Prevalence and misdiagnosis of chronic heart failure in nursing home residents: the role of B-type natriuretic peptides

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Background/objectives. Without knowing the exact CHF prevalence, chronic heart failure (CHF) occurs frequently in elderly people both inside and outside nursing homes. For a diagnosis we have to rely on physical examination and additional tests. We therefore run the risk of missing CHF diagnoses or of diagnosing CHF when we should not. Natriuretic peptide assays have emerged as a diagnostic test but their use in nursing home residents is limited. We examined the number of misdiagnoses, the CHF prevalence and the role of natriuretic peptide.

Method. Residents in one centre without aphasia, cognitive impairments or metastatic cancer were screened for CHF; the natriuretic peptide levels were measured separately.

Results. Of the 150 residents, 103 (64%) were included (79±11 years). The diagnosis of CHF was established in 24 of these 103 residents with NT-proBNP 1871 (IQR 539 to 4262) and BNP 194 (IQR 92 to 460) pg/ml. A striking result was that of the 24 residents found to have CHF after the screening, 15 (66%) had previously been undetected: NT-proBNP 1146 (interquartile range (IQR) 228 to 3341) and BNP 200 (IQR 107 to 433) pg/ml. Moreover, in 13 out of 22 residents (62%) who had previously been thought to have

CHF, the diagnosis was rejected: NT-proBNP 388 (IQR 174 to 719) and BNP 90 (IQR 35 to 128) pg/ml). Regarding the diagnostic accuracy of NT-proBNP and BNP, the optimal cut-off level of NT-proBNP was 450 pg/ml with a sensitivity of 0.71 and specificity of 0.67, and for BNP it was 100 pg/ml with a sensitivity of 0.71 and specificity of 0.70.

Conclusion. Both undetected and incorrect diagnoses of CHF were common. NT-proBNP and BNP were moderately accurate at diagnosing CHF. CHF prevalence was 23%. (*Neth Heart J* 2008;16: 123-8.)

Keywords: heart failure, prevalence, misdiagnosis, B-type natriuretic peptide, elderly, comorbidity, nursing home

Nursing home residents are characterised by high age and comorbidity. Chronic heart failure (CHF) occurs frequently, but is a relatively neglected diagnosis.¹ The main reasons why CHF is less frequently detected are the non-specific symptoms, comorbidity and limited access to echocardiography.²⁻⁴ On the other hand, in some residents the diagnosis of CHF is made while their symptoms are caused by other disorders. Both undetected diagnosis and incorrect diagnosis will lead to inadequate treatment of the underlying disease, and will impair the quality of life.

Natriuretic peptides are increasingly being used to aid the diagnosis of CHF. Its diagnostic value is particularly strong in dyspnoeic patients admitted to the emergency department but less strong in general practice.⁵ Nursing home residents are usually of a high age and have multiple chronic diseases, such as renal dysfunction and diabetes. The role of natriuretic peptides for the diagnosis of CHF in this specific population may be limited, but so far it has not been extensively studied. In the present study we therefore aim to look at the prevalence of CHF, both undetected and incorrect diagnoses of CHF, and the diagnostic accuracy of NT-proBNP and BNP in nursing home residents.

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Method

During the course of this study, 150 residents stayed on wards for diseases of somatic origin in 'Het Zonnehuis' nursing home. Their impairments were based on cardiovascular, pulmonary, neurodegenerative, skeletal muscle and other disorders. Most of them were receiving long-term care. Some residents with skeletal muscle or cerebrovascular disorders were rehabilitated, one-third of whom could be discharged (short stay) but they remained dependent on care. Persons from both these groups who stayed in the nursing home between 25 September 2004 and 24 May 2005 were invited to take part in the study. The long-term and short-stay residents were included if they understood what the impact of the study would be for them (competent) and if they agreed to participate by written informed consent.

Persons with aphasia or a cognitive impairment measured by the mini-mental state estimation (MMSE) test of ≤ 20 were excluded. The MMSE test contains 30 questions and an MMSE ≤ 20 is suggestive of cognitive impairment.⁶ Patients with metastatic cancer who stayed in a department specialised in palliative terminal care were excluded. Persons were also excluded if the echocardiographic frames could not be adequately visualised or if they refused to have their blood sample taken.

CHF was defined according to the definition of the Chronic Heart Failure Guidelines of the European Society of Cardiology.⁷ Two experienced heart failure cardiologists independently decided on the diagnosis of CHF, based on medical history, physical examination, ECG, routine blood tests and echocardiography. In case of disagreement, a third cardiologist reviewed the case and made the final diagnosis. At this stage none of the cardiologists knew what the levels of BNP or NT-proBNP were. The study was approved by the Medical Ethics Committee in Groningen, University Medical Center, the Netherlands (MEtC number 2004.207).

Materials

In this cross-sectional study, all data were collected anonymously within one week (questionnaire, neuro-hormonal sampling, ECG, echocardiography).

One physician collected the data on the patients' medical history (CHF with New York Heart Association

(NYHA) classification, coronary artery diseases (CAD), hypertension, peripheral vascular disorders, diabetes mellitus and other comorbidity), their symptoms (fatigue and dyspnoea at great or light effort and at rest, when laying down and at night, chest pain, palpitations), and on their medications. He also took the blood pressure, and examined jugular venous pressure (JVP), the heart (third heart sound, gallop rhythm, cardiomegaly by percussion), the lungs (rales), the liver (liver percussion), height and weight, and looked for periphery oedema.⁸

A 12-lead electrocardiogram (ECG) was taken using a Cardioline delta three plus electrocardiograph (Cardioline, Milan, Italy, www.cardioline.it) with the patient in a horizontal position.

One blood sample per resident (12 ml) was taken with the person fasting and at rest. Assessments of creatinine, haemoglobin and mean corpuscular volume (MCV) were performed in the nursing home laboratory. Since the coefficient of variation of neuro-hormones is reported to be about 100%, we chose not to repeat the neurohormone sampling.⁹ For determination of levels of (NT-pro)BNP, a 5 µl aprotinin solution was adjusted to the 250 µl plasma samples in EDTA and to 250 µl serum samples. At the clinical chemical laboratory (CCL) of the UMCG both were frozen at -20°C and stored in batches for a maximum of ten months. The assays were run in one go for both NT-proBNP and BNP. Both NT-proBNP and BNP were measured by immunoassays (Elecys 1010/2010/modular analytics 2004 Roche Diagnostics Indianapolis IN US, and AXSYM system BNP 2003 Axis-shield diagnostics LTD ABBOT Wiesbaden Germany). NT-proBNP and BNP had coefficients of variation of 3.3 and 7.8%, respectively, and measuring ranges of 5 to 35,000 pg/ml and 0 to 3465 pg/ml.

The renal function was defined as glomerular filtration rate (GFR) measured by the Cockcroft and Gault formula in ml/min.

The echocardiography was performed in the nursing home by four experienced echocardiographers using a hand-held cardiograph 'Opti Go' (Philips, Eindhoven, the Netherlands, www.philips.com). The residents were examined while lying comfortably in their own beds. The left ventricular ejection fraction was assessed semiquantitatively by the two-dimensional visual

Table 1. Three chronic heart failure groups found after the screening.

	N	NYHA				NT-proBNP	BNP
		I	II	III	IV		
CHF confirmed	9	1	5	3	0	2632 (1044-5737)	118 (59-706)
CHF rejected	13	7	5	1	0	388 (174-719)	90 (35-128)
CHF de novo	15	7	4	1	3	1146 (228-3341)	200 (107-433)

CHF=chronic heart failure, CHF confirmed=CHF diagnosed before the screening and confirmed afterwards, CHF rejected=CHF diagnosed before the screening and rejected afterwards, CHF de novo=CHF undetected before the screening and diagnosed afterwards, n=number, NYHA=New York Heart Association classification, NT-proBNP=N terminal pro B-type natriuretic peptide, BNP=B-type natriuretic peptide, median and interquartile range of pg/ml.

estimate method.¹⁰ An LVEF $\leq 45\%$ was considered to be a left ventricular systolic dysfunction (LVSD). If the echocardiogram was of insufficient quality, the subject was transported to the UMCG where an echocardiogram was taken with the General Electric Vingmed Ultrasound five (Zoetermeer, the Netherlands, www.gemedicalsystems.com).

Statistical analyses were performed using SPSS 12.0.1 software (SPSS Inc., 233 S. Wacker, 11th Floor, Chicago IL US). Differences in the basic characteristics

of residents with and without CHF were analysed using Student's t tests, χ^2 test and the Mann-Whitney test for nonparametric continuous data, as appropriate. ROC curves were made of NT-proBNP and BNP levels. The area under the curve (AUC) presents the test accuracy, and the significance of the difference of both AUCs was estimated by a χ^2 test. Influences of age, gender, renin-angiotensin system blocker (ACE inhibitor or angiotensin-receptor blocker) and renal dysfunction on (NT-pro)BNP cut-off points were determined by

Table 2. Baseline characteristics of nursing home residents (n=103).

		CHF+ (%)	CHF- (%)	P value
Age (years), (mean, SD)	78±11	80±9	78±11	0.351
Male (%)	39 (38)	11 (46)	18 (35)	0.358
Immobile (wheelchair/bed) (%)	40 (39)	13 (54)	27 (34)	0.078
Medical history				
- Hypertension (%)	57 (55)	13 (54)	44 (49)	0.680
- CAD (%)	28 (27)	14 (58)	14 (18)	<0.001
- Rhythm disorder (%)	24 (23)	9 (38)	15 (19)	0.060
- Diabetes (%)	26 (25)	9 (38)	17 (22)	0.114
- PAD (%)	16 (16)	66 (25)	10 (13)	0.144
Medication				
- ACEi and ARB (%)	42 (41)	14 (58)	28 (35)	0.046
- Beta blockers (%)	24 (23)	7 (29)	17 (22)	0.438
- Calcium antagonists (%)	10 (10)	4 (17)	6 (8)	0.189
- Anticoagulants (%)	63 (61)	19 (78)	44 (53)	0.055
- Diuretics (%)	50 (49)	15 (62)	35 (44)	0.118
- Antidiabetes agents (%)	21 (20)	8 (33)	13 (16)	0.072
Major symptoms				
- Fatigue (%)	40 (39)	15 (52)	25 (32)	0.007
- Dyspnoea (%)	31 (30)	11 (45)	20 (25)	0.055
Physical examination				
- Raised JVP (%)	11 (11)	7 (29)	4 (5)	<0.001
- Cardiomegaly	22 (21)	10 (42)	12 (15)	0.006
- Murmur	24 (23)	9 (38)	25 (32)	0.587
- Third heart sound, gallop	20 (19)	9 (39)	11 (8)	0.010
- Rales	17 (17)	9 (40)	8 (8)	<0.001
- Hepatomegaly	4 (4)	1 (4)	3 (3)	0.935
- Oedema	40 (39)	15 (60)	35 (44)	0.116
Systolic BP (mmHg), mean, SD		143±27	140±20	0.534
Diastolic BP (mmHg), mean, SD		79±13	81±13	0.590
BMI, mean, SD	25±5	25±5	25±5	0.897
Electrocardiogram				
- Atrial fibrillation (%)	10 (10)	3 (13)	7 (8)	0.598
- Ischaemia (%)	24 (23)	2 (8)	3 (28)	0.365
- LVH (%)	32 (31)	16 (67)	16 (20)	<0.001
Laboratory				
- Haemoglobin, mean, SD	7.7±1	7.7±1	7.7±1	0.834
- GFR, median, SD	76±32	63±26	80±32	0.022
- NT-proBNP, median (IQR)	324 (163-1146)	1871 (539-4262)	239 (118-674)	<0.001
- BNP, median (IQR)	87 (28-187)	194 (92-460)	68 (20-123)	<0.001
Echocardiogram (median %, SD)	51±9	43±9	54±6	0.016

CAD=coronary artery diseases, PAD=peripheral artery disease, ACEi=angiotensin converting enzyme inhibitor, ARB=angiotensin II receptor blocker, anticoagulants=anticoagulants and antiplatelets, JVP=jugular venous pressure, BP=blood pressure, BMI=body mass index, LVH=left ventricular hypertrophy, GFR=glomerular filtration rate, NT-proBNP=N terminal-pro B-type natriuretic peptide, BNP=B-type natriuretic peptide, IQR=interquartile range, SD=standard deviation.

Table 3. Median NT-proBNP and BNP concentrations in residents with the diagnosis of chronic heart failure (CHF+) or no CHF (CHF-) before the screening versus residents with CHF or no CHF as established after the screening.

	CHF + Median (IQR) (n)	CHF – Median (IQR) (n)	P value
NT-proBNP			
- Before screening	552 (309-2477) (22)	241 (128-892) (81)	0.013
- After screening	1871 (539-4262) (24)	239 (118-674) (79)	<0.001
BNP			
- Before screening	92 (33-187) (22)	76 (23-187) (81)	0.270
- After screening	194 (92-460) (24)	68 (20-123) (79)	<0.001

IQR=interquartile range, n=number of subjects. Natriuretic peptides are in pg/ml. Medians of NT-proBNP in residents with and without CHF (CHF+ and CHF-) before the screening differed ($p=0.013$) while the medians of BNP in CHF+ and CHF- did not differ ($p=0.270$). After the screening, the medians of both NT-proBNP and BNP differed significantly (NT-proBNP in CHF+ 1871 and in CHF- 239, $p<0.001$, BNP in CHF+ 194 and in CHF- 68 pg/ml, $p<0.001$).

Mann-Whitney tests. All statistical comparisons were two-tailed, and a p value <0.05 was considered to be statistically significant.

Results

A total of 150 individuals were screened. Fourteen residents refused to participate, 30 were excluded because of cognitive impairment and aphasia. Three persons were excluded because of incomplete data (two poor-quality echocardiograms and one person refused the blood sample). The remaining 103 residents were all included. The mean age of the population was 79 ± 11 years.

The diagnosis of CHF had been made in 22 persons before the study. After the screening, 24 persons were found to have CHF and three groups were distinguished: subjects diagnosed with CHF before the screening whose diagnosis was confirmed afterwards (CHF confirmed), subjects diagnosed with CHF before the screening whose diagnosis was rejected afterwards (CHF rejected) and subjects not diagnosed with CHF before the screening but diagnosed with CHF after being screened (CHF de novo). Of the 24 people with CHF, nine had CHF confirmed and 15 had CHF de novo. In 13 subjects the diagnosis of CHF was rejected (table 1). The CHF prevalence was 23% (24/103).

Residents with CHF were more likely to have CAD, take a renin-angiotensin system blocker, complain of fatigue, have a raised JVP, have a cardiathoracic ratio of more than a half, have a third heart sound and or gallop rhythm, have pulmonary rales, have left ventricle hypertrophy, suffer more from renal dysfunction and from left ventricular dysfunction (table 2).

Residents in whom the diagnosis of CHF was made after the screening compared with those without CHF had NT-proBNP medians of 1871 and 239 pg/ml ($p<0.001$), respectively, and BNP medians of 194 and 68 pg/ml ($p<0.001$). Residents with CHF diagnosed before the screening compared with those without CHF had NT-proBNP medians of 552 and 241

pg/ml ($p=0.013$) and BNP medians of 92 and 76 pg/ml respectively ($p=0.270$) (table 3).

The predictive values of the two neurohormones presented by the AUC of NT-proBNP (0.815) and of BNP (0.758) did not differ significantly ($p=0.234$) as is shown in figure 1. Table 4 presents the sensitivity, specificity, and positive and negative predictive values at several cut-offs points of NT-proBNP and BNP. In search of threshold values with the best combination of excluding and including CHF, threshold values of NT-proBNP at 450 pg/ml (sensitivity 0.71, specificity 0.67, positive and negative predictive values of 0.42 and 0.91) and of BNP at 100 pg/ml (sensitivity 0.71, specificity 0.70, positive and negative predictive values

Figure 1. Receiver operating characteristics curve (ROC) showing the relationship between sensitivity (true positive) and specificity (true negative) in determining the predictive value of B-type natriuretic peptide (BNP) and N-terminal- proBNP (NT-proBNP) for chronic heart failure (CHF). The P-value refers to the comparison of the areas under the curve of the two neurohormones (not significant).

Table 4. N-terminal-pro B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) cut-off values with positive and negative predictive values (PPV and NPV).

Cut-off pg/ml	Sensitivity	Specificity	PPV	NPV
NT-proBNP 450	0.71	0.67	0.42	0.91
NT-proBNP 900	0.67	0.85	0.56	0.89
NT-proBNP 1350	0.58	0.86	0.56	0.86
NT-proBNP 1800	0.46	0.94	0.69	0.85
Cut-off pg/ml	Sensitivity	Specificity	PPV	NPV
BNP 50	0.88	0.63	0.42	0.94
BNP 100	0.71	0.70	0.42	0.89
BNP 150	0.54	0.79	0.43	0.85
BNP 200	0.50	0.87	0.57	0.85

PPV=positive predictive value, NPV=negative predictive value.

of 0.42 and 0.89 respectively) were found. Both BNP and NT-proBNP were influenced by renal function and estimated in subjects with GFR >75 ml/min and <75 ml/min: NT-proBNP medians and IQRs were 224 (19-7309) compared with 324 (163-1146) pg/ml ($p=0.005$), BNP medians and IQRs were 66 (0-110) compared with 86 (28-187) pg/ml ($p=0.004$) respectively. BNP and NT-proBNP were influenced significantly by age and renal dysfunction (age and BNP $Z=-2.220$, $p=0.026$; renal dysfunction and BNP $Z=-2.824$, $p=0.045$; age and NT-proBNP $Z=-4.196$, $p=0.000$; renal dysfunction and NT-proBNP $Z=-2.82$, $p=0.000$). NT-proBNP and BNP cut-off points were not significantly influenced by gender nor by use of renin-angiotensin blockers.

Discussion

In this nursing home study, CHF was present in almost one quarter of the residents. We found that in the majority of these residents the diagnosis of CHF had not been made previously. In addition, there were several residents who had been diagnosed with CHF before the screening, whose diagnosis had to be rejected after careful examination. Blinded values of both BNP and NT-proBNP differed significantly between residents who were diagnosed with CHF and those whose previous CHF diagnosis was rejected. In initial screening, NT-proBNP, and to a lesser extent BNP, were moderately accurate in predicting the presence of CHF.

The prevalence of 23% in this nursing home cohort is roughly twice as high as the prevalence of CHF in the general population, but it is in line with another nursing home population and with a population of 70 years and over.¹¹⁻¹³

Both undetected diagnoses and incorrect diagnoses of CHF were expected, but they greatly exceeded our expectations. Reasons for an incorrect diagnosis of CHF were a history of atrial fibrillation (5 cases) and the coexistence of COPD (3 cases). COPD as a reason for misdiagnosis has already been described by Rutten.¹⁴ In addition, the majority of individuals with rejected

CHF had NYHA class I and II (12/13) and one had class III. Eleven out of 15 cases of CHF de novo may have been overlooked because of mild symptoms (7 NYHA class I and 4 class II). The four other subjects with CHF de novo with NYHA class III and IV were missed because multiple comorbidity confused their symptoms of cardiovascular origin. Thus, both incorrect CHF diagnoses and undetected CHF diagnoses seemed to have been caused by the existence of comorbidity. The unspecific clinical presentation of elderly people and the unspecificity of the diagnostic tools add to the number of misdiagnoses.

Moreover, this study shows that thorough physical examination in combination with echocardiography can improve the accuracy of CHF diagnostics. In addition, natriuretic peptides can improve the CHF diagnostics if added to the usual diagnostic procedure, even without cardiac ultrasound.

Failures of the expert panel are possible but unlikely, since the standard diagnostic tests were performed, and the panel existed of specialised heart failure cardiologists. In addition, NT-proBNP and BNP levels supported both undetected diagnoses and incorrect CHF diagnoses.

Both NT-proBNP and BNP were moderately accurate in predicting CHF. However, depending on the cut-offs, the CHF diagnosis will still be missed in a substantial number of residents. And, one should realise that (NT-pro)BNP levels will increase not only with CHF but also in conditions such as high age and renal dysfunction. So, the use of natriuretic peptides alone will not be sufficient for an adequate diagnosis, although the results have been significantly improved when compared with the baseline situation, especially for physicians not specialised in cardiology.¹⁵ If natriuretic peptides are used as an initial test, we suggest NT-proBNP and BNP cut-offs of 450 and 50 pg/ml, respectively, for excluding CHF, and 900 and 200 pg/ml for establishing CHF. When values are within the cut-off values, a regular assessment should be performed. The NT-proBNP cut-off of 450 pg/ml is suggested as an age specific cut-off point. The BNP

cut-off of 50 pg/ml is lower than in other studies where 100 pg/ml is proposed. NT-proBNP and BNP were influenced by age and renal dysfunction in accordance with other studies.¹⁶⁻¹⁹ In contrast with other studies, they were not influenced by gender nor by the use of renin-angiotensin system blockers.²⁰⁻²²

A limitation of the study is the small population of 103 nursing home residents, in one centre, which could lead to a selection bias in arriving at the prevalence of CHF of 23%. On the other hand, our prevalence of chronic heart failure is in line with the prevalence in other nursing home residents and in the elderly.^{12,23,24} Moreover, the population studied is representative of other nursing home populations in terms of distribution of gender, age, diabetes and the use of ACE inhibitor therapy, although not representative in terms of the presence of hypertension and renal dysfunction.^{24,25} Furthermore, despite good criteria, setting the diagnosis of CHF remains difficult because of the lack of diagnostic accuracy of physical examination and the lack of easy access to echocardiography.

Conclusion

At present the overall accuracy of the diagnosis CHF is limited. In this study undetected diagnoses and incorrect diagnoses on CHF were observed in a large number of residents. Moreover, the study shows that a more thorough investigation of residents on CHF will lead to more accurate diagnostics, which in turn will improve residents' quality of life.

The use of NT-proBNP and BNP as additional diagnostic instruments is promising also in nursing home residents but needs further evaluation. The CHF prevalence in care-dependent elderly people was almost 25%, which is twice as much as in old people living independently.

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