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Community Screening for Left Ventricular Systolic Dysfunction Using Plasma and Urinary Natriuretic Peptides

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OBJECTIVES We sought to compare urinary and plasma N-terminal pro-brain natriuretic peptide (N-BNP) in left ventricular systolic dysfunction (LVSD) diagnosis.

BACKGROUND Plasma N-BNP is elevated in LVSD. Renal tubule cells produce BNP. We tested the incremental value of urinary N-BNP in LVSD diagnosis.

METHODS In this prospective, community-screening study of undiagnosed LVSD, 1,360 subjects (45 to 80 years of age) were invited, and 1,308 had analyzable echocardiographic scans and urine and plasma specimens. The criterion standard for LVSD was defined as a wall motion score over 1.8 (ejection fraction ≤40%).

RESULTS Twenty-eight patients with LVSD had elevated urinary and plasma N-BNP levels compared with normal subjects ($p < 0.0005$). Receiver-operating characteristic (ROC) areas under the curve (AUCs) for urinary and plasma N-BNP were 0.831 and 0.840, respectively. Both tests had high negative predictive values (>99%) for excluding LVSD. Urinary N-BNP was more specific (67.2%) than plasma N-BNP (41%). The plasma/urinary N-BNP product yielded a higher ROC-AUC (0.923) and specificity (78%), reducing the number of cases to scan to detect one case of LVSD to 11.4 (compared with 16.6 [urinary N-BNP] and 29.0 [plasma N-BNP]). Sequential application of tests (urinary N-BNP, then plasma N-BNP in the urine-"positive" cases) achieved similar reductions in the number of cases to scan (10.8), while limiting the number of N-BNP tests to be performed. Urinary N-BNP performed poorly in detection of other cardiac abnormalities with preserved systolic function. It was less costly to test urinary N-BNP in the whole population as compared with other strategies, including scanning high-risk cases with N-BNP testing in the remainder.

CONCLUSIONS Urinary N-BNP used together with plasma N-BNP could reduce the echocardiographic burden in screening programs. (J Am Coll Cardiol 2005;45:1043–50) © 2005 by the American College of Cardiology Foundation

Left ventricular systolic dysfunction (LVSD) is increasingly common in elderly populations and is often asymptomatic. These features support screening for LVSD. Although echocardiography is the criterion standard for diagnosis of LVSD, inadequate access to primary care physicians and expense have limited its application to screening.

Plasma natriuretic peptides, especially the B-type peptides, are elevated in LVSD (1–3). Both B-type natriuretic peptide (BNP) and its N-terminal precursor (N-BNP) have been utilized for LVSD exclusion due to their high negative predictive values (NPV). Recent guidelines in Europe and the U.S. have supported this use of plasma BNPs (4,5).

We recently reported the detection of N-BNP in urine of patients with LVSD (6). B-type natriuretic peptide is synthesized in renal tubule cells (7), so that urine levels may reflect renal synthesis, as well as filtered peptide. Ease of urine, as opposed to plasma sampling, would facilitate community screening. We therefore compared the performance of plasma and urinary N-BNP in the detection of undiagnosed LVSD in a prospective, community study.

METHODS

Recruitment. Randomly selected men (45 to 80 years of age) and women (55 to 80 years of age) from 21 general practices (stratified by list size and deprivation) in the former Leicestershire Health Authority area (population ~1 million) were invited for screening (between September 1999 and May 2002). Excluded were subjects with a previous diagnosis of LVSD or heart failure and those for whom screening was considered inappropriate (e.g., housebound or terminally ill patients). The study was approved by the Leicestershire Research Ethics Committee.

Echocardiography. Patients underwent echocardiography and blood and urine sampling. Transthoracic echocardiography was performed by one operator (I.W.L.) in all patients using a Sonos 5500 instrument (Philips Medical Systems, Reigate, Surrey, United Kingdom). A 16-segment

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Abbreviations and Acronyms

AF = atrial fibrillation
AUC = area under the curve
IHD = ischemic heart disease
LVSD = left ventricular systolic dysfunction
LVWMI = left ventricular wall motion index
N-BNP = N-terminal pro-brain natriuretic peptide
NPV = negative predictive value
PPV = positive predictive value
ROC = receiver-operating characteristic

wall motion index (LVWMI) based on the American Society of Echocardiography model was calculated as described (3), and those with a LVWMI score of ≥1.8 (equivalent to a left ventricular ejection fraction (LVEF) of 40%) (3) were considered to have LVSD.

Laboratory methods. Twenty milliliters of venous blood or urine was collected into pre-chilled Na-EDTA tubes containing aprotinin. Unextracted plasma and urine were assayed for N-BNP using a noncompetitive immunoluminometric assay, as described (3,6). Urinary creatinine was quantified by the Jaffe reaction (6).

Stability of N-BNP in urine. Urinary N-BNP was measured in specimens where the urine was frozen immediately, compared with the same specimens left at room temperature for 24, 48, and 72 h.

Cost of different screening strategies. These are based on costs reported by Heidenreich et al. (8), who performed a cost-effectiveness study of the use of plasma BNP in screening for LVSD. Echocardiographic scans, plasma BNP tests, and electrocardiograms (ECGs) cost $420, $32, and $30, respectively.

Statistical analysis. Statistical analysis was performed using SPSS Version 11.0 (SPSS Inc., Chicago, Illinois). The receiver-operating characteristic (ROC) areas under the curve (AUCs) and their associated 95% confidence intervals were estimated. Binary logistic regression analysis was performed with SPSS with the stated variables, including a constant in the model and probability for entry or removal set at $p < 0.05$ and $p < 0.10$, respectively.

RESULTS

Screening invitations were accepted by 1,360 of 2,392 patients approached. The number of participants with an analyzable echocardiogram and available simultaneous blood and urine samples was 1,308 (Table 1). The 28 subjects with LVSD as defined earlier (LVWMI ≥1.8 or LVEF ≤40%) had elevated plasma N-BNP and urinary

Table 1. Study Population Characteristics (n = 1,308)

	All	No LVSD	LVSD
Men/women	742/566 (56.7/43.3)	720/560 (56.2/41.7)	22/6 (78.6/21.4)†
Age (yrs), mean (range)	63 (45 to 80)	63 (45 to 80)	68 (51 to 80)‡
Practice Jarman score, mean (range)	6.96 (−16.0 to 41.4)	6.92 (−16.0 to 41.4)	8.51 (−10.9 to 41.4)
Body mass index (kg/m^2)	26.7 ± 4.4	26.7 ± 4.4	27.2 ± 5.3
Systolic blood pressure	135 ± 19	135 ± 19	138 ± 19
Diastolic blood pressure	78 ± 12	78 ± 12	79 ± 14
Current smoker	254 (19.4)	247 (19.3)	7 (25)
Plasma creatinine	89.5 ± 30.3	89.3 ± 30.5	99.9 ± 18.3§
Creatinine clearance (ml/min)	77.8 ± 22.4	77.9 ± 22.4	71.4 ± 21.6
Medical history			
Myocardial infarction	32 (2.4)	26 (2.0)	6 (21.4)
Angina	90 (6.9)	82 (6.4)	8 (28.6)¶
Hypertension	310 (23.7)	302 (23.6)	8 (28.6)
Diabetes mellitus	63 (4.8)	61 (4.8)	2 (7.1)
Other cardiac abnormalities			
AF	16	14	2
ECG LVH	118	115	3
Valvular abnormalities*	9	8	1
Prescribed therapy			
ACE inhibitor/ARB	115 (8.8)	109 (8.5)	6 (21.4)†
Loop diuretic	36 (2.7)	34 (2.7)	2 (7.1)
Other diuretic	165 (12.6)	163 (12.7)	2 (7.1)
Beta-blocker	147 (11.2)	143 (11.2)	4 (14.3)
Nitrate	51 (3.9)	44 (3.4)	7 (25)¶
Calcium channel blocker	128 (9.8)	122 (3.4)	6 (21.4)†
Natriuretic peptides, median (range)			
Plasma N-BNP (fmol/ml)	44.5 (5.7 to 1,230.2)	42.2 (5.7 to 1,166.4)	360.3 (5.7 to 1,230.2)§
Urinary N-BNP (fmol/ml)	0.54 (0.54 to 1,103.8)	0.54 (0.54 to 1,103.8)	69.3 (10.8 to 839.9)§
Urinary N-BNP/creatinine (fmol/mg)	3.04 (0.14 to 17,407)	2.87 (0.14 to 17,407)	136.2 (7.0 to 4,275.7)§

Data are presented as the number (%) of patients or mean value ± SD, unless specified otherwise. *Valvular abnormalities include moderate/severe mitral regurgitation or aortic stenosis. p values for comparisons between LVSD and no LVSD groups: †$p < 0.05$ and ¶$p < 0.001$ (chi-square test); ‡$p < 0.005$ and §$p < 0.001$ (Mann-Whitney test).

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ECG LVH = electrocardiographic left ventricular hypertrophy; LVSD = left ventricular systolic dysfunction; N-BNP = N-terminal pro-brain natriuretic peptide.

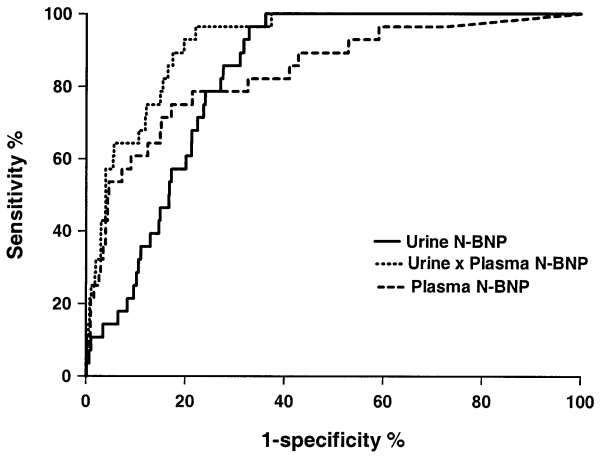

Figure 1. The receiver-operating characteristic curves for plasma and urinary N-terminal pro-brain natriuretic peptide (N-BNP) and the plasma/urinary N-BNP product in left ventricular systolic dysfunction detection. **Solid line** = urinary N-BNP; **dotted line** = urinary × plasma N-BNP; **dashed line** = plasma N-BNP.

N-BNP, whether or not corrected for creatinine, compared with normal subjects (Table 1). The LVSD group was older and had more males (Table 1).

In the 1,280 normal subjects, there was no significant correlation between plasma and urinary N-BNP (r_s = −0.02). On stratification of plasma N-BNP into quartiles, there were no significant differences in urinary N-BNP levels. Although plasma N-BNP rose with age (r_s = 0.41, $p < 0.0005$), urinary N-BNP fell with age (r_s = −0.08, $p < 0.005$). Plasma N-BNP was correlated with creatinine clearance (r_s = −0.357, $p < 0.005$), but urinary N-BNP was not (r_s = −0.052, p = NS). The calculated filtered load of N-BNP was not related to the measured urinary N-BNP (r_s = 0.031, p = NS). Unlike plasma N-BNP, urinary N-BNP was not dependent on heart rate (r_s = 0.01, p = NS) or gender (plasma N-BNP: male 24.8 [5.7 to 1,155] vs. female 72.7 [5.7 to 1,166] fmol/ml; $p < 0.0005$); urinary N-BNP: male 0.5 [0.5 to 785] vs. female 0.5 [0.5 to 1,103] fmol/ml; p = NS). The ROC-AUCs (Fig. 1 and Table 2) showed both plasma and urinary N-BNP to be as effective in excluding LVSD, irrespective of correction for urinary creatinine. Although both urinary and plasma N-BNP have a NPV, the specificity and positive predictive value (PPV) of urinary N-BNP were higher than those of plasma N-BNP. Hence, the number of subjects needed to scan to detect one case of LVSD is lower with urine than with plasma N-BNP testing (Table 2).

Ejection fractions were available from 1,037 subjects, 29 of whom had values under 40%. The ROC-AUCs for detection of ejection fraction <40% using plasma and urine N-BNP were 0.830 and 0.833, respectively. These values resemble those for detecting a LVWMI >1.8 for the whole population (Table 2).

A history suggestive of heart failure (e.g., dyspnea or exercise intolerance) was not useful in diagnosing LVSD

Table 2. ROC-AUCs for Plasma and Urinary N-BNP for Diagnosis of Systolic Heart Failure With Sensitivities, Specificities, and PPV and NPV

Peptide(s)	ROC-AUC	95% CI	Cut-Off Value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Number of Echos Needed (%)	Number to Echos to Detect 1 Case of LVSD	Probability of LVSD Given a Positive Test
Plasma N-BNP (fmol/ml)	0.840	0.761–0.920	26.2	96.4	41.0	3.4	99.8	783 (59.8%)	29.0	0.034
Urinary N-BNP (fmol/ml)	0.831	0.791–0.871	16.2	96.4	67.2	6.0	99.9	447 (34.2%)	16.6	0.060
Urinary N-BNP/creatinine (fmol/mg)	0.802	0.757–0.847	21.1	96.4	65.4	5.7	99.8	471 (36.0%)	17.4	0.057
Logistic model (plasma and urinary N-BNP)	0.920	0.874–0.966	0.0108*	96.4	76.6	8.3	99.9	343 (26.2%)	12.7	0.079
Plasma × urinary N-BNP (fmol/ml^2)	0.923	0.889–0.956	1424	96.4	78.0	8.7	99.9	308 (23.5%)	11.4	0.088
Sequential tests (urine, then plasma N-BNP for the urine-"positive" cases)†	0.834†	0.753–0.915	25.8†	96.4	41.2†	8.7†	99.5†	291 (22.2%)	10.8†	0.093

*Predicted probability from logistic model. †Figures refer to plasma N-BNP tests in the 490 urine-"positive" cases only. Total number of echocardiograms needed (% of initial population) and number of subjects that have to be scanned in order to detect a case of heart failure are also reported. The ROC-AUCs for the logistic model and the plasma/urinary N-BNP product are reported. Finally, the same parameters are reported for sequential application of urine (cut-off 10.7 fmol/ml) followed by plasma N-BNP tests on those urine-"positive" cases are described. A sensitivity of 96.4% will miss one case of LVSD. The final column reports the probability of LVSD (from Bayes theorem) when a positive test was detected.

CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value; ROC-AUC = receiver-operating characteristic area under the curve; other abbreviations as in Table 1.

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Table 3. Binary Logistic Regression Analysis of Various Predictors of Left Ventricular Systolic Dysfunction

	B	SEM	p Value	OR
Log_{10} plasma N-BNP	2.345	0.532	0.0005	10.431
Log_{10} urinary N-BNP	1.346	0.286	0.0005	3.843
Log_{10} creatinine	−0.580	2.076	NS	0.560
Age	0.005	0.031	NS	1.005
Male gender	1.333	0.537	0.013	3.791
Hypertension	−0.354	0.557	NS	0.702
Diabetes	0.397	0.950	NS	1.487
Ischemic heart disease	0.870	0.502	NS	2.386

p values and odds ratios (OR) are reported for the predictor variables and factors. B and SEM refer to the regression coefficient and its standard error.
N-BNP = N-terminal pro-brain natriuretic peptide; NS = not significant.

(ROC-AUC 0.59). Sensitivity was poor at 32.1%, although the specificity was 89.7%.

Regression analysis. Variables included in binary logistic regression analysis for LVSD are reported in Table 3. Independent predictive factors for LVSD included plasma N-BNP, urinary N-BNP, and male gender, accounting for 41.4% of the variance (Nagelkerke r^2, $p < 0.0005$). The ROC-AUC plotted from the calculated probabilities of the model, associated specificity, sensitivity, PPV, and NPV are reported in Table 2. Variables in logistic regression equations are multiplied to calculate log_e(odds ratio). The product of the urinary and plasma N-BNP level was thus examined (Fig. 1 and Table 2) as a simplified LVSD predictor. Both the logistic model and this product yielded higher specificity and PPV for detection of LVSD than either plasma N-BNP or urinary N-BNP considered alone, while maintaining a high NPV, hence effectively reducing the number of subjects needed to scan in order to detect one case of LVSD.

Application of sequential tests. We sought to minimize the number of N-BNP tests needed for LVSD detection. The higher specificity of urinary N-BNP suggested its use as a first-line LVSD screening test. In order to detect 100% of the cases, the cut-off level for urinary N-BNP was determined from ROC curves to be 10.7 fmol/ml. A total of 490 subjects had a positive urinary N-BNP test, including all 28 LVSD subjects. There was no significant correlation between plasma and urinary N-BNP in the subjects with or without LVSD ($r_s = 0.002$ and 0.283, respectively; p = NS) (Fig. 2). Plasma N-BNP was elevated in LVSD subjects (360.3 [5.7 to 1,230] vs. 45.4 [5.7 to 1,166] fmol/ml, $p < 0.0005$). The ROC-AUC for these urine-positive cases was 0.834 (Table 2), with PPV and the number of cases needed to scan to detect one case of LVSD very similar to that in the logistic model or plasma/urinary N-BNP product for all subjects. Only one subject with LVSD who was urine-positive was below this plasma cut-off point. Sequential testing (i.e., applying urinary N-BNP tests for all samples and then testing for plasma N-BNP in those with urinary N-BNP >10.7 fmol/ml [~37.5% of plasma specimens]) would achieve rates of detection and echocardiography

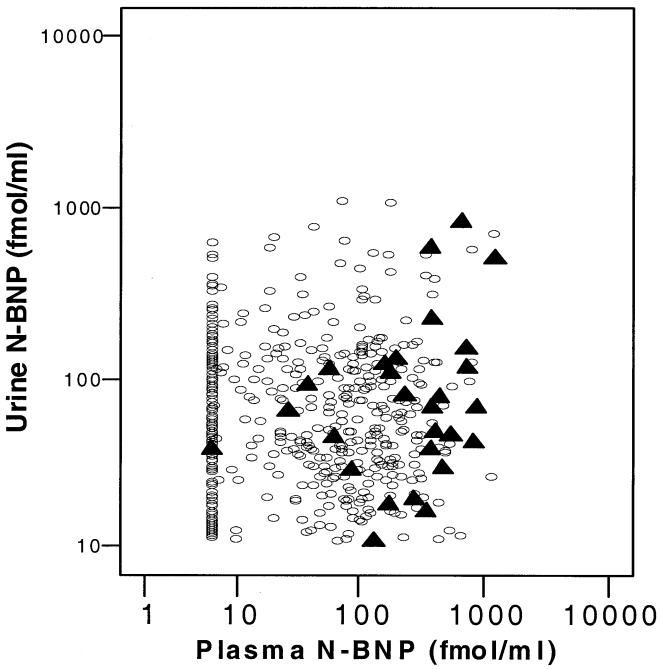

Figure 2. A scatterplot of urinary and plasma N-terminal pro-brain natriuretic peptide (N-BNP) in those subjects with a positive urine test (defined as >10.7 fmol/ml). Normal subjects **(open circles)** or subjects with left ventricular systolic dysfunction **(solid triangles)**.

usage similar to those in the logistic model or the plasma/urinary N-BNP product (Table 2).

Application of tests to high-risk subjects. For those with a history of ischemic heart disease (IHD; n = 103, of whom 11 had LVSD), both plasma and urinary N-BNP ROC curves had reasonable AUCs (0.799 and 0.797, respectively). Another high-risk group would be those >65 years of age with hypertension or IHD. Of 699 subjects in this group, 23 had LVSD. The ROC curves and other data for plasma and urinary N-BNP, as well as the product of these two parameters, are presented in Figure 3 and Table 4. Specificities and PPVs of the urinary tests are better than those of the plasma N-BNP tests, and both are higher than

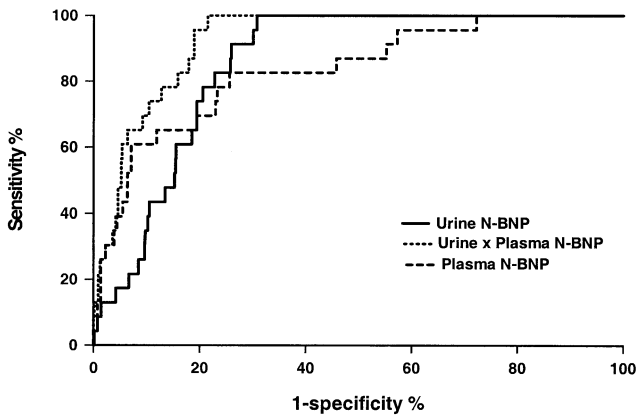

Figure 3. The receiver-operating characteristic curves for plasma and urinary N-terminal pro-brain natriuretic peptide (N-BNP) and the plasma/urinary N-BNP product in left ventricular systolic dysfunction detection within a high-risk group (age >65 years, hypertension, ischemic heart disease).

Table 4. ROC-AUCs for Plasma and Urinary N-BNP for Diagnosis of LVSD in High-Risk Subjects (Age >65 Years, History of Hypertension, or Ischemic Heart Disease)

Peptide(s)	ROC-AUC	95% CI	Cut-Off Value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Number of Echocardiograms Needed (%)	Number to Echocardiograms to Detect 1 Case of LVSD
Plasma N-BNP (fmol/ml)	0.834	0.748–0.920	26.3	95.7	42.8	5.4	99.7	409 (58.5%)	18.6
Urinary N-BNP (fmol/ml)	0.855	0.813–0.896	19.6	95.7	70.0	9.8	99.8	225 (32.2%)	10.2
Plasma × urinary N-BNP (fmol/ml^2)	0.926	0.894–0.958	2335	95.7	79.1	13.5	99.8	163 (23.3%)	7.4

Total number of echocardiograms needed (% of at-risk population) and number of subjects that have to be scanned in order to detect a LVSD case are reported. High-risk individuals numbered 699, of whom 23 had LVSD. A sensitivity of 95.7% would miss one LVSD case.
Abbreviations as in Tables 1 and 2.

when the same tests are applied to the whole population. The plasma/urinary N-BNP product yielded the highest specificities and PPVs, enabling detection of one case of LVSD with about seven scans.

We examined ROC curves for other high-risk groups in whom an echocardiogram was warranted (such as various combinations of the presence of IHD, hypertension, diabetes mellitus, LVH, AF, or valve disease) (Table 5) and compared them with the remainder of the population (in whom there was no a priori reason for an echocardiogram). The ROC areas and specificities for urine or plasma N-BNP in both the population in whom echocardiography was warranted and in those with no such indication were very similar (Table 5). Urinary N-BNP had better specificities and a lower number of cases to be scanned than plasma N-BNP in every population considered. Only slight improvements in specificity and the number of cases to be scanned were evident with the plasma/urinary N-BNP product.

Cost of different screening strategies. We examined the costs of different screening strategies compared with obtaining echocardiograms for the whole population (strategy A, Table 6). Strategy B (measuring plasma N-BNP in the whole population and scanning those with positive results) had previously been shown to be cost effective (9). Use of urinary N-BNP (strategy C) saves about one-third of the cost of strategy B. Further savings are possible by either using the plasma/urinary N-BNP product in all patients (strategy D) or testing urinary N-BNP first and then performing the plasma N-BNP test on the urine-positive cases (strategy E). In strategy F, G, and H, all patients with IHD or other conditions that would warrant an echocardiogram are scanned, and urinary N-BNP tests applied to the remainder. All these strategies are actually more costly than performing urinary N-BNP tests on the whole population, mainly because only 4% to 10.7% of the group who warrant a scan had LVSD, and echocardiography is relatively more expensive than the N-BNP test (Table 5).

Detection of other cardiac abnormalities in those with preserved systolic function. Other cardiac abnormalities in subjects with preserved systolic function (LVWMI <1.8 or LVEF >40%) included AF (n = 14), LVH by ECG (n = 115), and occult valvular abnormalities (moderate or severe mitral regurgitation or aortic stenosis, n = 8). Table 7 documents the ROC-AUCs for detection of these individual abnormalities, as well as when all were combined. Plasma N-BNP showed significant ROC-AUCs for detection of AF and valvular abnormalities that were not replicated with urinary N-BNP. Neither test was clinically useful for detection of LVH. For detection of a combination of LVSD, AF, or valvular abnormalities, both plasma and urinary N-BNP had significant ROC-AUCs, although plasma N-BNP performed better than urinary N-BNP.

Stability of N-BNP in urine. Urinary N-BNP was stable for 24 h at room temperature (Fig. 4). However, degradation was evident within 48 and 72 h of storage at room temperature (n = 6, $p < 0.02$ by the Bonferroni test for

Table 5. ROC-AUCs With 95% CI for Plasma, Urinary, and Plasma × Urinary N-BNP Product for Diagnosis of LVSD in At-Risk Groups (as Defined) and Also in Remainder of Population Without Risk Factors Indicated

At-Risk Group	Number With LVSD/Total in Group (%)	Number With LVSD/Remainder of Population (%)	Plasma N-BNP: ROC-AUC for At-Risk Group (95% CI) [Specificity %] {NNTS}	Plasma N-BNP: ROC-AUC for Remainder of Population (95% CI) [Specificity %] {NNTS}	Urinary N-BNP: ROC-AUC for At-Risk Group (95% CI) [Specificity %] [NNTS]	Urinary N-BNP: ROC-AUC for Remainder of Population (95% CI) [Specificity %] {NNTS}	Plasma × Urine Product: ROC-AUC for At-Risk Group (95% CI) [Specificity %] {NNTS}	Plasma × Urine Product: ROC-AUC for Remainder of Population (95% CI) [Specificity %] {NNTS}
Angina or MI	11/103 (10.7)	17/1,205 (1.4)	0.799 (0.658–0.941) [27.2] {7.5}	0.809 (0.692–0.926) [28.7] {50.5}	0.797 (0.707–0.888) [60.9] {4.0}	0.830 (0.778–0.883) [64.8] {24.9}	0.865 (0.789–0.940) [66.3] {3.5}	0.911 (0.864–0.956) [66.2] {23.9}
Angina, MI, hypertension, diabetes	15/393 (3.8)	13/915 (1.4)	0.766 (0.649–0.882) [28.0] {20.2}	0.866 (0.735–0.997) [31.3] {52.4}	0.836 (0.784–0.888) [67.7] {9.1}	0.829 (0.763–0.895) [64.0] {27.5}	0.907 (0.865–0.949) [77.8] {6.2}	0.922 (0.867–0.978) [64.4] {27.2}
Angina, MI, hypertension, diabetes, LVH, AF, valve disease	19/474 (4)	9/834 (1.1)	0.772 (0.664–0.880) [29.2] {18.6}	0.871 (0.703–1.0) [32.2] {70.7}	0.846 (0.799–0.893) [66.8] {8.7}	0.804 (0.725–0.882) [64.4] {37.1}	0.913 (0.876–0.950) [77.8] {5.9}	0.912 (0.841–0.984) [65.7] {35.8}

Specificities for diagnosis of systolic heart failure at sensitivities of 92.3% to 94.7% sensitivities are reported in [brackets]. At this level of sensitivity, one case of LVSD will be missed. The number needed to scan (NNTS) to detect one case of LVSD is reported in {brackets}.

AF = atrial fibrillation; LVH = left ventricular hypertrophy; MI = myocardial infarction; other abbreviations as in Tables 1 and 2.

Table 6. A Number of Different Strategies for Screening Are Analyzed for the Total Number of Scans and N-BNP Tests Resulting From the Screening

Strategy	Initial Echo Scans	Plasma or Urinary N-BNP Tests	ECGs	Echo Scans Resulting From Positive N-BNP Tests	Total Echo Scans	Cost of Echo ($)	Cost of N-BNP Tests ($)	ECG Costs ($)	Total Cost ($)	Cost/1,000 Subjects ($)	Cost to Detect One Case of LVSD ($)
A	1,308				1,308	549,360	0	0	549,360	420,000	15,555
B		1,308		783	783	328,860	41,856	0	370,716	283,422	10,497
C		1,308		447	447	187,740	41,856	0	229,596	175,532	6,501
D		2,616		308	308	129,360	83,712	0	213,072	162,899	6,033
E		1,798		291	291	122,220	57,536	0	179,756	137,428	5,089
F	103	1,205		434	537	225,540	38,560	0	264,100	201,911	7,478
G	393	915		338	731	307,020	29,280	0	336,300	257,110	9,522
H	474	834	915	303	777	326,340	26,688	27,450	380,478	290,885	10,773

Strategies: A = scan all patients; B = plasma N-BNP tests in all patients and scan the positive tests; C = urinary N-BNP tests in all patients and scan the positive tests; D = plasma and urinary N-BNP tests in all patients and scan the positive tests; E = urinary N-BNP tests in all patients and plasma N-BNP in urine-positive cases, then scan the positive tests from sequential plasma testing; F = scan all ischemic heart disease (IHD) patients and urinary N-BNP in remainder, then scan the positive tests; G = scan all IHD, hypertensive (HT), and diabetic (DM) patients and urinary N-BNP in remainder, then scan the positive tests; H = scan all IHD, HT, DM, AF, LVH, valve lesion patients and urinary N-BNP in remainder, then scan the positive tests.

ECG = electrocardiogram; other abbreviations as in Tables 1 and 2.

Table 7. ROC-AUCs for Detection of Other Cardiac Abnormalities in Those With Preserved Systolic Function and in a Combined Group Comprising Those With Atrial Fibrillation, Valvular Abnormalities, and LVSD (These Diagnoses Are Not Mutually Exclusive)

	Number	Plasma N-BNP ROC-AUC (SEM)	p Value	Urinary N-BNP ROC-AUC (SEM)	p Value
Other cardiac abnormalities with preserved systolic function					
AF	14	0.857 (0.065)	<0.0005	0.586 (0.064)	NS
ECG LVH	115	0.601 (0.028)	<0.0005	0.553 (0.029)	NS
Valvular abnormalities	8	0.836 (0.056)	<0.001	0.401 (0.075)	NS
Combined (AF, LVH, valvular abnormalities)	133	0.644 (0.027)	<0.0005	0.549 (0.026)	NS
LVSD, AF, or valvular abnormalities	50	0.849 (0.031)	<0.0005	0.693 (0.034)	<0.0005

AF = atrial fibrillation; ECG = electrocardiographic; LVH = left ventricular hypertrophy; SEM = standard error of mean; other abbreviations as in Tables 1 and 2.

both). Urine stored for two weeks at −70°C showed no evidence of degradation.

DISCUSSION

This prospective study assessed the utility of urinary and plasma N-BNP for community screening of previously undiagnosed LVSD. Urinary N-BNP was only detectable in 45.8% of the population, which included all cases of LVSD. The source of urinary N-BNP is unknown, although as a small molecule (~8 kd), it is likely to be filtered through the glomerulus. It is possible that the filtered or secreted peptide could be either partially degraded or reabsorbed within the renal tubules, leading to a lack of correlation between filtered load of N-BNP and measured urinary N-BNP. Our previous study on hospitalized patients with New York Heart Association functional class IV heart failure (6) who had very high plasma and urinary N-BNP levels demonstrated a modest correlation between urinary and plasma N-BNP. This finding was not confirmed in the present study involving less symptomatic patients who had lower plasma and urinary N-BNP values. Totsune et al. (9) reported increased urinary excretion of BNP in patients with impaired renal function. In vitro, renal tubule cells may produce BNP (7). Taken in conjunction with our findings, urinary N-BNP may reflect both filtered plasma N-BNP (produced from the myocardium) and renally produced N-BNP. The latter may be a surrogate marker of systolic dysfunction, although the actual mechanisms regulating renal N-BNP production need to be further investigated. For example, volume loading may lead to increased urinary N-BNP excretion (10).

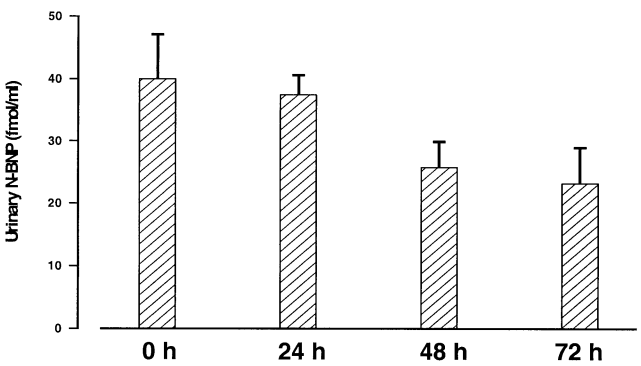

Figure 4. Stability of urinary N-terminal pro-brain natriuretic peptide (N-BNP) when stored at room temperature for up to 72 h.

Urinary N-BNP performs as well as plasma N-BNP for excluding LVSD. The specificities we report are similar to those in the literature (3,4). Due to its higher specificity and PPV, the number of positive cases subsequently requiring echocardiography is less than that if plasma N-BNP were employed as the first investigation. The reasons for the improved performance of urinary compared with plasma N-BNP include the lack of a relationship with age, gender, or heart rate.

Ease of urine sampling without the need to consider age- and gender-dependent normal ranges are advantages relevant to consider in a screening program. Our present data on urinary N-BNP suggest it is stable for 24 h at room temperature, although prolonged storage at room temperature leads to degradation. It is therefore recommended that both urine and plasma specimens be frozen within 24 h of collection for analysis.

Both urinary and plasma N-BNP have an independent predictive value for LVSD detection in logistic modeling. A similar outcome could be obtained by the plasma/urinary N-BNP product. However, the most cost-effective strategy would be to apply these tests sequentially, using the urinary N-BNP test first to rule out LVSD and then subjecting the urine-positive cases to plasma testing. This minimizes the number of assays needed but achieves similar specificity, PPV, NPV, and number of scans to detect one LVSD case as testing both specimens in all subjects.

It has previously been concluded that screening with plasma BNP has a cost-effectiveness similar to other accepted health interventions (<$50,000 per quality of life adjusted year gained), provided the prevalence of LVSD exceeds 1% of the population (8). Based purely on the cost of the screening program, testing urinary N-BNP with or without the plasma N-BNP may be less costly than a program based on plasma N-BNP alone. Focusing on high-risk groups was not cost-effective.

When detection of other cardiac abnormalities in those with preserved systolic function was considered, plasma N-BNP

performed better than urinary N-BNP. This may perhaps relate to more severe systemic or renal disturbance in LVSD (with the kidneys a possible source of N-BNP) than in AF or valve disease. These tests are therefore more specific for systolic dysfunction than other cardiac abnormalities.

Study limitations. The validity of our findings in other populations remains to be established. In particular, the value of urinary and plasma N-BNP in larger groups of high-risk subjects, as well as in ethnic minorities, should be examined. As with any screening study, we could not approach subjects who declined the offer of screening to examine reasons for their refusal.

Conclusions. In this community cohort, both plasma and urinary N-BNP are effective at excluding the presence of LVSD, with urinary N-BNP exhibiting a higher specificity. The plasma/urinary N-BNP product further enhances the specificity and PPV of LVSD diagnosis. However, sequential testing (urine, followed by plasma N-BNP in the urine-positive cases) is likely to achieve similar specificity while limiting the number of echocardiograms and the total number of N-BNP measurements.

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REFERENCES

1. McDonagh TA, Robb SD, Murdoch DR, et al. Biochemical detection of left ventricular systolic dysfunction. Lancet 1998;351:9–13.
2. Hobbs FDR, Davis RC, Roalfe AK, et al. Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: cohort study in representative and high risk community populations. BMJ 2002;324:1498–500.
3. Ng LL, Loke I, Davies JE, et al. Identification of previously undiagnosed left ventricular systolic dysfunction: community screening using natriuretic peptides and electrocardiography. Eur J Heart Failure 2003;5:775–82.
4. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. J Am Coll Cardiol 2001;38:2101–13.
5. The Task Force for the Diagnosis and Treatment of Chronic Heart Failure, European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001;22:1527–60.
6. Ng LL, Geeranavar S, Jennings SC, Loke IW, O'Brien RJ. Diagnosis of heart failure using urinary natriuretic peptides. Clin Sci 2003;106:129–33.
7. Mistry SK, Hawksworth GM, Struthers AD, McLay JS. Differential expression and synthesis of natriuretic peptides determines natriuretic peptide receptor expression in primary cultures of human proximal tubular cells. J Hypertens 2001;19:255–62.
8. Heidenreich PA, Gubens MA, Fonarow GC, Konstam MA, Stevenson LW, Shekelle PG. Cost-effectiveness of screening with B-type natriuretic peptide to identify patients with reduced left ventricular ejection fraction. J Am Coll Cardiol 2004;43:1019–26.
9. Totsune K, Takahashi K, Satoh F, et al. Urinary immunoreactive brain natriuretic peptide in patients with renal disease. Regul Pept 1996;63:141–7.
10. Heringlake M, Heide C, Bahlmann L, et al. Effects of tilting and volume loading on plasma levels and urinary excretion of relaxin, NT-pro-ANP, and NT-pro-BNP in male volunteers. J Appl Physiol 2004;97:173–9.