis.” Their impairments were based on cardiovascular, pulmonary, endocrine, neurodegenerative, skeletal muscle, renal dysfunction,¹⁶ and other disorders. Most of them received long-term care. Some residents with skeletal muscle or cerebrovascular disorders were reactivated, one third of whom could be discharged (short stay) but who remained care dependent in primary care. Both groups were invited to take part if they were 65 years or older. The long-term and short-stay residents were included if they understood the impact of the study on themselves (competent) and if they agreed to participate by written informed consent.

Persons with aphasia or a cognitive impairment as measured by the Mini-Mental State Examination (MMSE) with a score of 20 or less were excluded. The MMSE contains 30 questions and an MMSE score of 20 or less is suspect for cognitive impairments.¹⁷ Persons with metastatic cancer who stayed in a department specialized in palliative terminal care were excluded. Persons were also excluded if the echocardiographic frames could not be sufficiently visualized or if they refused to have a blood sample taken.

The study was approved of by the Medical Ethical Committee in Groningen, University Medical Center Groningen, the Netherlands (METc number 2004.107).

Diagnostics

In this cross-sectional study, all data were collected anonymously and within 1 week (questionnaire, neurohormone sampling, ECG, echocardiography). One physician collected the data on the patients’ medical history ([chronic] diseases of the cardiovascular, pulmonary, endocrine, neurodegenerative, and skeletal muscle system), their symptoms, and their medications. He also examined blood pressure, height, and weight and performed a full physical examination.¹⁸ Aside from number and type of chronic disorders, we registered immobilization defined as being wheelchair dependent or bedridden. We regarded immobilization as a consequence of the chronic diseases on the individual and therefore as a parameter of progression of the present chronic diseases. The diagnosis of chronic heart failure (CHF) was made by 2 experienced cardiologists. A third colleague decided in cases of disagreement. Of note, the cardiologists were unaware of a resident’s BNP and NT-proBNP levels. A 12-lead electrocardiogram (ECG) was made with the electrocardiograph Cardioline delta three plus (Cardioline, Milan, Italy, www.cardioline.it), with the patient in a horizontal position.

The left-ventricular ejection fraction (LVEF) was assessed semiquantitatively by the 2-dimensional visual estimate method.¹⁹ An LVEF of 45% or less was considered to be a left-ventricular systolic dysfunction (LVSD) or diminished LVEF (dLVEF). The hand-held cardiograph “Opti Go” (Philips, Eindhoven, the Netherlands, www.philips.com) was used. One blood sample per resident (12 mL) was taken if one was

fasting and at rest. Assessments of creatinine, hemoglobin, and mean corpuscular volume (MCV) were performed in the NH laboratory. Since neurohormone levels may vary by about 100%, we choose not to repeat the neurohormone sampling. For determination of levels of NT-proBNP, a 5- μ L aprotinine solution was adjusted to the 250- μ L plasma samples in EDTA and to 250- μ L serum samples. At the University Medical Centre Groningen Clinical Chemical Laboratory (CCL), both were frozen at -20°C and stored in batches for a maximum of 10 months. The assays were run in one go for both NT-proBNP and BNP. Both NT-proBNP and BNP were measured by immunoassays (Elecsys 1010/2010/modular analytics 2004, Roche Diagnostics, Indianapolis, IN, and AX-SYM system BNP 2003, Axis-Shield Diagnostics LTD AB-BOT, Wiesbaden, Germany). NT-proBNP and BNP had coefficients of variation of 3.3% and 7.8% (ranges of 5 to 35,000 pg/mL and 0 to 3465 pg/mL, respectively).

Renal function has been defined as glomerular filtration rate (GFR) measured by the Modification of Diet in Renal Disease (MDRD) formula in mL/min/1.73 m². Renal dysfunction was defined as GFR MDRD less than 30 mL/min/1.73² (serious renal dysfunction according to K-DOQI stage 4).²⁰

Anemia was defined as hemoglobin (Hb) less than or equal to 7.5 mmol/L \approx 12 g/dL.²¹ Whether each resident was dead or alive was recorded after 1 year following initial data collection.

Statistical Analysis

To address if BNP and NT-proBNP predict 1-year mortality in a cohort of elderly patients with multiple chronic diseases, we used different statistical tests. Differences in basic characteristics of survivors and nonsurvivors were analyzed using Student *t* test, chi-square test, or the Fisher exact test for categorical data and the Mann-Whitney test for nonparametric continuous data, as appropriate. The association between underlying diseases or immobilization and NT-proBNP and BNP levels divided into tertiles, was tested with chi-square statistics.

The adjusted value of the 6 predefined chronic diseases, immobilization, NT-proBNP and BNP, unadjusted and adjusted for age and sex were estimated by means of Cox proportional hazard regression analyses. The 6 chronic diseases were CHF all cases (or CHF with dLVEF or CHF pLVEF), COPD, diabetes, renal dysfunction, neurodegenerative diseases, and skeletal-muscle system diseases (Table 3).

Finally, both for NT-proBNP and BNP, a mutually adjusted multivariate Cox proportional hazard analysis was made with the covariates in the equation. The quantitative relationship between NT-proBNP and BNP levels and mortality is expressed in Figures 1 and 2.

Statistical analyses were performed using SPSS 12.0.1 software (SPSS Inc., Chicago, IL). All statistical comparisons were 2-tailed, and a *P* value less than .05 was considered to be statistically significant.

RESULTS

A total of 93 (62%) individuals out of 140 residents were included. Individuals were excluded because of cognitive im-

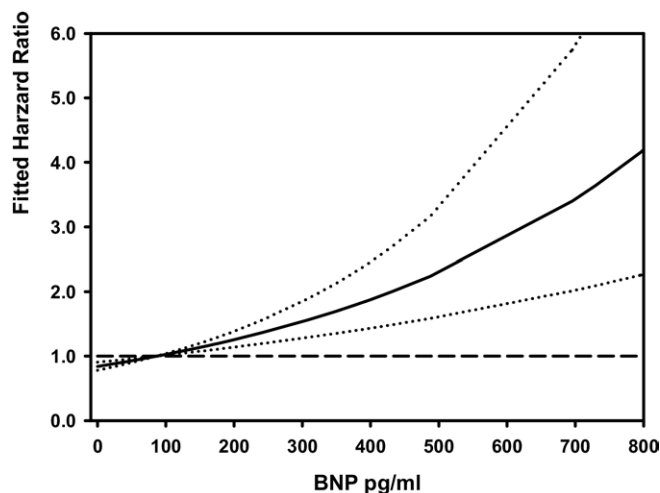


Fig. 1. Hazard ratio's of BNP and 1-year mortality risk.

pairment (30 [21%]), missing ECG data (2 [1.4%]), missing laboratory values (1 [0.7%]), and unwillingness to participate (14 [10%]).

The mean age of the studied population was 81 ± 3 years and approximately 66% of the residents were females (Table 1).

After a follow-up period of 1 year, 18 of 93 individuals had died. Patients who survived did not differ in age from nonsurvivors (80 ± 7 versus 81 ± 9 years, $P = .796$). In comparison with survivors, nonsurvivors more often had CHF (all cases), diabetes, and higher BNP levels.

Of the 10 nonsurvivors with CHF, 2 subjects had symptoms and 8 had no symptoms of heart failure, 4 of 10 had pLVEF, and 6 of 10 had dLVEF. BNP and NT-proBNP were elevated in CHF compared with no-CHF, and both BNP and NT-proBNP differed significantly (median BNP in CHF 194, IQR 92–460 versus BNP in no-CHF 87, IQR 28–187 pg/mL, $P < .001$; and NT-proBNP in CHF 1871, IQR 539–4262 versus NT-proBNP in no-CHF 324, IQR 163–1146 pg/mL, $P < .001$).

CHF all cases ($P = .014$ and $P = .004$) and CHF with dLVEF ($P = .018$ and $P = .001$) were observed more in the highest BNP and NT-proBNP tertiles (P values respectively) (Table 2).

BNP and NT-proBNP predicted 1-year mortality significantly after adjustment for age, sex, the 6 chronic diseases, and immobilization (with CHF all cases in the analysis had a hazard ratio [HR] of 1.67 and $P = .000$, HR 0.60 and $P = .000$; with CHF with pLVEF HR 1.76 and $P = .000$, HR 2.06 and $P = .000$; with CHF with dLVEF HR 1.03 and $P = .000$, HR 0.93 and 4.86, respectively) (Table 3).

The mortality risk was increasing at rising NT-proBNP and BNP levels. An increase of 10 pg/mL BNP was related to a 2.2% rise of the HR of the mortality risk. Moreover, an increase of 10 pg/mL NT-proBNP was associated with a 0.27% rise of the HR of mortality risk (Figures 1 and 2, Table 3).

DISCUSSION

The major finding of this study is that in NH residents, BNP and NT-proBNP are independent predictors of mortal-

ity, after adjustment for age, sex, chronic diseases, and immobilization. One of the main characteristics of NH residents is the presence of multiple morbid conditions. Residents have an average of 4 chronic diseases each. Moreover, CHF all cases and diabetes are more frequently represented in those who died, compared with those who did survive (Table 1). We had to consider the skewed distribution of BNP and NT-proBNP caused by extended comorbidity in a relatively small population. Therefore medians instead of means of neurohormones were used and an adjustment for all confounders of neurohormone levels was made as is presented in Tables 2 and 3. After adjustment for all confounders, the neurohormones predicted 1-year mortality significantly in NH residents. Another aspect of morbidity, aside from number and type, is the progression of each chronic disease. In this study, however, we did not register the progression of chronic diseases. To address this shortcoming we determined immobilization as a parameter of consequences of morbidity.^{22–24} Aside mortality risks such as age and sex, we had to count with chronic diseases and their consequences influencing individuals. So, after adjustment for age, sex, and morbidity, BNP and NT-proBNP still remained predictors of 1-year mortality in NH residents (Table 3). Moreover, the quantitative relation between natriuretic peptides and mortality revealed high levels of natriuretic peptides required for prognosis compared to their use for diagnosis (Figures 1 and 2). For instance, an increase of BNP or NT-proBNP of 10 pg/mL is related to an increase of mortality risk of 2.2% or 0.27%, respectively. To date, there is a scarcity of reports on the value of BNP and NT-proBNP in elderly in nursing homes. Comparisons with other populations should therefore only be made taking these flaws into account.

In NH residents, BNP and NT-proBNP are of prognostic value at higher levels, compared to a non-elderly population.^{25,26} In a study of ambulatory CHF patients (mean age 76 ± 11 years) with preserved LVEF and with readmission or death for cardiac reasons as end points, Valle and colleagues²⁷

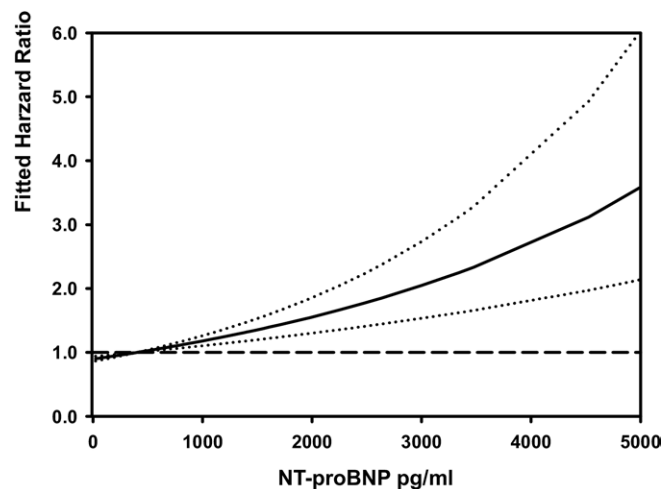


Fig. 2. Hazard ratios of NT-proBNP and 1-year mortality risk.

Table 1. Baseline Clinical Characteristics of Nursing Home Residents; Survivors Compared With Nonsurvivors

	Survivors	Nonsurvivors	P value
Number (% of 93)	75 (81)	18 (19)	
Age, y, mean ± SD	80 ± 7	81 ± 9	.796
Female	49 (53)	12 (13)	.740
BP diastolic, mm Hg, mean ± SD	80 ± 12	74 ± 11	.050
BP systolic, mm Hg, mean ± SD	142 ± 26	133 ± 23	.155
Haemoglobin, mmol/L, mean ± SD	7.7 ± 1	7.4 ± 1	.352
Creatinine, μmol/L, mean ± SD	76 ± 27	102 ± 78	.175
BMI, kg/m ² , mean ± SD	26 ± 6	23 ± 3	.780
LVEF, %, mean ± SD	52 ± 8	49 ± 10	.254
CHF all cases	13 (14)	10 (10)	.007
CHF with dLVEF	10 (11)	6 (6)	.053
CHF with pLVEF	3 (3)	4 (4)	.190
COPD	17 (18)	7 (7)	.161
Diabetes	16 (17)	9 (9)	.038
Renal dysfunction	27 (84)	5 (16)	.507
Neurodegenerative diseases	39 (41)	7 (7)	.231
Skeletal-muscle diseases	35 (37)	4 (4)	.060
Immobilization	26 (27)	9 (9)	.232
BNP, pg/mL, median (IQR)	87 (27–162)	138 (49–753)	.029
NT-proBNP, pg/mL, median (IQR)	335 (175–900)	1382 (193–5683)	.059

Data are numbers (% of the 93 subjects) unless otherwise indicated.

LVEF, echocardiogram $\leq 45\%$, left ventricular ejection fraction; dLVEF, diminished LVEF; pLVEF, preserved LVEF; COPD, chronic obstructive pulmonary disease; BP, blood pressure; BMI, body mass index; renal dysfunction, GFR with Modification of Diet in Renal Disease (MDRD) formula ≤ 30 mL/min/1.73 m²; immobilization, subjects in wheelchair or bed; IQR, interquartile range; NT-proBNP, N terminal-pro B-type natriuretic peptide; BNP, B-type natriuretic peptide.

found predictive values of BNP at 200 to 499 and greater than 500 pg/mL (HRs of 2.2 and 5.8) after 6 months of follow-up. Although there were differences in design and population between Valle et al's and the present study, both studies suggest that BNP levels for prognostic use were found to be two- to fourfold higher than advised for diagnostic purposes. Bibbins et al²⁸ found NT-proBNP to be a marker of long-term mortality, independently of other prognostic markers. In subjects with stable coronary heart disease with a mean age of 67 to 72 ± 9 years, they also found increasing mortality risks at incremental NT-proBNP levels. McKie et al²⁹ studied a younger community-based cohort without heart and renal failure (mean age of 62 years) and found BNP and NT-

proBNP to be biomarkers for mortality at much lower levels (Biosite assay of BNP was 63 versus 22 and NT-proBNP was 206 versus 63 pg/mL median levels, nonsurvivors versus survivors). Regarding a different range, the relationship between increasing mortality risk and elevating natriuretic peptide levels was comparable to our results.

Altogether, we demonstrated in this study that BNP and NT-proBNP are of prognostic value also in the care of dependent elderly with multiple morbidity. However, the cut-off points for prognostic purposes of neurohormones seem higher and should be identified in future studies keeping track of comorbidity. There is overlap in neurohormone values, which may hamper the delivery of prog-

Table 2. BNP and NT-proBNP Concentrations Divided in Tertiles and Linear Related to Chronic Diseases and Immobilization

Tertiles	Total % of 93	BNP				NT-pro BNP			
		I, %	II, %	III, %	P value	I, %	II, %	III, %	P value
COPD	25	8	13	4	.276	11	8	6	.507
Diabetes	26	12	6	8	.433	13	5	8	.254
Renal dysfunction	34	11	11	12	.936	10	15	9	.304
Skeletal-muscle D.	41	17	15	9	.089	16	13	12	.443
Neurodegenerative	48	15	18	15	.904	18	11	19	.800
CHF all cases	24	4	6	14	.014	3	6	15	.004
CHF pLVEF	6	1	2	3	.559	2	1	3	.586
CHF dLVEF	18	3	4	11	.018	1	5	12	.001
Immobilized	36	11	15	10	.870	10	12	14	.434

BNP, B-type natriuretic peptide; NT-proBNP, N-terminal proBNP; COPD, chronic obstructive pulmonary disease; renal dysfunction, Glomerular Filtration Rate (GFR) according to Modification of Diet in Renal Disease (MDRD) formula < 30 mL/min/1.73 m²; D., disease; neurodegenerative, neurodegenerative disease; CHF, chronic heart failure; CHF pLVEF, CHF with preserved left ventricular ejection fraction; CHF dLVEF, CHF with diminished LVEF.

Table 3. Association of BNP and NT-proBNP with 1-Year Mortality After Adjustment for Mortality Risk Factors

Neurohormone Nursing Home	BNP			NT-proBNP		
	HR	95% CIs	P	HR	95% CIs	P
NH, unadjusted	1.22	1.13–1.32	.000	1.03	1.02–1.04	.000
NH, age- and sex-adjusted model	1.23	1.13–1.33	.000	1.03	1.02–1.04	.000
NH, age- and sex-adjusted model plus each of the following added 1 at a time:						
Diabetes	3.56	1.31–9.67	.000	0.27	0.10–0.78	.000
COPD	1.98	0.69–5.62	.000	0.60	0.21–1.66	.000
Renal function	1.00	0.99–1.01	.000	1.00	0.44–1.01	.000
Skeletal muscle D.	1.49	0.44–5.00	.000	1.60	0.50–5.42	.000
Neurodegenerative D.	2.51	0.81–7.76	.000	3.42	1.99–10.71	.000
Immobilization	0.30	0.10–0.90	.000	0.34	0.11–1.99	.000
CHF all cases*	1.67	0.43–6.41	.000	0.60	0.16–2.26	.000
CHF with pLVEF*	1.76	0.44–7.06	.000	2.06	0.51–8.32	.000
CHF with dLVEF*	1.03	0.19–5.51	.000	0.93	0.18–4.86	.000

COPD, chronic obstructive pulmonary disease; D., disease; HR, hazard ratios; CIs, confidence intervals; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal proBNP. BNP/100 pg/mL, NT-proBNP/100 pg/mL.

* One of the 3 chronic heart failure (CHF) categories is inserted in the model at a time: CHF all cases or CHF with preserved left ventricular ejection fraction (pLVEF) or CHF with diminished LVEF (dLVEF).

nostic information on an individual level, but the relation of increasing mortality risk at rising neurohormone levels emerges in this old morbid population. This means that NH residents with high neurohormone levels have a substantial risk of dying within a year, if the underlying cause of high neurohormone levels is not remedied. A limitation of this study is the small population of 93 NH residents, in 1 center. On the other hand, the population studied is representative of other NH populations in terms of distribution of age, gender, diabetes, CHF, the use of ACE-inhibitor therapy, and number of chronic diseases, although not representative in terms of the presence of hypertension and renal dysfunction.^{30–33}

CONCLUSION

In a cohort of NH residents, BNP and NT-proBNP levels are independent predictors of 1-year mortality, after adjustment for age, sex, chronic morbidity, and immobilization. With respect to the prognosis, mortality risk increases with elevated natriuretic peptide levels. We postulate that plasma levels of BNP and NT-proBNP are also of use to predict prognosis in institutionalized elderly with multiple comorbidities.

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