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Amino-Terminal Pro-B-Type Natriuretic Peptide and B-Type Natriuretic Peptide in the General Community Determinants and Detection of Left Ventricular Dysfunction

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Abstract

OBJECTIVES—This study sought to characterize factors influencing amino-terminal pro-B-type natriuretic peptide (NT-proBNP) and to evaluate the ability of NT-proBNP to detect left ventricular (LV) dysfunction in a large community sample.

BACKGROUND—Secretion of BNP increases in cardiac disease, making BNP an attractive biomarker. Amino-terminal proBNP, a fragment of the BNP prohormone, is a new biomarker. We evaluated factors influencing NT-proBNP in normal patients and compared the ability of NT-proBNP and BNP to detect LV dysfunction in a large community sample.

METHODS—Amino-terminal pro-BNP was determined in plasma samples of a previously reported and clinically and echocardiographically characterized random sample (n = 1,869, age ≥ 45 years) of Olmsted County, Minnesota.

RESULTS—In normal patients (n = 746), female gender and older age were the strongest independent predictors of higher NT-proBNP. Test characteristics for detecting an LV ejection fraction ≤ 40% or ≤ 50% were determined in the total sample with receiver operating characteristic curves. Amino-terminal pro-BNP had significantly higher areas under the curve for detecting an LV ejection fraction ≤ 40% or ≤ 50% than BNP in the total population and in several male and age subgroups, whereas areas were equivalent in female subgroups. Age- and gender-adjusted cutpoints improved test characteristics of NT-proBNP. Both assays detected patients with systolic and/or moderate to severe diastolic dysfunction to a similar degree, which was less robust than the detection of LV systolic dysfunction alone.

CONCLUSIONS—Amino-terminal pro-BNP in normal patients is affected primarily by gender and age, which should be considered when interpreting values. Importantly, in the entire population

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sample NT-proBNP performed at least equivalently to BNP in detecting LV dysfunction and was superior in some subgroups in detecting LV systolic dysfunction.

Brain natriuretic peptide (BNP) is secreted from the heart primarily in response to stretch, and its plasma levels increase in heart failure (HF), in which it aids in diagnosis and management (1). We recently reported that age, gender, and left atrial (LA) volume index were independently associated with BNP in normal patients identified from a random sample of residents in Olmsted County, Minnesota, suggesting that age and gender be considered when developing partition values (2). We also reported that BNP detected an ejection fraction (EF) ≤ 40% in each age and gender stratum of the random sample with good sensitivity and specificity. However, its use as a screening tool for the general population to identify preclinical left ventricular (LV) dysfunction remains to be established (2,3). Other investigators examined the effects of clinical factors influencing BNP, such as heart rate (HR), obesity (4,5), renal function (6,7), and medications such as beta blockers (8) and hormone replacement therapy (2).

Amino-terminal pro-BNP (NT-proBNP), the physiologically inactive 1–76 amino acid fragment that is secreted with mature 32-amino acid BNP after cleavage from the prohormone, is an additional biomarker for HF (9–15). With a longer plasma half-life, NT-proBNP may behave differently than BNP (16,17). Multiple factors seem to influence NT-proBNP, especially age and gender (13,18). Importantly, studies are limited that provide an in-depth comparison of NT-proBNP and BNP in detecting left ventricular systolic dysfunction (LVSD) using a large population-based random sample that has been characterized for LVSD and diastolic dysfunction (DD) by detailed echocardiograms (14,19–25).

Natriuretic peptide secretion may increase with DD, and studies have suggested that BNP is increased with LV hypertrophy or increased LV filling pressures (26–28). Another study that excluded patients with systolic dysfunction reported that BNP may detect DD (29). We reported that BNP may be suboptimal for screening the general population for DD (3). To the best of our knowledge, there are no studies comparing NT-proBNP and BNP with regard to detecting either DD and/or LVSD in a large random sample of the general population.

Using our large, well-characterized random sample of residents in Olmsted County, Minnesota, we sought to identify factors that influenced NT-proBNP and to establish reference ranges for normal people. In the total population sample, we also compared the test characteristics of NT-proBNP and BNP in detecting an EF ≤ 40%, an EF ≤ 50%, and either LVSD or DD. We hypothesized that NT-proBNP would be influenced by factors similar to those that influence BNP and that NT-proBNP is at least as good a diagnostic marker for LV dysfunction as BNP.

METHODS

The Mayo Institutional Review Board approved this study.

Study population

Medical records review and detailed two-dimensional and color Doppler echocardiography were done on participating residents (n = 2,042, age ≥ 45 years) of Olmsted County, Minnesota, and were previously reported (2), as was DD in this population, which was classified as mild, moderate, and severe (3,30). Patients were considered clinically normal when they had no history of cardiovascular, pulmonary, or renal disease; had no diabetes; took no cardiovascular medications; had normal echocardiograms for systolic and diastolic function; and were in normal sinus rhythm (2). Participants with LV dysfunction but without a chart history of HF were considered as having preclinical LV dysfunction (3,31).

Assays

B-type natriuretic peptide was measured by immunoassay (Biosite) as previously reported (2). Plasma NT-proBNP was measured with the Elecsys proBNP electrochemiluminescence immunoassay run on the Elecsys 2010 (Roche Diagnostics, Indianapolis, Indiana). This sandwich assay uses two different polyclonal antibodies, one to amino acids 1 to 21 and one to amino acids 39 to 50. The lower limit of detection is 5 pg/ml with inter-assay and intra-assay variabilities of 3.1% and 2.5%, respectively.

Influence of clinical characteristics

Influences on NT-proBNP were assessed with univariate and multivariate analysis for age, gender, body mass index (BMI), HR, LA volume index, LV mass index, LV volume index, systolic and diastolic blood pressure, serum creatinine, and calculated glomerular filtration rate (GFR; by Cockcroft-Gault formula).

Detection of LV dysfunction

The abilities of NT-proBNP and BNP to identify EF ≤ 40%, EF ≤ 50%, and LVSD or DD were determined for the total population and for age/gender-specific strata.

Statistical methods

Because the variability of NT-proBNP increased with its mean level, the natural log transformation was used in the regression analyses to satisfy modeling assumptions. Nomograms based on age and gender were established using the least-squares regression fit of log-transformed NT-proBNP with age and gender as predictor variables. From the fitted model, the 5th, 50th, and 95th percentiles were estimated and back-transformed to the natural scale. An interaction term with age and gender was also evaluated to determine whether the association of age with NT-proBNP differed between the genders. The Spearman correlation coefficient was used to investigate the influence of patient characteristics on NT-proBNP levels in univariate analysis. Linear least-squares regression with stepwise selection was used to identify those characteristics that independently predicted NT-proBNP levels. Diagnostic abilities of NT-proBNP or BNP were evaluated using receiver-operating characteristic (ROC) curves. The method described by DeLong et al. (32) was used to compare areas under the curve (AUCs) obtained from paired assays. The optimal discriminatory value for each assay was estimated by the point along the ROC curve that provided the minimum Euclidean distance between that of a perfect assay with 100% sensitivity and specificity. The positive likelihood ratio (+LR = sensitivity/[1 − specificity]) and negative likelihood ratio (−LR = [1 − sensitivity]/specificity) were calculated for the optimal discriminatory values. Statistical significance was accepted at $p \leq 0.05$.

RESULTS

Table 1 provides characteristics of the participating patients.

Effect of clinical characteristics on NT-proBNP

The NT-proBNP values were available for 1,869 patients, of whom 746 were clinically normal. Table 2 reports age- and gender-specific NT-proBNP. Table 3 summarizes the multivariate analysis and gives the relative effect of these different clinical variables on NT-proBNP in the normal subgroup as well as for the total population and the abnormal subgroup.

In univariate analysis (supplemental Tables 1 and 2 available online), increasing age, calculated GFR (which accounts for age), LA volume index, LV dimension index, and gender had the highest correlation coefficients with NT-proBNP in the normal subgroup. Correlations were

significant but weak for systolic and diastolic blood pressure, BMI, and HR. In the multivariate analysis for normal patients, female gender and age were the strongest independent predictors of higher NT-proBNP, with LA volume index, LV dimension index, and HR contributing only slightly. When the multivariate analysis was performed in the abnormal subgroup and in the total population, serum creatinine, BMI, calculated GFR, and LV mass were also found to affect independently NT-proBNP.

When adjusted for age and gender in a multivariate analysis, BMI had no significant effect on NT-proBNP in the normal population (regression coefficient, −0.01; p = 0.09). Even when analyzed in BMI categories and adjusted for age and gender, there was still no effect in the normal patients (BMI < 25 kg/m^2: 0.0007, p = 0.98; 25 ≤ BMI< 30 kg/m^2: 0.032, p = 0.37; BMI ≥ 30 kg/m^2: −0.002, p = 0.89). Multivariate analysis in the abnormal population showed that BMI inversely but minimally affects NT-proBNP (−0.015, p = 0.012). Analyzing this group in BMI categories in an age- and gender-adjusted model found that BMI affected non-overweight patients (BMI < 25 kg/m^2: − 0.09, p = 0.007) but not individuals with increased BMI (25 kg/m^2 ≤ BMI < 30 kg/m^2: −0.05, p = 0.17; BMI ≥ 30 kg/m^2: 0.012, p = 0.35). In multivariate analysis of the total population (normal and abnormal combined), the effect of BMI was inverse but minimal (−0.012, p = 0.01).

Impact of estrogen and beta-blockers

By univariate analysis, use of estrogen influenced NT-proBNP in normal patients (p < 0.0001), but after accounting for age and gender it contributed only 3.4% to the model r^2 (p = 0.0152). In the total population, use of beta-blockers was significant by univariate analysis (p < 0.0001), but contributed only 0.9% of the model r^2 (p = 0.0017) after adjusting for age, gender, and cardiac conditions in which beta-blockers are frequently used.

Detection of LVSD

Both NT-proBNP and BNP were available for 1,869 patients. Of these, 37 had an EF ≤ 40% and 115 had an EF ≤ 50%. Of note, 45.9% of those with an EF ≤ 40% had preclinical LV dysfunction. Table 4 summarizes the estimated AUC, sensitivity and specificity for NT-proBNP and BNP for the total sample and for age- and gender-specific strata. For detecting an EF ≤ 40%, NT-proBNP had a significantly higher AUC in comparison with BNP in the total population and for the subgroups of male patients and patients ≥ 65 years old. For detecting an EF ≤ 50%, the AUC for NT-proBNP was significantly higher than that for BNP in all patients, patients ≥ 65 years old, patients < 65 years old, male patients, male patients ≥ 65 years old, male patients < 65 years old, and female patients < 65 years old. There was a tendency for better detection of an EF ≤ 50% in female patients overall (p = 0.09). Figures 1A through 1D depict the ROC curves of NT-proBNP and BNP in detecting an EF ≤ 40% for all, age >65 years old, male patients, and female patients, respectively.

To better understand the implications for screening the general population for early LVSD with NT-proBNP as opposed to BNP, we calculated further test characteristics based on the optimal age- and gender-specific cutpoints. Table 5 shows +LR and −LR, the percentage of patients screened who would need echocardiography secondary to an abnormal test result, the percent of echocardiograms that would be negative, the percent of those with a reduced EF who would be missed, and the odds ratio for NT-proBNP and BNP. Comparison of the odds ratio for the two assays for detecting an EF ≤40% suggests that NT-proBNP may be superior to BNP for screening certain subgroups, especially male patients and elderly patients. For female patients, the two assays perform equivalently.

Developing age- and gender-specific reference ranges

Given that age and gender had the greatest impact on NT-proBNP concentrations, age- and gender-specific partition values should help to improve specificity of NT-proBNP as a screening tool. Table 6 provides cutpoints based on discriminatory values derived from the ROC curves. For younger women (ages 45 to 54 years), no systolic dysfunction was noted in our population and hence no discriminatory values are given. Table 7 reports NT-proBNP test characteristics for the total, male-only, and female-only populations for the detection of an EF ≤40% when using a single optimal cutpoint for the respective population as compared with using optimal age- and gender-adjusted cutpoints. For this analysis, women younger than 65 years of age were treated as a single stratum because of the absence of an EF ≤40% in women younger than 55 years old. Age- and gender-adjusted cutpoints improved the test characteristics as compared with a single cutpoint.

Detection of combined LVSD and moderate to severe DD

Results for both assays and evaluations for LVSD and DD were available for 1,866 patients. Of these, 129 had an EF ≤40% and/or moderate to severe DD, and 204 had an EF ≤50% and/or moderate to severe DD. In this community sample, neither assay seemed superior in detecting LV dysfunction defined as LVSD or DD (see online supplement). In most strata, the AUC decreased as compared with detecting LVSD only.

DISCUSSION

We report that age and gender were the major factors influencing NT-proBNP plasma concentrations in normal patients and conclude that age and gender should be considered when establishing normal ranges. The NT-proBNP was at least as effective as BNP in detecting LVSD, and in some subgroups it was superior. Using age- and gender-adjusted cutpoints improved the test characteristics of NT-proBNP. Both NT-proBNP and BNP lost sensitivity and specificity when used to detect LV dysfunction defined as LVSD or DD, with neither assay outperforming the other.

Impact of clinical factors on NT-proBNP

In normal patients, NT-proBNP, like BNP, tends to be higher in female patients and older individuals. Reasons for this elevation with age and female gender remain unclear. Kawai et al. (33) and others have suggested a reduction in the clearance receptor for BNP with aging (33–36). Alternatively, increased production with age could explain the findings. Regarding gender, hormone replacement therapy was associated with higher BNP levels in women, suggesting that estrogen status may be partly responsible (2). In addition, as with BNP, LA volume index and LV dimension index had slight, independent associations with NT-proBNP in normal patients, reflecting atrial as well as ventricular production (37–40).

We found no independent correlation between serum creatinine or calculated GFR and NT-proBNP in normal patients. Because NT-proBNP does not have a clearance receptor (41), some suggested that clearance for NT-proBNP may be renal and influenced by renal function (42). Others have reported no interdependence between renal impairment and elevated NT-proBNP (43). Our data suggest that the impact is minor if the degree of renal dysfunction is small and if factors such as age and gender are considered.

Regarding obesity, when normal patients, abnormal patients, and the total population were analyzed separately, the impact of BMI on NT-proBNP values was minimal in comparison with the effects of age and gender. Wang et al. (44) reported a tendency for an inverse relationship between BNP and BMI in a non-obese, healthy subgroup of the Framingham Heart Study offspring cohort, and an inverse relationship in another study that included overweight

and obese patients (4). Similarly, BMI was an independent negative correlate of BNP in HF patients (5). Although BMI may negatively impact NT-proBNP, the degree is not as impressive as that of age and gender.

Amino-terminal pro-BNP in detection of LV dysfunction

Amino-terminal pro-BNP identified those with EF ≤40% with high sensitivity and specificity. When comparing ROC curves, NT-proBNP was superior or equal to BNP in detecting an EF ≤40%, especially for the entire study population, male patients, and persons ≥65 years of age. The number of women with an EF ≤40% in this population was small, and in general, no significant difference could be found between the two assays in the female subgroups. Given the small number of individuals with EF ≤40% in the subcategories of female patients < 65 years old, female patients ≥65 years old, all female patients combined, and male patients < 65 years old, one is cautious in reporting results in these groups. This is a limitation of using a general population sample rather than a selected diseased population. We also showed that age- and gender-adjusted cut-points further improved the test characteristics of NT-proBNP in detecting an EF ≤40%.

Using this population sample, we previously examined BNP as a screening test in patients with preclinical LV dysfunction. Considering the prevalence of preclinical LVSD or DD, screening with BNP for asymptomatic disease was considered suboptimal, requiring confirmatory echocardiography (3). Heidenreich et al. (45) reported that screening asymptomatic patients with BNP, followed by echocardiography in patients with an abnormal test result, increased lifetime cost of care and improved outcome for men but not women. Specifically, for populations with a reduced EF prevalence of ≥1%, this screening strategy may provide a health benefit at a cost comparable to or less than that of other accepted interventions (45). The cost-effectiveness of NT-proBNP for detecting a reduced EF remains to be determined.

Amino-terminal pro-BNP and BNP performed similarly for the detection of LV dysfunction of any type (systolic or diastolic), both losing sensitivity and specificity. This loss of sensitivity and specificity when DD is included may be reflective of the influence of chamber “stretch” (as seen in LVSD) as opposed to chamber stiffness or hypertrophy (as seen in DD). Thus, stretch may be more important with respect to stimulating secretion of natriuretic peptides.

Differences in NT-proBNP and BNP immunoassays

The immunochromatographic Biosite Triage BNP assay recognizes amino acids 1 through 32 of BNP and was approved as a point-of-care device (24). It correlates relatively well with the automated Roche NT-proBNP assay, although the results are not directly interchangeable (46). The NT-proBNP assay does not cross-react with BNP and is precise over a wide range (30 to 35,000 ng/l) (24). This precision may explain its higher efficacy for detecting reduced EF in selected groups compared with the Biosite BNP. Alternatively, the reported greater stability of NT-proBNP in plasma may be a factor. Also, NT-proBNP may have lower intraindividual and interindividual variation than Biosite BNP (47).

Perspective

Three smaller studies have compared BNP and NT-proBNP in detecting reduced EF in the general population or in cardiac patients. Hobbs et al. (25) reported that BNP and NT-proBNP detected 33 patients with LVSD equivalently in 591 prospective patients of the general population. In 339 patients hospitalized for angiography, Pfister et al. (14) reported similar AUCs for detecting LVSD for NT-proBNP and BNP. Seino et al. (48) reported that in 105 chronic HF patients and 67 normal patients, both NT-proBNP and BNP progressively increased in proportion to New York Heart Association functional class, with the increment being greater for NT-proBNP than BNP. The AUCs were similar for detecting an EF < 40%, but tended to

be greater for NT-proBNP for the detection of EF < 50%, suggesting that NT-proBNP may be a more discerning marker for HF detection than BNP.

Our studies benefited from a robust number of patients undergoing BNP, NT-proBNP, and comprehensive echocardiography, and support the conclusion that both BNP and NT-proBNP can detect reduced EF. In some subgroups, especially male patients and elderly patients, NT-proBNP may be superior to BNP in detecting LVSD. When applied to the identification of patients with LVSD and/or moderate to severe DD, there was a decrease or neutral effect on the test characteristics of both assays in all subgroups.

A limitation of this study is that because of the limited number of patients with a reduced EF, we did not differentiate between clinical HF and preclinical LV dysfunction for the screening analysis. Of note, the AUCs for detecting an EF ≤40% for NT-proBNP were similar if patients with known HF were excluded (all, 0.95; age ≥65 years, 0.91; age < 65 years, 0.98; male patients, 0.95; female patients, 0.98; male patients age ≥65 years, 0.91). A larger study is needed and seems warranted to determine more definitively the diagnostic characteristics of NT-proBNP.

In summary, gender and age were the major factors influencing NT-proBNP in normal patients, with other clinical factors only minimally contributing. We conclude that in this community sample of patients ≥45 years old, NT-proBNP detects an EF ≤40% with good sensitivity and specificity and has a performance that is superior or equivalent to that of BNP. The test characteristics of NT-proBNP are further improved when age- and gender-adjusted cutoffs are used.

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Abbreviations and Acronyms

AUC
: area under the curve

BMI
: body mass index

BNP
: B-type natriuretic peptide/brain natriuretic peptide

DD
: diastolic dysfunction

EF
: ejection fraction

GFR
: glomerular filtration rate

HF
: heart failure

HR
: heart rate

NT-proBNP
: amino-terminal pro-B-type natriuretic peptide

LA
: left atrial

LR
: likelihood ratio

LV
: left ventricular

LVSD
: left ventricular systolic dysfunction

ROC
: receiver-operating characteristic

APPENDIX

For Supplemental Tables 1 and 2, please see the online version of this article.

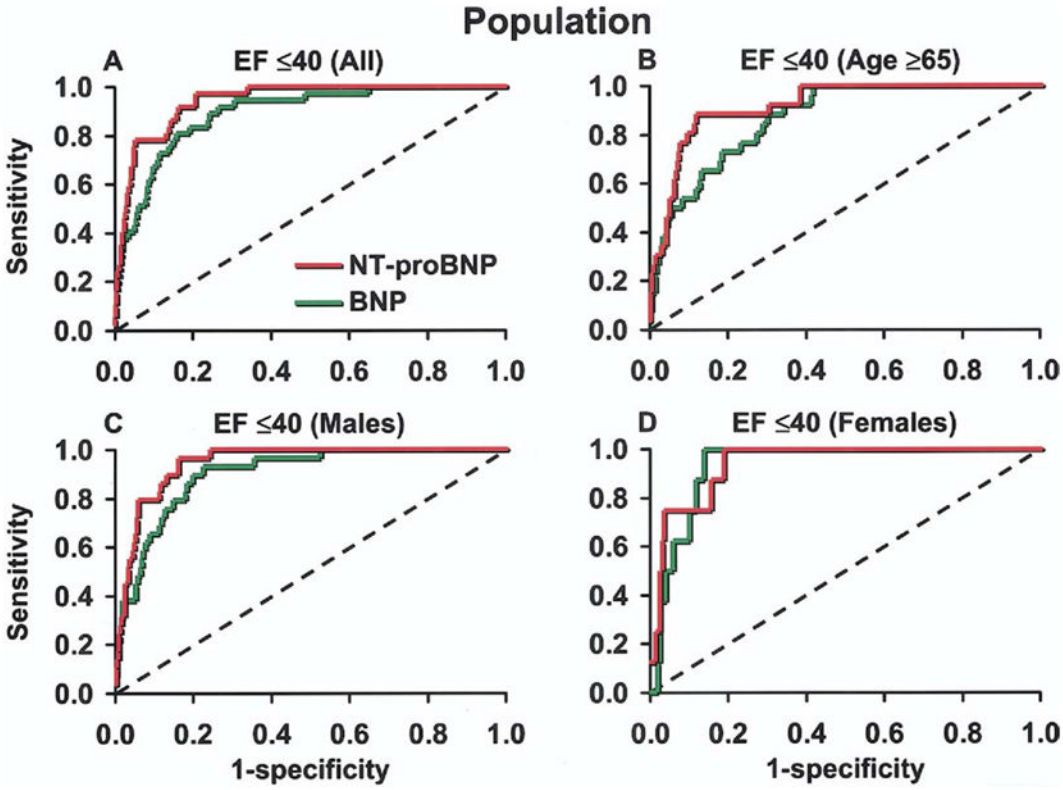

Figure 1.

The receiver operating characteristic (ROC) curves of amino-terminal pro-B-type natriuretic peptide (NT-proBNP) **(red)** and BNP **(green)** for detecting an ejection fraction (EF) ≤40% for the entire population (all) **(A)**, patients ≥65 years old **(B)**, male patients **(C)**, and female patients **(D)**.

Table 1
Characteristics of the Total Study Population and Subgroups

	Total Population (n = 1,869)	Normal Patients (n = 746)	Patients With EF ≤ 40% (n = 37)
Patient gender			
Male, %	48.0	47.2	78.4
Female, %	52.0	52.8	21.6
Age, yrs, mean ± SD (range)	62 ± 10 (45–96)	57 ± 9 (45–96)	71 ± 11 (50–89)
Age categories			
45–54 yrs, %	29.4	47.8	10.8
55–64 yrs, %	30.3	32.6	18.9
65–74 yrs, %	25.6	14.9	35.1
75+ yrs, %	14.7	4.7	35.1
Diabetes, %	7.8	0	16.2
Past or current atrial fibrillation, %	4.7	0	37.8
Coronary artery disease, %	12.4	0	64.9
Past heart failure diagnosis, %	2.2	0	54.1
Hypertension, %	37.1	0	64.9
Obesity, BMI > 30 kg/m^2, %	32.2	21.2	54.1

BMI = body mass index; EF = ejection fraction; SD = standard deviation.

Table 2

Age- and Gender-Specific Ranges (5th to 95th Percentiles) for Plasma NT-proBNP (pg/ml) in Normal Patients

NT-proBNP	Age 45–54 yrs Median (5th–95th Percentile) N	Age 55–64 yrs Median (5th–95th Percentile) N	Age 65–74 yrs Median (5th–95th Percentile) N	Age 75–96 yrs Median (5th–95th Percentile) N
Women	54 (8–141)	77 (17–226)	114 (25–458)	124 (42–587)
	190	137	57	18
Men	13 (5–87)	25 (5–88)	45 (14–140)	57 (46–68)*
	187	114	41	2

*Because n = 2, actual values are given for reference only.

NT-proBNP = amino-terminal pro-B-type natriuretic peptide.

Table 3

Parameters That Significantly Contributed to NT-proBNP Values in Multivariate Analysis

Parameters Included in the Model	Regression Coefficient	Standard Error	Partial r^2	p Value
Normal population				
Female gender	1.098	0.082	0.296	< 0.0001
Age	0.041	0.005	0.077	< 0.0001
LA volume index	0.029	0.007	0.025	< 0.0001
LV dimension index	0.373	0.146	0.009	0.0109
Heart rate	−0.009	0.004	0.005	0.0223
Total population				
Age	0.052	0.003	0.296	< 0.0001
LA volume index	0.041	0.003	0.077	< 0.0001
Female gender	1.176	0.076	0.071	< 0.0001
Serum creatinine	1.167	0.159	0.018	< 0.0001
LV dimension index	0.441	0.107	0.016	< 0.0001
GFR	0.004	0.001	0.003	0.0025
BMI	−0.029	0.008	0.003	< 0.0001
LV mass	0.002	0.000	0.003	0.0012
Abnormal population				
Age	0.047	0.004	0.276	< 0.0001
LA volume index	0.041	0.004	0.074	< 0.0001
Female gender	1.057	0.095	0.055	< 0.0001
Serum creatinine	1.409	0.184	0.036	< 0.0001
LV dimension index	0.385	0.132	0.019	0.0035
BMI	−0.035	0.009	0.006	0.0002
GFR	0.004	0.002	0.004	0.0089
LV mass	0.003	0.000	0.003	0.0026

Parameters included in the model that were not significant in any of the subgroups were systolic and diastolic blood pressure. The NT-proBNP values were log-transformed for this analysis.

BMI = body mass index; GFR = glomerular filtration rate; LA = left atrial; LV = left ventricular; NT-proBNP = amino-terminal pro-B-type natriuretic peptide.

Table 4

Test Characteristics for NT-proBNP and BNP for the Detection of Left Ventricular Systolic Dysfunction in the Total Population and Subgroups

				NT-proBNP				BNP			
Population	**EF**	**n**	**p***	**AUC**	**Cutpoint†**	**Sens**	**Spec**	**AUC**	**Cutpoint†**	**Sens**	**Spec**
All (n = 1,869)	≤ 40	37	0.0087	0.94	228	86.5	86.0	0.89	66	81.1	81.1
	≤50	115	< 0.0001	0.78	129	73.9	73.8	0.72	40	68.7	68.7
Age ≥65 yrs (n = 747)	≤40	26	0.0360	0.92	452	88.5	88.4	0.87	97	76.9	76.9
	≤50	70	0.0011	0.85	233	75.7	75.7	0.79	73	71.4	71.4
Age <65 yrs (n = 1,122)	≤40	11	0.0912	0.96	163	90.9	90.9	0.88	42	81.8	81.8
	≤50	45	< 0.0001	0.65	59	62.2	61.3	0.56	19	55.6	55.5
All men (n = 907)	≤40	29	0.0152	0.95	209	86.2	87.4	0.91	55	82.8	82.4
	≤50	85	< 0.0001	0.80	92	75.3	74.8	0.73	28	70.6	70.2
All women (n = 962)	≤40	8‡	0.8107	0.91	372	83.3	83.3	0.94	102	87.5	87.5
	≤50	30	0.0908	0.83	246	75.0	73.1	0.77	57	73.3	73.3
Men, age ≥65 yrs (n = 350)	≤40	20	0.0718	0.93	462	85.7	88.0	0.89	79	75.0	75.9
	≤50	50	0.0036	0.88	211	79.2	79.4	0.82	61	72.0	72.1
Women, age ≥65 yrs (n = 397)	≤40	6‡	0.5178	0.91	372	83.3	83.3	0.88	124	83.3	81.0
	≤50	20	0.1867	0.83	246	75.0	73.1	0.78	79	70.0	69.7
Men, age < 65 yrs (n = 557)	≤40	9‡	0.0921	0.97	109	88.9	90.0	0.90	24	77.8	77.7
	≤50	35	0.0002	0.69	32	62.9	62.8	0.58	12	57.1	56.7
Women, age < 65 yrs (n = 565)	≤40	2‡	0.3627	0.97	245	100	94.3	0.98	108	100	96.4
	≤50	10	0.0278	0.75	105	70.0	69.9	0.64	30	60.0	60.0

*p for comparison of AUCs for NT-proBNP and BNP.

†The NT-proBNP or BNP concentration (pg/ml) resulting in a sensitivity and specificity closest to 100%.

‡Note the limited number of subjects with EF ≤40% in this subgroup.

AUC = area under the curve; EF = ejection fraction; NT-proBNP = amino-terminal pro-B-type natriuretic peptide; Sens = sensitivity; Spec = specificity.

Table 5

Test Characteristics for NT-proBNP and BNP for the Detection of Systolic Dysfunction in the Total Population and Subgroups

Population	EF	+LR*	−LR*	% Screened Needing Echocardiogram*	% Echocardiograms That Are Negative*	% With Disease Missed*	Odds Ratio*
All	≤40	6.2/4.3	0.16/0.23	15.4/20.1	88.9/92.0	13.5/18.9	39.4/18.4
	≤50	2.8/2.2	0.35/0.46	29.1/33.6	84.4/87.4	26.1/31.3	8.0/4.8
Age ≥65 yrs	≤40	7.6/3.3	0.13/0.30	12.7/23.9	89.8/95.3	11.5/23.1	58.6/11.1
	≤50	3.1/2.5	0.32/0.40	29.1/32.6	75.6/79.5	24.3/28.6	9.7/6.2
Age < 65 yrs	≤40	10.0/4.5	0.10/0.22	11.0/19.7	80.8/90.4	9.1/18.2	99.8/20.2
	≤50	1.6/1.2	0.62/0.80	39.6/44.9	93.7/95.0	37.8/44.4	2.6/1.6
All men	≤40	6.8/4.7	0.16/0.21	15.0/19.7	81.6/86.6	13.8/17.2	43.3/22.5
	≤50	3.0/2.4	0.33/0.42	29.9/33.6	76.4/80.3	24.7/29.4	9.0/5.7
All women	≤40	5.0/7.0	0.20/0.14	17.3/13.1	96.0/94.5	16.7/12.5	24.9/49.0
	≤50	2.8/2.7	0.34/0.36	28.4/28.2	91.8/91.9	25.0/26.7	8.2/7.5
Men, age ≥65 yrs	≤40	7.1/3.1	0.16/0.33	16.2/27.0	69.8/84.1	14.3/25.0	43.9/9.4
	≤50	3.8/2.6	0.26/0.39	29.0/34.2	60.9/69.9	20.8/28.0	14.7/6.6
Women, age ≥65 yrs	≤40	5.0/4.4	0.20/0.20	17.7/20.0	92.9/93.7	16.7/16.7	24.9/21.3
	≤50	2.8/2.3	0.34/0.43	29.3/32.3	87.1/89.0	25.0/30.0	8.2/5.4
Men, age < 65 yrs	≤40	8.9/3.5	0.12/0.29	11.3/23.2	87.3/94.6	11.1/22.2	72.1/12.2
	≤50	1.7/1.3	0.59/0.76	38.8/44.2	89.8/91.9	37.1/42.9	2.9/1.7
Women, age < 65 yrs	≤40	17.5/27.8	0/0	6.0/3.9	94.1/91.0	0/0	–/–
	≤50	2.3/1.5	0.43/0.67	30.8/40.4	95.8/97.4	30.0/40.0	5.4/2.3

* NT-proBNP/BNP.

EF = ejection fraction; +LR = positive likelihood ratio; −LR = negative likelihood ratio.

Table 6

NT-proBNP Cutpoints, Sensitivity, and Specificity for Age and Gender Strata for the Detection of an Ejection Fraction ≤ 40%

	Men			Women		
Age	**NT-proBNP**	**Sens**	**Spec**	**NT-proBNP**	**Sens**	**Spec**
45–54 yrs	108	100	96	ND	ND	ND
55–64 yrs	234	100	94	246	100	90
65–74 yrs	462	91	94	773	100	98
≥75 yrs	1,024	89	84	879	75	86

Cutpoints are based on optimal discriminatory value obtained from stratum-specific ROC curves.

ND = not determined; NT-proBNP = amino-terminal pro-B-type natriuretic peptide; Sens = sensitivity; Spec = specificity.

Table 7

Test Characteristics*

	Prevalence	NT-proBNP Partition Value	Sensitivity %	Specificity %	% Screened Needing Echocardiogram	% Echocardiograms That Are Negative	% With Missed Disease	+LR	−LR	Odds Ratio
Unadjusted										
Population	2.0	228	86.5	86.0	15.4	88.9	13.5	6.2	0.16	39
Male only	3.2	209	86.2	87.4	15.0	81.6	13.8	6.8	0.16	43
Female only	0.8	372	83.3	83.3	17.3	96.0	16.7	5.0	0.20	25
Adjusted										
Population	2.0	Variable	91.9	93.6	8.1	77.5	8.1	14.4	0.09	166
Male only	3.2	Variable	93.1	93.4	9.4	68.2	6.9	14.1	0.07	190
Female only	0.8	Variable	87.5	93.8	6.9	89.4	12.5	14.1	0.13	106

* Characteristics for the total population, male patients only, and female patients only for strategies based on a single NT-proBNP cutpoint (unadjusted) or a variable age- and gender-adjusted NT-proBNP cutpoint. +LR = positive likelihood ratio; −LR = negative likelihood ratio; NT-proBNP = amino-terminal pro-B-type natriuretic peptide.