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Retrospective Analysis of the Cost-Effectiveness of Using Plasma Brain Natriuretic Peptide in Screening for Left Ventricular Systolic Dysfunction in the General Population

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OBJECTIVES We sought to assess the cost-effectiveness of using plasma brain natriuretic peptide (BNP) as a pre-echocardiographic screening test for left ventricular systolic dysfunction (LVSD) in the general population.

BACKGROUND We hypothesized that plasma BNP and simple clinical parameters would reduce the number of echocardiograms needed and cost when screening for LVSD in the general population.

METHODS A random sample of 1,257 community subjects (age 25 to 74 years) was examined. Three risk groups were formed: one group with symptomatic ischemic heart disease (IHD); a second group with blood pressure >160/95 mm Hg and/or an abnormal electrocardiogram (high risk); and a group with none of these risk factors (low risk). The BNP assay was adjusted to give a high sensitivity.

RESULTS Left ventricular systolic dysfunction was prevalent in 0.7% (6/823), 6% (16/269), and 19% (26/140) of low-risk and high-risk subjects and IHD subjects, respectively. Raised BNP concentrations (>8 pg/ml) occurred in 41%, 64%, and 71%. Sensitivities of BNP for detecting LVSD were 83% (5/6), 94% (15/16), and 92% (24/26); and the negative predictive values were 99.8%, 99.0%, and 95.1%. Brain natriuretic peptide was not associated with LVSD in low-risk subjects ($p = 0.087$), but in IHD subjects ($p = 0.015$) and high-risk subjects ($p = 0.023$). Screening high-risk subjects by BNP before echocardiography could have reduced the cost per detected case of LVSD by 26% for the cost ratio of 1/20 (BNP/echocardiogram).

CONCLUSIONS Subjects at low and high risk of LVSD can be identified by simple clinical parameters, and BNP testing further reduces the number of echocardiograms needed and the costs of screening in subjects at risk <75 years of age in the general population. (J Am Coll Cardiol 2003;41:113–20) © 2003 by the American College of Cardiology Foundation

Chronic heart failure is a serious condition with a recognizable latent phase of asymptomatic left ventricular systolic dysfunction (LVSD). Both symptomatic and asymptomatic LVSD are common (1–3), and modern advances in medical therapy have been shown to decrease both its mortality and progression (4–6). However, its detection requires access to cardiac imaging, which is still restricted, as it requires highly specialized personnel and technology. It is now well known that brain natriuretic peptide (BNP) is raised in patients with chronic heart failure and asymptomatic LVSD. Other predictors of LVSD include a history of ischemic heart disease (IHD; including ischemic-like changes on the electrocardiogram [ECG]), male gender, diabetes, hypertension (2), and tachycardia (7). We have previously demonstrated that BNP can accurately detect LVSD in the general population (8), but there have been conflicting reports on the diagnostic value of BNP. Also, its cost-effectiveness has not been evaluated, and it is not quite clear how BNP will supplement other simple tests available in clinical practice.

In this report we hypothesized that a sensitive assay for plasma BNP would be both useful and cost-effective in ruling out LVSD in certain patients at risk in the general population. We have therefore evaluated the diagnostic value of BNP, along with other clinical parameters, in individuals without acute symptoms of heart failure in the general population. Patients with symptomatic IHD were examined separately, as they have indications for a cardiological assessment anyway. The purpose of this study was to examine in whom, to what extent, and at what cost BNP will predict LVSD in various subgroups of the general population.

METHODS

Population. This study included 1,257 subjects (age 25 to 74 years) who were randomly sampled from North Glasgow and had attended the Third Glasgow Monica Risk Factor Survey in 1992. Of the 2,000 individuals invited, 1,653

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Abbreviations and Acronyms

BNP = brain natriuretic peptide
CI = confidence interval
ECG = electrocardiogram or electrocardiographic
EF = ejection fraction
IHD = ischemic heart disease
LVSD = left ventricular systolic dysfunction
MI = myocardial infarction
NNE = number of subjects needed to be examined by echocardiography to detect one case of LVSD
OR = odds ratio
ROC = receiver-operating characteristics

attended (83%), and 1,257 (63%) had an analyzable echocardiogram and a venous blood sample available. The random sampling procedure has been described in an earlier study (2). The present sample of 1,257 subjects is representative of the invited parent cohort in terms of all relevant criteria, with the exception that the attendees were more affluent and there were fewer smokers. The prevalence of coronary heart disease and hypertension was the same as that of the parent cohort.

Clinical tests. A self-reported questionnaire and blood pressure value were obtained for all subjects, and the criteria for abnormal clinical tests are given in Table 1. Blood pressure was measured using a random zero sphygmomanometer (mean value of two readings). Elevated blood pressure was considered as ≥160 mm Hg systolic or ≥95 mm Hg diastolic. Hypertension was defined as a measured elevated blood pressure or current treatment with an antihypertensive agent. The Medical Research Council (MRC) Breathlessness questions were used (9), and cardiac-type dyspnea required breathlessness in the absence of cough and sputum production for more than three days of the week for three months of the year and/or current therapy with a loop diuretic.

Electrocardiography. Standard 12-lead ECGs were coded using the Minnesota Coding Criteria (9). The ECGs showed signs of ischemia if there was a pathologic Q-wave (Minnesota codes 1-1 and 1-2), left bundle branch block, or a major ST/T-segment abnormality (Minnesota codes 4-1, 4-2, 4-3, 4-4, 5-1, 5-2, 5-3, 1-3, and 7-1). Two readers coded all of the ECGs, and discrepancies in coding were adjudicated by a third coder.

Table 1. Signs Indicating an Abnormal Clinical Test

Questionnaire
Do you get short of breath when walking with other people of your own age on level ground? (yes/no)
Do you have to stop for breath when walking at your own pace on level ground? (yes/no)
Do you get short of breath when washing or dressing? (yes/no)
Have you ever been told by a doctor that you have or have had any of the following: angina, heart attack (coronary thrombosis, myocardial infarction), stroke, or diabetes? (yes/no)
Are you now taking any medication for high blood pressure? (yes/no)
Are you regurlarly taking any other medication at present? (positive if the patient takes a loop diuretic or anti-anginal, antihypertensive, or antidiabetic drug)
Blood pressure
The measured blood pressure at consultation exceeds 160 mm Hg systolic or 95 mm Hg diastolic.

Symptomatic IHD. This was defined as subjects with a self-reported myocardial infarction (MI), combined with signs of ischemia on the ECG or with physician-diagnosed angina and the need for anti-anginal treatment.

Echocardiography. We used a left ventricular ejection fraction (EF) calculated by the biplane disc summation method (Simpson's rule) as our gold standard for left ventricular function. The echocardiogram methodology is described in more detail in an earlier report (2). Abnormal EF values were gathered from the distribution of EF in normal subjects (n = 494), defined as those with a blood pressure <140 mm Hg systolic and <85 mm Hg diastolic and without self-reported MI, angina, diabetes, stroke, cardiovascular treatment, ischemia on the ECG, or dyspnea. Their mean EF was 0.473 (SD 0.067), and the 2.5th percentile was 0.34 with 95% confidence interval (CI) of 32 to 35. Left ventricular systolic dysfunction was defined as EF <0.32, which is significantly lower than the 2.5th percentile. The median percentage error of EF readings by the same observer was 7%, and that between observers was 10%.

Brain natriuretic peptide. After 20 min of supine rest, venous blood was withdrawn into chilled tubes containing EDTA and aprotinin (Trasylol; 50 IU/ml). Concentrations of BNP were measured after extraction from plasma (8); BNP was measured in the extract (1:4) using a radioimmunoassay kit for human BNP obtained from Peninsula Laboratories (RIK 9086). This has an IC_{50} of 20 pg/tube. The intra-assay and inter-assay coefficients of variations were 18% (n = 16) and 15% (n = 46), respectively.

Figure 1 shows the distribution of plasma concentrations of BNP in the 48 subjects with and 1,209 without LVSD. We used the fifth percentile of plasma BNP in subjects with LVSD as the cutoff point for an abnormality.

Statistical and cost-effectiveness analysis. Independent predictors of LVSD, before the use of BNP screening, were identified in multiple logistic regression models (Statsoft, Tulsa, Oklahoma) for subjects with and without symptomatic IHD, separately. The number of subjects needed to be examined (NNE) by echocardiography to detect one case of LVSD was calculated as 1/prevalence of LVSD. The NNE was calculated before and after applying BNP. Statistically significant changes were p values < 0.05 by the Yates-corrected chi-squared test. The cost of screening by an echocardiogram (cost = number in population × price of echocardiogram) was compared to the cost of combined screening with BNP first and an echocardiogram second (cost = number in population × price of BNP + number in population with a positive BNP × price of echocardiogram). Different calculations were made to illustrate the effect of varying ratios for the cost of a BNP assay compared with an echocardiogram.

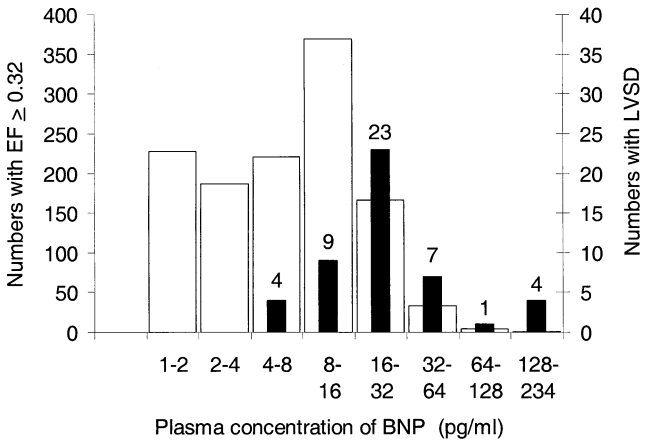

Figure 1. Histogram showing the distribution of plasma brain natriuretic peptide (BNP) in subjects with left ventricular systolic function (LVSD) **(solid bars, right y-axis)** and without LVSD **(open bars, left y-axis)**. The *x* axis is logarithmically scaled to approach normality. The interval 1–2 means ≥1.0 and ≤2.0; the interval 2 to 4 means >2.0 and ≤4.0, etc. The *y* axis contains the number of subjects with a plasma value within the specified interval. EF = ejection fraction.

Ethics. The local Committee on Ethics approved the study, and all examined subjects gave written, informed consent.

RESULTS

Forty-eight subjects had LVSD (3.8%), and 1,209 had an EF ≥0.32. Figure 1 shows a great overlap of plasma BNP concentrations in subjects with and without LVSD. Four subjects with LVSD (8%) had a BNP value ≤8 pg/ml, as compared with 636 patients without LVSD (52.6%).

Univariate Prediction of LVSD. Table 2 shows that LVSD was significantly associated with abnormal clinical tests, ECG abnormalities, and an elevated plasma BNP. Ischemic-like changes on the ECG had a low sensitivity (57%) for detecting LVSD, but the diagnostic value improved when combined with the clinical tests. It was comparable to that of BNP, with a positive predictive value of 7%, meaning that about 14% echocardiograms would be needed to detect one case of LVSD (NNE = 1/0.07). However, BNP added further information to that of the ECG and clinical tests (chi-squared statistic = 20), but not in those with normal clinical tests and a normal ECG (chi-square = 1.88).

Risk stratification for LVSD in the general population. First, 140 subjects with symptomatic IHD were analyzed separately in a multiple logistic regression model. They had an 18.6% prevalence of LVSD (26/140), and LVSD was strongly associated with a history of diabetes (odds ratio [OR] = 20.4, with 95% CI 4.7 to 88) and modestly with ECG signs of ischemia (OR 3.0, 95% CI 1.05 to 8.5). Other evaluated co-variates were: over 55 years, male gender, diabetes, high blood pressure (systolic ≥160 mm Hg and/or diastolic ≥95 mm Hg), cardiac-type dyspnea, New York Heart Association (NYHA) functional class, signs of ischemia on the ECG, cardiovascular medication, self-reported MI, self-reported hypertension, low blood pressure (systolic <100 mm Hg and/or diastolic <60 mm Hg), tachycardia (heart rate >95 beats/min from

Table 2. Diagnostic Value of Clinical Test, Electrocardiogram, and BNP to Detect LVSD

All Subjects	EF ≥ 32% (n = 1,209)	LVSD (n = 48)	Total (n = 1,257)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Yates-Corrected Chi-Squared Value
Clinical test								
Abnormal	469	41	510	85%	61%	0.08	0.991	42
Normal	740	7	747					
Electrocardiogram								
With signs of ischemia	182	27	209	57%	85%	0.13	0.980	57
No sign on ischemia	999	20	1,019					
Clinical test and ECG								
At least one abnormal	533	43	576	90%	56%	0.07	0.993	39
Both normal	676	5	681					
BNP								
>8.0 pg/ml	573	44	617	92%	53%	0.07	0.994	36
≤8.0 pg/ml	636	4	640					
Subjects With Abnormal Clinical Test or ECG	**n = 533**	**n = 43**	**n = 576**					
BNP >8.0 pg/ml	304	40	344	93%	43%	0.12	0.987	20
BNP ≤8.0 pg/ml	229	3	232					
Subjects With Normal Clinical Test and ECG	**n = 676**	**n = 5**	**n = 681**					
BNP >8.0 pg/ml	269	4	273	80%	60%	0.015	0.998	1.9
BNP ≤8.0 pg/ml	407	1	408					

An abnormal ECG was pronounced by ischemic-like changes. Criteria for an abnormal questionnaire are explained in the text (25 patients had a missing ECG).
BNP = brain natriuretic peptide; ECG = electrocardiogram; EF = ejection fraction; LVSD = left ventricular systolic dysfunction.

Table 3. Characteristics of Risk Groups

	Low Risk* (%)	High Risk† (%)	Symptomatic IHD† (%)	Total (%)
Demographic data				
Males (n)	48 (395)	49 (133)	59 (82)	50 (610)
Age	46.5 ± 13.4	58.6 ± 11.7	61.8 ± 7.6	50.9 ± 14.0
BMI	24.9 (22.6–27.6)	26.6 (23.7–29.3)	26.9 (24.4–29.7)	25.5 (23.0–28.2)
Risk factors in questionnaire				
Smoking, current	40	33	36	38
Smoking, former	29	30	19	28
Diabetes	1.4	3.5	8.9	2.7
Stroke	1.1	1.8	5.7	1.6
Hypertension	12	36	45	20
Cardiovascular treatment	3.8	18	30	9.2
Hypertension and treatment	4.6	70	45	23
MI	0.4	0.7	43	5.3
Blood pressure				
Systolic (mm Hg)	123 (113–135)	160 (138–171)	139 (125–155)	130 (116–147)
Diastolic (mm Hg)	76 (69–82)	86 (78–97)	79 (69–87)	78 (70–85)
Electrocardiogram				
Minor changes	0	5.6	1.5	1.4
Major changes	0	43	34	13
MI changes	0	4.8	12	2.4
LBBB	0	2.6	1.5	0.7
Any sign of ischemia	0	54	47	17
Symptomatic IHD				
Treated angina	0	0	96	11
Self-reported MI and ECG signs of QRS changes, MI, LBBB	0	0	27	3.0
Breathlessnes and loop diuretic				
FEV_1 <75 of predicted	25	25	31	25
Loop treatment	2.2	10	3.1	3.9
Cardiac-type dyspnea	6.9	13	39	12
Echocardiography				
LV hypertrophy (n/N)	4.2 (25/591)	13 (17/129)	18 (10/56)	6.7 (52/776)
LVSD	0.7	5.9	19	3.9
EF	0.471 ± 0.067	0.461 ± 0.094	0.421 ± 0.113	0.46 ± 0.081
Brain natriuretic peptide (pg/ml)				
≤8	59.2	35.7	29.3	50.6
>8	40.8	64.3	70.7	49.4
Median	6.7 (2.6–10.9)	11.1 (5.5–17.0)	13.8 (6.8–23)	8.0 (3.5–13.7)
ROC curve analysis				
AUC of BNP to detect LVSD	0.79	0.81	0.77	0.86
Optimal BNP cutoff point (pg/ml)	8.0	19.0	16.9	12.0

*Low-risk group (n = 823) without risk factors of other two groups. †High-risk group (n = 269) with elevated blood pressure and/or ischemic changes on electrocardiogram (ECG). ‡Symptomatic ischemic heart disease (IHD) group (n = 140) with ischemic heart disease, as defined in the text. Data are presented as the percentage (n/N), mean value ± SD, or median value (interquartile range).

AUC = area under curve from the receiver-operating curve (ROC) analysis; BMI = body mass index; FEV_1 = forced expiratory volume in 1 s; LBBB = left bundle branch block; MI = myocardial infarction; other abbreviations as in Table 2.

sitting ECG, before exercise test). The model was improved by adding the BNP test (OR 6.3, 95% CI 1.2 to 33), diabetes was retained, and the ECG became insignificant.

A total of 1,092 subjects without symptomatic IHD were examined in a separate multiple logistic regression model to predict LVSD by using the aforementioned co-variates. Now LVSD was associated with a high blood pressure, signs of ischemia on the ECG, male gender, and tachycardia. The risk stratification ignored male gender and tachycardia because of ethical considerations and missing values, respectively. Diabetes was not significantly associated with LVSD in subjects without symptomatic IHD. The model was improved by adding the BNP test (OR 7.5, 95% CI 1.7 to 33), whereas high blood pressure (OR 4.6, 95% CI 1.9 to 11) and signs of ischemia on the ECG (OR 3.5, 95% CI 1.4 to 8.7) remained significant. Subjects without symptomatic IHD were consequently classified into a high-risk group (n = 269) if they had a high blood pressure and/or signs of ischemia on the ECG and a low-risk group (n = 823) if they had none of these.

Table 3 shows the characteristics of the three risk groups. The low-risk group was younger and had more smokers and less diabetes, cardiovascular medication, cardiac-type dyspnea, and LVSD, as well as a lower median BNP concentration.

A receiver-operating characteristic (ROC) curve analysis examined the BNP's prediction of LVSD in the three

Table 4. Diagnostic Value of BNP in Relation to Risk Group

	EF ≥0.32 (n)	LVSD (n)	Total (n)	NNE Without BNP	NNE After BNP	Percentage With Raised BNP	Sensitivity of BNP Test	Negative Predictive Value	Yates-Corrected Chi-Square p Value
Low-risk group	817	6	823						
BNP ≤8 pg/ml	486	1	487	137	67	41%	83%	0.998	0.087
BNP >8 pg/ml	331	5	336						
High-risk group	253	16	269						
BNP ≤8 pg/ml	95	1	96	17	12	64%	94%	0.990	0.023
BNP >8 pg/ml	158	15	173						
IHD group	114	26	140						
BNP ≤8 pg/ml	39	2	41	5.4	4.1	71%	92%	0.951	0.015
BNP >8 pg/ml	75	24	99						

NNE = number of subjects needed to be examined to detect one case of LVSD; other abbreviations as in Tables 2 and 3.

groups. The area under the curve was, not surprisingly, largest in the undivided total sample. The BNP cutoff point with the highest combination of sensitivity and specificity, as determined from the ROC analysis, covered values from 8 to 19 pg/ml.

Diagnostic value of BNP in different risk groups. Tables 3 and 4 show that two-thirds (64%) of the high-risk subjects had a raised BNP concentration, as compared with 41% of the low-risk subjects. In the high-risk group, the effect of using BNP was a change in NNE from 17 to 12 corresponding to a 29% ([17-12]/17) reduction in the number of echocardiograms needed to detect one case of LVSD; only 1 in 96 subjects with normal BNP values had LVSD. There was no statistically significant association between raised BNP and LVSD in the low-risk group.

A recalculation of our data using a more conventional limit of EF <0.40 in the combined group of high-risk subjects and IHD subjects yielded a negative predictive value of 90% (104/116), a positive predictive value of 31% (71/227), a sensitivity of 86% (71/83), and a specificity of 40% (104/260).

Cost-effectiveness of BNP. Table 5 shows the cost of screening by echocardiography, as compared with the strategy of screening by both BNP and echocardiography. In high-risk subjects, for example, the actual cost per detected case of LVSD was $1,681 by echocardiography and $1,243 by the combined procedure for the price ratio of 5/100 (BNP/echocardiogram). This compares to a 26% cost reduction ([1,681–1,243]/1,681). In low-risk subjects, BNP reduced the cost by 45%, but the price per detected case of LVSD remained very high.

DISCUSSION

Main Results. Low- and high-risk subjects can be identified by simple clinical parameters, and a subsequent sensitive BNP assay significantly rules out LVSD in subjects at risk <75 years of age in the general population. Screening by BNP before echocardiogram was more cost-effective than referring all subjects to echocardiography. The present sensitive BNP test was adjusted to have a very high negative predictive value, and it would reduce the cost of screening from 21% to 26%, provided that the ratio of the cost of BNP to the cost of an echocardiogram was between 1:10 and 1:20.

Diagnostic value of BNP in other studies. A great number of studies have examined the diagnostic value of natriuretic peptides in relation to the following: LVSD in the general population (8), health-screening programs (10), general practice (7,11–13), high-risk subjects (14,15), subjects referred because of presumed heart failure (16,17), subjects undergoing cardiac catheterization (18), the urgent-care setting (19), and patients after MI (20). The cutoff points for BNP in these studies were defined as the best

Table 5. Price and Cost-Effectiveness of BNP Compared With Echocardiogram in Relation to Risk Group

	Price of Echo ($)	Price of BNP Screening ($)			Cost Reduction by BNP Screening			
	Actual Cost at Price Echo = $100	Actual Cost at Ratio (Price BNP/Price Echo)			(Echo-BNP)/(Echo)% at Ratio (Price BNP/Price Echo)			Price in Terms of Lost Cases With LVSD
		(20/100)	(10/100)	(5/100)	(20/100)	(10/100)	(5/100)	
Low-risk group								
Total (n = 823)	82,300	50,060	41,830	37,715	39%	49%	54%	1 in 6
per LVSD	13,717	10,012	8,366	7,543	27%	39%	45%	
High-risk group								
Total (n = 269)	26,900	22,680	19,990	18,645	16%	26%	31%	1 in 16
per LVSD	1,681	1,512	1,333	1,243	10%	21%	26%	
IHD group								
Total (n = 140)	14,000	12,700	11,300	10,600	9%	19%	24%	2 in 26
per LVSD	538	529	471	442	2%	13%	18%	

Echo = echocardiogram; other abbreviations as in Tables 2 and 3.

combination of sensitivity and specificity from a ROC analysis, but rarely from the question of ruling in or out a cardiac abnormality or event. It is not possible to compare cutoff points between studies because of the lack of standards for both BNP assays and LVSD, and there have been widespread reports on the value of BNP for detecting LVSD. Areas under the ROC curve have ranged from 0.59 (21) to 0.95 (17), and negative predictive values were generally high, whereas positive predictive values were as low as 0.1 or 0.30. Nonetheless, all studies agreed that the natriuretic peptides were the strongest correlates of LVSD, congestive heart failure, cardiac abnormalities, and, most recently, mortality (22,23). The key task is to implement the unique information from this novel test.

Cowie et al. (24) showed how BNP could rule out congestive heart failure in newly symptomatic subjects in general practice. Dao et al. (19) showed its usefulness in the diagnosis of congestive heart failure in an urgent-care setting. We will now discuss the use of BNP to screen for LVSD in subjects at risk in the general population who presently have no clear indication for a cardiac assessment. Brain natriuretic peptide is raised in many types of cardiac dysfunction, but screening was aimed at LVSD because evidence-based treatment exists for this condition.

Choice of cutoff point for BNP. The purpose of a screening test is to detect as many subjects with a disorder as possible, for example, 95%. We therefore chose the fifth percentile of BNP in subjects with LVSD. This value is, of course, arbitrary, as there were only 48 subjects altogether with LVSD. In contrast, cutoff points for diagnostic purposes are usually defined as the value that gives the highest combination of sensitivity and specificity—for example, a BNP value of 17.9 pg/ml in a previous report from our group (2).

Other cutoff points may be considered in the future—for example, those dependent on gender and age and perhaps prognosis. In that respect, our choice of 8 mg/ml can be compared with a value of 7.8 pg/ml, which was the median BNP concentration of subjects who survived four years of follow-up in a recent publication from our group (22). A value >10 pg/ml was associated with a poor prognosis in that study.

This and other studies evaluated BNP in subjects who had already received cardiovascular treatment, which can affect the plasma levels of BNP. The present analysis indicates that BNP testing is cost effective, despite medical treatment that may lead to some false-negatives. This may not be so harmful if those missed are already receiving effective medical treatment. Nonetheless, the present study shows that BNP is cost reducing as a pre-echocardiographic screening test, even at low cutoff points with a high number of false-positives.

Use of other screening tests for LVSD. A normal ECG indicates a significantly low likelihood of LVSD in the general population, but sensitivity is poor. In that respect, our large unselected population study compares with the 57% sensitivity rate seen in the Rotterdam study (25). A better diagnostic value was demonstrated in subjects at risk or with a history of cardiac disease, as seen in general practice (7).

This study cannot comment on whether or not a chest X-ray could have changed the value of BNP screening in the general population. A chest X-ray would nonetheless complicate the screening procedure and increase the cost, and it would probably not be efficient in these medically stable subjects. This is opposite to the situation of symptomatic patients referred to a rapid-access clinic where the combination of a normal chest X-ray and ECG rules out heart failure (26). There was no diagnostic value of adding plasma values of N-terminal atrial natriuretic peptide to plasma BNP in the present study (data not shown) (2).

Left ventricular systolic dysfunction was associated with a high blood pressure (≥160/95 mm Hg) in subjects without IHD. This is the opposite of previous studies of selected patients with heart disease in whom a low blood pressure was associated with LVSD (7). One explanation may be the screening scenario of the present study, which has the potential of catching early LVSD.

Cost-effectiveness of BNP. Ideally, prospective studies are needed to answer whether BNP testing is cost effective in screening for LVSD, in terms of cost and years of life saved by the screening and subsequent treatment. While waiting for such data (if they will ever come), an analysis based on a large series of randomly selected subjects, such as the present one, gives a reasonable preliminary answer regarding the cost of screening.

Whether early intervention is beneficial in truly asymptomatic patients detected incidentally has not yet been evaluated. In the Studies Of Left Ventricular Dysfunction (SOLVD) prevention trial, treatment with enalapril was associated with a significant reduction in the risk of developing heart failure requiring medical therapy and the composite end point of death or development of heart failure. Although patients were in NYHA functional class I, they had all been referred for evaluation of cardiac disease and were therefore not truly incidentally detected.

The cost-effectiveness analysis is, of course, dependent on the sensitivity of the BNP assay for detecting LVSD. We used a very sensitive BNP assay and therefore report minimal estimates for the savings. Cost-effectiveness will improve if more specific assays are used, because the number of subjects with a false-positive BNP test will decrease.

Cost-effectiveness analyses are also highly dependent on the pricing of both an echocardiogram and a BNP assay. Calculations may vary considerably between countries, departments, and health-care systems, so three alternative price ratios for BNP/echocardiogram were examined in this study.

Methodologic limitations. Values of BNP were clearly not normally distributed in subjects without LVSD. A logarithmic transformation alleviated this, but many had a value of 1 pg/ml, which can be ascribed to the plasma extraction

method. A value of 1 pg/ml was not observed in subjects with LVSD.

Large areas under the ROC curves were produced in studies that used a strict definition of the end point—for example, a very low EF cutoff point (8), concomitant indicators of restrictive left ventricular filling (17), and diagnostic agreement between three cardiologists (24). Studies using looser criteria for LVSD similarly observed lower areas under the curves (11,12,21). Studies that used strict criteria are resistant to random errors because the BNP signal vastly exceeds the measurement errors where a coefficient of variation of 18% means that in about 95% of cases, one measurement of BNP will vary at least from 36% below to 36% above the unknown true value. The coefficients of variation for repetitive measurements of N-terminal pro-BNP are larger for low than for high concentrations (27). Low-amplitude cutoff points are therefore subject to larger signal-to-noise ratios than high-amplitude cutoff points. Another source of error is the day-to-day variation, which is poorly described, however.

Areas under the ROC curves are not only affected by the technical and biologic variations of BNP, but also by variations of the end point that it is compared with; for example, EF by echocardiography affects the diagnostic value.

The measured EF values and corresponding limits for normality were significantly lower than those reported in other studies. It would be meaningless to use conventional limits of normality in this study because the median EF in the supranormal subjects was only 0.47. This systematic difference was caused by the hardware, software, personnel, and equations used to measure EF (2), and comparison of EF values between different subgroups are still valid. The randomly selected population was large enough for subgroup analysis, and we applied the conservative chi-squared test, with Yates' contingency correction, to be sure of the validity of statistically significant findings. This procedure minimized the chance of showing any significant associations in smaller subgroups. The limitations of the present study should therefore not disturb the overall conclusion.

Perspective. This retrospective analysis applies to population screening or general health checks for volunteer subjects <75 years old. Under these circumstances, we have shown that a simple questionnaire and blood pressure measurement is useful as a first rule-out test for LVSD. We have also shown that a BNP-based selection for echocardiography in those at risk is more cost effective than referring all subjects for an echocardiogram. More specific BNP tests would clearly be more cost effective but would also miss more subjects with LVSD. It is now time for well-defined and standardized cutoff points for BNP to facilitate implementation of this novel cardiac blood test in clinical practice. We recommend such limits to be defined from prospective studies of both mortality and morbidity, so that those with a false-negative test will still have a favorable prognosis.

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