The Epidemiology of "Asymptomatic" Left Ventricular Systolic Dysfunction: Implications for Screening

Thomas J. Wang, MD; Daniel Levy, MD; Emelia J. Benjamin, MD, ScM; and Ramachandran S. Vasan, MD

Congestive heart failure is a progressive disorder that is frequently preceded by asymptomatic left ventricular systolic dysfunction. We reviewed the epidemiology, diagnosis, and natural history of asymptomatic left ventricular systolic dysfunction and evaluated community-wide screening for this condition as a potential strategy to reduce the incidence of heart failure. Asymptomatic left ventricular systolic dysfunction has an estimated prevalence of 3% to 6%, and is at least as common in the community as systolic heart failure. Because it often occurs in the absence of known cardiovascular disease, this condition may go unrecognized and undertreated. In randomized trials, individuals with asymptomatic left ventricular systolic dysfunction have high rates of incident heart failure and death. However, little is known about the prognosis of individuals with this condition in the community, who have a substantially lower prevalence of myocardial infarction, have milder degrees of systolic dysfunction, and are older than patients enrolled in clinical trials. Current evidence is inadequate to support community-wide screening for asymptomatic left ventricular systolic dysfunction, either with echocardiography or with assays for natriuretic peptides. Given the increasing prevalence of heart failure, additional studies are needed to develop effective strategies to detect and optimally manage individuals with asymptomatic left ventricular dysfunction in the community.

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For author affiliations, see end of text.

Congestive heart failure (CHF) is a progressive disorder that often begins with left ventricular systolic dysfunction (LVSD) and culminates in symptoms from fluid overload and poor end-organ perfusion (1, 2). Individuals in the early stages of LVSD are typically asymptomatic, partly because of compensatory mechanisms involving the autonomic nervous system, neurohormones, and changes in cardiac structure and function (2). However, ventricular systolic dysfunction may progress despite these adaptations, even without recurrent myocardial injury (1–6).

The progressive nature of CHF has generated increased interest in its early, preclinical stages. The current American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines for CHF divide the disorder into four stages, two of which (stages A and B) are asymptomatic (7). Stage A denotes a "high risk for heart failure but without structural heart disease" (7) and includes individuals with hypertension, diabetes, or known atherosclerotic disease. Individuals with asymptomatic LVSD fall into stage B: "structural heart disease but without symptoms of CHF" (7). Randomized, controlled trials have established that therapy with angiotensin-converting enzyme (ACE) inhibitors for selected patients with asymptomatic LVSD can delay or prevent the onset of overt CHF (8, 9). Accordingly, some investigators have advocated widespread screening for asymptomatic LVSD, in the hope that early identification of this condition followed by intervention may substantially reduce the risk for CHF (10). The availability of serum markers of LVSD (such as natriuretic peptides) has further intensified the enthusiasm for community-wide screening (11).

There are widely held beliefs about the clinical course of asymptomatic LVSD, but these are based on the highly selected participants in randomized clinical trials. Given the recent interest in asymptomatic LVSD, we critically reviewed published reports that investigated the epidemiology, diagnosis, and natural history of LVSD, and we examined questions related to the potential utility of community-wide screening (**Figure**) (12–14). We identify areas where current knowledge is lacking and outline directions for future clinical research.

METHODS

Studies were identified by searching MEDLINE for English-language articles (1975 through November 2002) by using the following Medical Subject Heading (MeSH) terms and keywords alone or in combination: *left ventricular dysfunction*, *left ventricular systolic dysfunction*, *asymptomatic*, *subclinical*, *systole,* and *ventricular remodeling*. The reference lists of published reports were also searched. Two authors critically reviewed all studies and abstracted the relevant data.

The prevalence of LVSD was derived from community-based studies in which ventricular function was assessed by using standardized techniques. When several reports based on the same cohort used similar analytic techniques, the study with the most participants with asymptomatic LVSD was selected for data abstraction to obtain prevalence estimates with the best possible precision. Data on the natural history of asymptomatic LVSD were abstracted from community-based studies and randomized, controlled trials. Data from trials that enrolled participants with both symptomatic and asymptomatic LVSD were used if the experiences of the asymptomatic participants were reported separately.

Case series, referral series, or reports focusing on idiopathic-dilated cardiomyopathy were excluded (15–22). Patients in these reports may have a natural history distinct from that in the community because of selection bias and spectrum bias. Furthermore, given our focus on the clinical epidemiology of LVSD, our search did not include studies

Table 1. **Prevalence of Left Ventricular Systolic Dysfunction by Ejection Fraction Threshold***

Study (Reference)	Country	Participants	Mean Age	Men	LVSD Criteria	Prevalence of LVSD	Prevalence of LVSD without CHF†
		n	*y*	%		%	
EF > 0.40, or equivalent							
Strong Heart Study (26)	United States	3184	58	37	EF ≤ 0.54	14.0	12.5
HyperGEN Study (27)	United States	2086	55	38	EF ≤ 0.54	14.0	12.9
Davies et al. (28)	England	3960	61	50	EF ≤ 0.50	5.3	3.3
MONICA project (Augsburg) (29)	Germany	1566	50	48	EF < 0.48	2.7	1.1‡
Hedberg et al. (30)	Sweden	412	75	50	WMI < 1.7	6.8	3.2
Nielsen et al. (31)	Denmark	126	70	55	WMI ≤ 1.5 or FS < 0.26	2.9	1.0
Rotterdam Study (32)	Netherlands	2267	66	45	FS ≤ 0.25	3.7	2.9§
Helsinki Ageing Study (33)	Finland	501	—‖	27	FS < 0.25	10.8	8.6
EF ≤ 0.40							
Strong Heart Study (26)	United States	3184	58	37	EF < 0.40	2.9	2.1
HyperGEN Study (27)	United States	2086	55	38	EF < 0.40	4.0	3.4
Davies et al. (28)	England	3960	61	50	EF < 0.40	1.8	0.9
MONICA project (Glasgow) (34)	Scotland	1467	50	48	EF ≤ 0.35	7.7	5.9
MONICA project (Glasgow) (34)	Scotland	1467	50	48	EF ≤ 0.30	2.9	1.4
Qualitatively "reduced" EF							
Cardiovascular Health Study (35)	United States	5532	73	42	Qualitative¶	3.5	2.5
Morgan et al. (36)	England	817	76	46	Qualitative	7.5	3.9

* CHF = congestive heart failure; EF = ejection fraction; FS = fractional shortening; HyperGEN = Hypertension Genetic Epidemiology Network; LVSD = left ventricular systolic dysfunction; MONICA = Monitoring Trends and Determinants in Cardiovascular Disease; WMI = wall-motion index. Adapted with permission from Elsevier Science, *The Lancet*. 2001;358:433.
† Uses entire sample as denominator.
‡ Without symptoms or known cardiovascular disease.
§ Based on 1698 participants.
‖ Range, 75–86 y.
¶ Categorized as "impaired" systolic dysfunction.

of the molecular or genetic determinants of LVSD or left ventricular remodeling, which have been reviewed elsewhere (2–6, 23–25).

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Does the Burden of Suffering Justify Screening?

As noted by Cadman and colleagues (14), a fundamental question in evaluating a screening program is, "Does the burden of suffering warrant screening?" To address this question, the prevalence and natural history of asymptomatic LVSD must be considered. Because a major goal of identifying asymptomatic LVSD is to prevent CHF, it is also important to consider what proportion of CHF cases is preceded by LVSD.

What Is the Prevalence of Asymptomatic LVSD?

We identified 11 studies that reported the prevalence of asymptomatic LVSD in the community (26–36). These estimates varied widely, from 0.9% to 12.9%, depending on the study design and setting, the characteristics of the study sample, the definition of LVSD, and the method for classifying participants as asymptomatic (**Table 1**). We address each consideration, with specific attention to important methodologic limitations, where appropriate.

Study Design and Setting

Of the 11 studies estimating prevalence of LVSD, 5 studies were based on participants enrolled in community-based, longitudinal cohort studies: the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) project (two reports) (29, 34), the Rotterdam Study (32), the Strong Heart Study (26), and the Cardiovascular Health Study (35). Five other community-based studies were based on random samples of population registries (30, 33), several primary care practices (28, 31), or a single group practice (36). One report was derived from a biracial, family-based study of hypertensive individuals (27).

Definition of LVSD

Although all of the studies used echocardiography to evaluate left ventricular systolic function, assessment methods and thresholds for determining abnormality varied substantially across studies (**Table 1**). The most commonly used index was ejection fraction, calculated by using the biplane Simpson rule (34), the Teichholz method (26, 27, 29), or a combination of methods (28, 30, 31). Two studies used endocardial fractional shortening as an index of systolic function (32, 33). Two studies relied primarily on visual estimation of left ventricular function (35, 36).

Ejection fraction thresholds for defining ventricular systolic dysfunction ranged from 0.30 to 0.54 (**Table 1**). Understandably, studies using higher ejection fraction thresholds to define abnormal systolic function yielded

higher prevalence estimates for asymptomatic LVSD (26, 27). Four studies reported prevalence estimates at several ejection fraction thresholds, and these data indicated that 70% to 90% of participants with asymptomatic LVSD had an ejection fraction between 0.40 and 0.54 (26–28, 34).

Despite the important influence of threshold values on prevalence estimates, the choice of the cut-point was empirical or unexplained in five of the nine studies that used quantitative echocardiography (28, 31–34). In the remaining four studies, the cut-point was determined by a statistically defined limit (26, 27, 29, 30) (2 or 3 standard deviations below the mean of a healthy reference sample). It is important to note that, without data on risk for adverse outcomes (such as CHF) associated with various cut-points of ejection fraction, the superiority of any one given threshold cannot be established.

Definition of Asymptomatic LVSD

"Asymptomatic LVSD" generally denotes LVSD without overt symptoms and physical signs of CHF. In most studies, more than 50% of individuals with LVSD were free of CHF (**Table 1**). However, only six studies specified criteria for defining CHF (28, 31–35). Not surprisingly, the use of more stringent criteria for CHF, such as the requirement for physical examination findings or established cardiac disease in addition to symptoms, resulted in a larger proportion of individuals classified as having asymptomatic LVSD (32, 33). As a corollary, although not meeting criteria for clinical CHF, some people with asymptomatic LVSD in published reports had shortness of breath or pedal edema. None of the studies examined whether individuals with LVSD and mild symptoms differed from those with no symptoms.

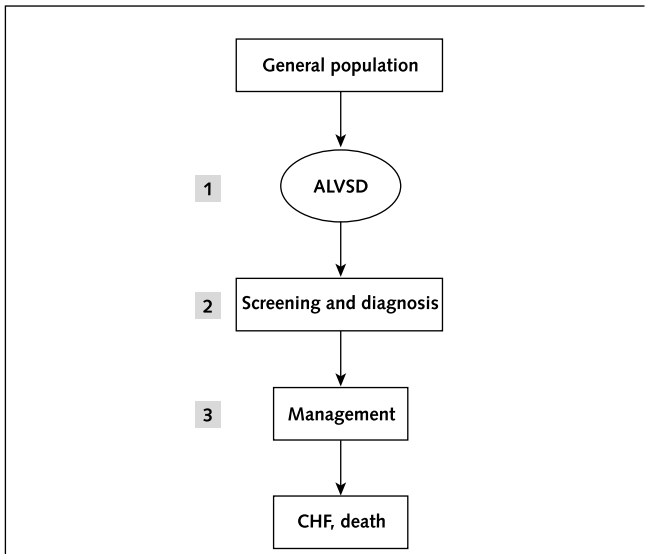
The definitions of "asymptomatic" LVSD in clinical trials, which most practice guidelines are based on, were even less stringent. Thirty-three percent of participants in the Studies of Left Ventricular Dysfunction (SOLVD) Prevention trial (8) were in New York Heart Association functional class II, and 41% of patients in the placebo group of the Survival and Ventricular Enlargement (SAVE) trial (9) were categorized as Killip class II or greater, although all study participants were described as "asymptomatic." We have chosen to use the term "asymptomatic LVSD" as it was used in previous studies and guidelines, although it is often a misnomer (7, 37). Alternative terms, such as "LVSD without clinical CHF," "preclinical LVSD," or "subclinical LVSD," may be more appropriate.

Prevalence of LVSD in High-Risk Subgroups and Comorbid Diagnoses

Given the potential expense of widespread echocardiographic screening, there is interest in identifying subgroups at high risk for LVSD who could be selectively screened (38, 39). Four studies reported the prevalence of asymptomatic LVSD in specific subgroups (27, 28, 34, 35). The prevalence of asymptomatic LVSD was twofold to eightfold higher in men than in women and higher in elderly persons. The prevalence of asymptomatic LVSD in women was low, ranging from 0.2% to 1.1% in community-based studies (28, 34, 35). When clinical features were considered, the prevalence was highest among individuals with known coronary heart disease, ranging from 4.8% to 8.5% (28, 34, 35).

Only three studies enrolled an appreciable number of nonwhite participants (26, 27, 35). A high prevalence of LVSD was reported in the Strong Heart Study, a community-based study of Native American participants (26). In the Cardiovascular Health Study and the Hypertension Genetic Epidemiology Network Study, the prevalence of LVSD was slightly higher in black participants than in white participants (27, 35). In the Hypertension Genetic Epidemiology Network study, there was a statistically significant association between black ethnicity and lower ejection fraction threshold after multivariable adjustment (27). Data for Hispanic and Asian-American populations are lacking.

Figure. **Chain of questions related to the epidemiology of asymptomatic left ventricular systolic dysfunction (*ALVSD*) and the effectiveness of screening (12–14).**



Questions	Quality of Data
1. Does the burden of suffering justify screening?	
a. What is the prevalence of ALVSD?	Good
b. What is the natural history of ALVSD?	Inadequate
c. What is the proportion of CHF cases preceded by ALVSD?	Inadequate
2. Is there an acceptable test strategy that detects disease accurately in presymptomatic patients?	Inadequate
3. Does treatment of ALVSD alter health outcomes?	Good (ACE inhibitor in select patients) to inadequate

ACE = angiotensin-converting enzyme; CHF = congestive heart failure.

Table 2. **Characteristics of Individuals with Left Ventricular Systolic Dysfunction***

Study (Reference)	Participants†	Criteria	Men	Age	Participants with CHF	Participants with Myocardial Infarction	Participants with Hypertension	Participants with Diabetes
	n		%	*y*	← % →			
LVSD without CHF: community studies								
MONICA project (Glasgow) (34)	21	EF ≤ 0.30	81	NR	71	14	67	NR
Davies et al. (28)	34	EF < 0.40	88	67	53	NR	35	6
Cardiovascular Health Study (35)	136	Qualitative	74	75	58	NR	46	15
Overall LVSD: community studies								
Hedberg et al. (30)	28	WMI < 1.7	75	75	86	79	48	22
MONICA project (Glasgow) (34)	43	EF ≤ 0.30	65	NR	83	33	73	19
Davies et al. (28)	72	EF < 0.40	81	69	53	NR	39	15
Strong Heart Study (26)	444	EF ≤ 0.54	59	61	NR	13	NR	NR
	92	EF < 0.40	60	63	NR	26	NR	NR
Morgan et al. (36)	61	Qualitative	79	NR	NR	39	41	10
MONICA project (Augsburg) (29)	43	EF < 0.48	56	NR	21	NR	23	NR
Rotterdam Study (32)	83	FS ≤ 0.25	67	68	NR	24	NR	NR
Cardiovascular Health Study (35)	196	Qualitative	71	74	64	NR	49	18
LVSD without CHF: randomized trials								
SOLVD Prevention trial (8)	2117	EF ≤ 0.35	89	59	83	79	37	15
SAVE trial (9)	1116	EF ≤ 0.40	82	60	100	100	42	23

* CHF = congestive heart failure; EF = ejection fraction; FS = fractional shortening; LVSD = left ventricular systolic dysfunction; MONICA = Monitoring Trends and Determinants in Cardiovascular Disease; NR = not reported; SAVE = Survival and Ventricular Enlargement; SOLVD = Studies of Left Ventricular Dysfunction; WMI = wall-motion index. Report from the Hypertension Genetic Epidemiology Network study was not included because all participants were hypertensive.
† Number of participants with LVSD; for randomized trials, data are based on the placebo group.

Although previous myocardial infarction and hypertension are common among individuals with LVSD, the absence of these conditions does not exclude the possibility of detecting LVSD (**Table 2**). For instance, in four of five studies, fewer than 50% of participants with asymptomatic or symptomatic LVSD had previous myocardial infarction (26, 30, 32, 34, 36). As shown in **Table 2**, participants in randomized trials of asymptomatic LVSD had a much higher prevalence of previous myocardial infarction than did participants in community-based studies (8, 9).

What Is the Natural History of Asymptomatic LVSD?

We identified three community-based studies (35, 40, 41) and five randomized trials that provided information on the prognosis associated with asymptomatic LVSD (8, 9, 42–44). In community-based observational studies, asymptomatic LVSD was associated with increased cardiovascular mortality (35); all-cause mortality (35, 40); and nonfatal cardiovascular events, such as myocardial infarction and stroke (35, 41). These data were based on relatively small numbers of events, however, because the number of people with asymptomatic LVSD in these studies ranged from only 20 to 136. Little is known about the rate of progression from asymptomatic LVSD to overt CHF in the community. In an earlier investigation from the Cardiovascular Health Study, Aurigemma and colleagues (45) reported an annual CHF incidence of 3% for individuals with LVSD, but this estimate was restricted to individuals without coronary heart disease.

In the placebo groups of five randomized, controlled trials that included more than 3500 participants with asymptomatic LVSD, average annual CHF rates ranged from 4.9% to 20.0% and average annual mortality rates ranged from 5.1% to 10.5% (8, 9, 42–44). These mortality rates are intermediate between those of persons with previous myocardial infarction and preserved systolic function and those of patients with systolic CHF (46, 47). Retrospective analyses of the SOLVD database suggest that the presence of renal insufficiency (48), atrial fibrillation (49), or diabetes (50) is associated with particularly poor outcomes, although it is unclear whether these conditions are markers of more severe underlying disease or of disease duration or whether they contribute to the progression of LVSD.

Although randomized trials provide the largest source of data on prognosis of patients with asymptomatic LVSD, extrapolating these data to individuals in the community is problematic for several reasons. First, with the exception of SOLVD, all other trials enrolled patients in the setting of a recent myocardial infarction; even in SOLVD, nearly 80% of participants had previous myocardial infarction (8). Second, many participants enrolled in trials are not truly asymptomatic but may have New York Heart Association class II symptoms or previous CHF. Third, most trials excluded people with mild LVSD (ejection fraction, 0.40 to 0.50), even though most people identified in community-based studies fall into this category. Finally, trial participants were younger than typical individuals with LVSD in the community.

What Proportion of Individuals with CHF Would Be Identified by Screening for LVSD?

In the community, 30% to 50% of patients with CHF have preserved ventricular systolic function (51). Screening for LVSD would not identify these individuals, nor would screening identify patients with systolic CHF due to an

acute decline in systolic function (for example, post–myocardial infarction). In the Cardiovascular Health Study, only 13% of participants with incident CHF had abnormal systolic function on echocardiography 5 years earlier (45). The true proportion of patients with CHF preceded by LVSD is probably higher, because the Cardiovascular Health Study report excluded people with coronary heart disease. Nonetheless, these data emphasize the importance of identifying other clinical and echocardiographic precursors of CHF.

Subclinical left ventricular dysfunction is not limited to systolic dysfunction (52). Subclinical ventricular diastolic dysfunction may exist, alone or in combination with systolic dysfunction, and may be particularly important in women because they are more likely to have diastolic CHF than systolic CHF (53). Unfortunately, there is limited information on the prevalence and prognosis of asymptomatic diastolic dysfunction in the community, partly because of the lack of a widely accepted definition (54).

Echocardiographic examination of Doppler mitral inflow and pulmonary venous flow patterns or tissue Doppler imaging may provide insight. Using these methods, one preliminary study reported a prevalence of left ventricular diastolic dysfunction of about 20% in people with normal left ventricular systolic function and more than 50% in those with LVSD (52). Regrettably, these Doppler indices are frequently indeterminate. Surrogate markers of left ventricular diastolic dysfunction are needed; potential candidates include left ventricular hypertrophy or left atrial enlargement (without reduced systolic function or valvular disease).

Is There an Acceptable Screening Strategy That Detects Disease Accurately in Presymptomatic Patients?

Assessment of screening strategies for asymptomatic LVSD should adhere to several principles. First, it is important to evaluate the diagnostic performance of the proposed screening test in community-based samples. The spectrum of LVSD encountered in the community differs from that observed in referral settings, and this will directly influence the performance characteristics of the test. Second, it is essential to emphasize a "rule-in" strategy (high specificity and positive predictive value) when screening large populations of asymptomatic individuals with a low prevalence of disease (55). Although a given test may perform well for identifying LVSD in symptomatic patients in referral settings (56–61) where a "rule-out" strategy (high sensitivity and negative predictive value) is desirable, the same test may perform poorly for asymptomatic individuals because false-positive test results will probably outnumber true-positive ones. Emphasizing high specificity will reduce the societal burden of expensive follow-up tests, such as echocardiography, as well as minimize the anxiety and labeling effects associated with false-positive test results. Third, performance of screening tests should be evaluated separately in men and women, especially when the prevalence of the disease condition and the distribution of the test results vary between the sexes. Given the extremely low prevalence of asymptomatic LVSD in women, it is unlikely that any screening test would yield a high positive predictive value even with very high specificity.

Echocardiography has been used as the criterion standard for diagnosing LVSD in community-based studies and most clinical trials. Although echocardiographically derived ejection fraction is influenced by changes in preload and afterload (62), the simplicity of its estimation (relative to more precise measures of myocardial contractility) makes it an attractive indicator of left ventricular systolic function. The major limitation in using echocardiography as a screening tool is its cost. It is unlikely that widespread screening for LVSD (a "screen and treat" strategy) with echocardiography would be cost-effective, although studies specifically addressing this topic have not been published.

An alternative three-stage strategy is to screen first with an inexpensive test, target individuals with a positive screening result for diagnostic testing with echocardiography, and treat people with definitive LVSD ("screen, diagnose, and treat" strategy). At least three approaches have been suggested for initial screening before referral for echocardiography: use of an electrocardiogram, use of natriuretic peptide levels, or use of a composite clinical score based on one or more high-risk characteristics alone or in combination with natriuretic peptide levels.

The performance of the surface electrocardiogram as an initial screening tool for LVSD has been examined in several investigations (63–65). While some reports have suggested that an abnormal electrocardiogram has a high sensitivity and high negative predictive value for detection of LVSD, it suffers from a low specificity and, consequently, a low positive predictive value (63).

The natriuretic peptides, such as brain natriuretic peptide, have emerged as attractive candidates for initial LVSD screening because plasma levels are elevated in LVSD (39, 66), are relatively cardiac-specific, and can be assayed rapidly (11, 56). The performance of brain natriuretic peptide or *N*-terminal proatrial natriuretic peptide for detecting LVSD has been evaluated in several referral series and some community-based studies (**Table 3**) (11, 56–61, 63, 67–74). In community-based studies using various cut-points and sex-pooled analyses (with one exception), sensitivities for LVSD ranged from 26% to 92% and specificities ranged from 34% to 89% (**Table 3**). Estimates for area under the receiver-operating characteristic curve (AUC) ranged from 0.56 to 0.88. In the largest community-based investigation of brain natriuretic peptide screening, the AUC estimates were 0.72 in men and 0.56 in women for detecting any LVSD (defined as reduced ejection fraction on visual assessment or a fractional shortening < 0.29) and 0.79 in men and 0.85 in women for detecting moderate or greater LVSD (defined as a reduced ejection fraction on

Table 3. **Use of Natriuretic Peptides To Identify Left Ventricular Systolic Dysfunction***

Study or Setting (Reference)	Participants	Definition of LVSD	Discrimination Limit	Sensitivity	Specificity	AUC
	n			%		
Community-based studies						
Framingham Heart Study (69)	1470 (men)	FS < 0.29†	BNP level > 21 ng/L	53	84	0.72
	1707 (women)	FS < 0.29†	BNP level > 21 ng/L	26	89	0.56
General practices, England (74)	653	EF < 0.40	NR	NR	NR	0.59
MONICA project (Augsburg) (67)	479	FS < 0.28	BNP level > 34 ng/L	28	86	0.61
General practices, Denmark (63)	126	EF ≤ 0.45	NT-ANP level > 800 pmol/L	43	89	NR
Population sample, Sweden (68)	205 (men)	EF ≤ 0.40	NT-ANP level > 398 pmol/L	86	75	0.83
General practices, England (72)	155	Qualitative	BNP level > 64.7 ng/L	92	65	0.85
General practices, England (73)	126	NR	BNP level > 17.9 ng/L	88	34	NR
MONICA project (Glasgow) (11)	1252	EF < 0.35	BNP level > 17.9 ng/L	43	88	NR
MONICA project (Glasgow) (11)	1252	EF < 0.30	BNP level > 17.9 ng/L	77	87	0.88
Referral series						
Echocardiography laboratory (58)	466	EF < 0.45	BNP level > 37 ng/L	79	64	0.79
Echocardiography laboratory (56)	400	EF < 0.50‡	BNP level > 87 ng/L	90	67	0.82
Nuclear laboratory (70)	75	EF ≤ 0.55	BNP level > 30 ng/L	58	76	0.70
Nuclear laboratory (59)	180	EF < 0.45§	NT-ANP level > 54 pmol/L	90	92	NR
Nuclear laboratory (61)	87	EF ≤ 0.35	BNP level > 13.8 ng/L	100	58	0.88
Catheterization laboratory (57)	94	EF < 0.45	BNP level > 61.2 ng/L	83	81	0.85
Catheterization laboratory (60)	254	EF < 0.45	NR	NR	NR	0.74
Catheterization laboratory (71)	221	EF ≤ 0.45	NR	NR	NR	0.85

* Where applicable, results for the better performing peptide (brain natriuretic peptide or *N*-terminal proatrial natriuretic peptide) are shown. Studies restricted to patients with myocardial infarction or congestive heart failure are not included. AUC = area under the receiver-operating characteristic curve; BNP = brain natriuretic peptide; EF = ejection fraction; FS = fractional shortening; MONICA = Monitoring Trends and Determinants in Cardiovascular Disease; NR = not reported; NT-ANP = *N*-terminal proatrial natriuretic peptide.
† Or mild or greater reduction in EF on visual estimation.
‡ Or wall-motion abnormalities.
§ At rest, or <0.55 with exercise.

visual assessment < 0.40 or a fractional shortening < 0.22) (69). An important reason for the suboptimal performance of brain natriuretic peptide for detecting LVSD in some studies may be that the peptide levels increase as a result of high left ventricular filling pressures, regardless of whether systolic or diastolic ventricular dysfunction is the underlying cause.

A third strategy for initial screening is to select patients with high-risk clinical characteristics for echocardiography (58). In the Framingham Heart Study report, AUC estimates for detecting LVSD using clinical characteristics were 0.72 in women and 0.75 in men (69). Of note, adding plasma brain natriuretic peptide levels to clinical characteristics did not result in a substantial improvement in AUC values.

In summary, an acceptable strategy for detecting asymptomatic LVSD in the community has not been identified. Further data are needed to determine whether clinical characteristics, perhaps in the form of a clinical risk score, could be used to select candidates for more definitive evaluation with echocardiography. The incremental value of using plasma brain natriuretic peptide levels as an initial screening tool for LVSD in the community has not been established (69).

Does Treatment of Asymptomatic LVSD Alter Health Outcomes?

Only ACE inhibitors have been shown to improve outcomes in patients with asymptomatic LVSD. In the SOLVD Prevention trial (8), treatment with enalapril was associated with a 37% reduction in CHF and a nonsignificant reduction in mortality. The SAVE trial (9) demonstrated reductions in both incidence of CHF requiring hospitalization (22%) and mortality (19%) associated with captopril treatment in patients with asymptomatic LVSD after myocardial infarction. Accordingly, both the ACC/AHA and the European Society of Cardiology recommend treatment with ACE inhibitors in patients with "reduced ejection fraction," with or without previous myocardial infarction (7, 37). However, most individuals with LVSD in the community who would be identified by screening would not have been eligible for the SOLVD or SAVE trials. Thus, it remains unclear whether they would benefit similarly from treatment.

Furthermore, there is lack of consensus in the guidelines over the definition of LVSD and the use of medications other than ACE inhibitors. The ACC/AHA guidelines do not specify a threshold for "reduced ejection fraction," while the European Society of Cardiology guidelines define an ejection fraction less than 0.40 to 0.45 as "abnormal" (7, 37). In addition, while the ACC/AHA guidelines recommend β-blockers for all patients with LVSD, the European Society of Cardiology guidelines restrict this recommendation only to patients with a history of myocardial infarction. There is a paucity of prospective data on the use of β-blockers in patients with asymptomatic LVSD (75, 76).

Because coronary heart disease is a prime contributor to LVSD, it may be argued that individuals with coronary heart disease should receive ACE inhibitors and β-blockers regardless of ejection fraction (77). However, as shown in **Table 2**, most individuals with LVSD in community studies do not report a history of myocardial infarction and thus may not be recognized as candidates for treatment with these medications. Previous studies suggest that even individuals with known coronary heart disease often do not receive the indicated medications or receive suboptimal doses (78). In the Cardiovascular Health Study, only 9% of individuals with asymptomatic LVSD were receiving ACE inhibitors and only 15% were receiving β-blockers (35).

CONCLUSIONS

Asymptomatic LVSD is widely accepted as a preclinical phase of CHF (7). Previous studies have provided substantial insight into the epidemiology of asymptomatic LVSD and indicate that its prevalence in the community is high (3% to 6%). Accordingly, screening for this condition has attracted considerable attention as a strategy to prevent CHF (10).

However, as summarized in this paper, the available evidence is inadequate to support screening for LVSD in the general population. While several landmark trials have enrolled patients with asymptomatic LVSD, the data on the prognosis and treatment of this condition apply to only a subset of individuals who would be identified by screening. We propose directions for future research to address the question of screening and to advance our understanding of the preclinical stages of CHF (**Table 4**).

Table 4. **Summary of Proposed Research Directions***

1. Determine the incidence of asymptomatic LVSD in community-based cohorts.
2. Characterize the natural history of asymptomatic LVSD in the community: a. Natural history in individuals with different degrees of LVSD b. Natural history in individuals with LVSD without previous MI
3. Examine the natural history of subclinical left ventricular diastolic dysfunction.
4. Examine the cost-effectiveness of various screening strategies for identifying left ventricular dysfunction and develop better screening tools.
5. Address the role of medications other than ACE inhibitors in managing patients with asymptomatic LVSD.
6. Increase representation of the following types of patients in clinical trials: patients with mild LVSD, those with LVSD and no history of MI, and those with isolated left ventricular diastolic dysfunction.

* ACE = angiotensin-converting enzyme; LVSD = left ventricular systolic dysfunction; MI = myocardial infarction.

Future Directions for Epidemiologic Research

The incidence of asymptomatic LVSD should be examined because this knowledge is essential for determining screening intervals. Serial echocardiographic evaluation of community-based samples within longitudinal epidemiologic investigations with rigorous quality-control measures (to ensure comparability over time) would be required for this purpose.

Another important direction for future research is better characterization of the natural history of ventricular dysfunction in the community, with attention to the risk for CHF and death, timing of these events, and prognostic factors. Because individual studies may have too few participants with asymptomatic LVSD, pooled analyses of existing databases drawn from well-characterized, community-based cohorts may be an attractive strategy. This may be particularly important for investigating the prognosis of LVSD in specific clinical, demographic, and ethnic subgroups.

Furthermore, the natural history of individuals with different degrees of LVSD should be defined. For instance, individuals with an ejection fraction (qualitative or quantitative) between 0.40 and 0.50 should be distinguished from those with an ejection fraction below 0.40, because their clinical courses probably differ. These longitudinal data will also be critical for validating threshold values for defining LVSD.

A similar approach is needed for defining the natural history associated with subclinical left ventricular diastolic dysfunction. Both functional indices, such as transvalvular or tissue Doppler, and structural changes, such as left atrial enlargement or left ventricular hypertrophy, are candidate markers of left ventricular diastolic dysfunction. Large cohort studies that can investigate both LVSD and diastolic dysfunction should provide insight into the relative contribution of each condition to CHF (45). Such data would enable a more comprehensive assessment of the cost-effectiveness of screening programs for detecting subclinical ventricular dysfunction and preventing CHF.

Finally, it is important to develop and test newer screening tools that perform better than currently available ones for detecting LVSD in the community. *N*-terminal pro-brain natriuretic peptide and cardiotrophin-1 are two potential markers that are being investigated for detecting LVSD and the performance of these peptides in a community setting would be of interest (79, 80).

Future Clinical Trials and Effectiveness Studies

Community-based studies should also provide important information for designing future clinical trials. Future trials should address the role of agents other than ACE inhibitors for managing patients with asymptomatic LVSD and the applicability of current therapies to under-represented subgroups, such as individuals with mild LVSD, those with isolated diastolic dysfunction, and those without previous myocardial infarction. These features probably describe most individuals who would be identified by screening.

Ultimately, the only definitive way to establish the benefits of any screening program is to perform a random-

ized clinical trial of screening versus no screening strategies (14). Again, community-based data would be critical for determining whether such a trial is warranted and for deciding how it should be designed. Even if the efficacy of screening for LVSD were demonstrated in such trials, additional studies would be required to examine whether a screening program is effective (that is, does it reach potential beneficiaries and do they comply with subsequent interventions) (14). In addition to reducing the incidence of hypertension and myocardial infarction, the two major CHF risk factors, a greater understanding of the early identification and treatment of left ventricular dysfunction may be an important step toward the prevention of CHF in the general population.

Note added in proof: Two important studies were published after the submission of our manuscript. Redfield and colleagues (81) recently published the full report of their Doppler echocardiographic survey of 2042 residents of Olmsted County, Minnesota. Among participants without CHF, 20.6% had mild diastolic dysfunction and 6.8% had moderate or severe diastolic dysfunction. Individuals with diastolic dysfunction had a higher mortality after adjustment for age, sex, and ejection fraction. In another recent study, Nielsen and colleagues (82) estimated the cost-effectiveness of brain natriuretic peptide for screening for LVSD, based on data from the Glasgow MONICA survey.

From the National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts; Massachusetts General Hospital, Harvard Medical School, Boston Medical Center, and Boston University School of Medicine, Boston, Massachusetts; and the National Heart, Lung, and Blood Institute, Bethesda, Maryland.

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Requests for Single Reprints: Ramachandran S. Vasan, MD, Framingham Heart Study, 73 Mt. Wayte Avenue, Suite 2, Framingham, MA 01702-5827; e-mail, vasan@fram.nhlbi.nih.gov.

Current author addresses are available at www.annals.org.

References

1. **Pfeffer MA, Braunwald E.** Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. Circulation. 1990;81:1161-72. [PMID: 2138525]

2. **Mann DL.** Mechanisms and models in heart failure: a combinatorial approach. Circulation. 1999;100:999-1008. [PMID: 10468532]

3. **Sutton MG, Sharpe N.** Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. Circulation. 2000;101:2981-8. [PMID: 10869273]

4. **Cohn JN, Ferrari R, Sharpe N.** Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol. 2000;35:569-82. [PMID: 10716457]

5. **Spinale FG.** Matrix metalloproteinases: regulation and dysregulation in the failing heart. Circ Res. 2002;90:520-30. [PMID: 11909815]

6. **MacLellan WR.** Advances in the molecular mechanisms of heart failure. Curr Opin Cardiol. 2000;15:128-35. [PMID: 10952417]

7. **Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, et al.** ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol. 2001;38:2101-13. [PMID: 11738322]

8. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigattors. N Engl J Med. 1992;327:685-91. [PMID: 1463530]

9. **Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ Jr, Cuddy TE, et al.** Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med. 1992;327:669-77. [PMID: 1386652]

10. **McMurray JV, McDonagh TA, Davie AP, Cleland JG, Francis CM, Morrison C.** Should we screen for asymptomatic left ventricular dysfunction to prevent heart failure? Eur Heart J. 1998;19:842-6. [PMID: 9651707]

11. **McDonagh TA, Robb SD, Murdoch DR, Morton JJ, Ford I, Morrison CE, et al.** Biochemical detection of left-ventricular systolic dysfunction. Lancet. 1998; 351:9-13. [PMID: 9433422]

12. **U.S. Preventive Services Task Force.** Guide to Clinical Preventive Services: Report of the U.S. Preventive Services Task Force. 2nd ed. Baltimore: Williams & Wilkins; 1996.

13. **Cogswell ME, Burke W, McDonnell SM, Franks AL.** Screening for hemochromatosis. A public health perspective. Am J Prev Med. 1999;16:134-40. [PMID: 10343890]

14. **Cadman D, Chambers L, Feldman W, Sackett D.** Assessing the effectiveness of community screening programs. JAMA. 1984;251:1580-5. [PMID: 6700057]

15. **Baig MK, Goldman JH, Caforio AL, Coonar AS, Keeling PJ, McKenna WJ.** Familial dilated cardiomyopathy: cardiac abnormalities are common in asymptomatic relatives and may represent early disease. J Am Coll Cardiol. 1998; 31:195-201. [PMID: 9426040]

16. **Giannuzzi P, Temporelli PL, Bosimini E, Silva P, Imparato A, Corrà U, et al.** Independent and incremental prognostic value of Doppler-derived mitral deceleration time of early filling in both symptomatic and asymptomatic patients with left ventricular dysfunction. J Am Coll Cardiol. 1996;28:383-90. [PMID: 8800114]

17. **Lestuzzi C, Nicolosi GL, Neri A, Pavan D, Mimo R, Dall'Aglio V, et al.** Familial dilated cardiomyopathy: a transverse and longitudinal clinical and echocardiographic study. Int J Cardiol. 1991;33:225-31. [PMID: 1743782]

18. **Hernández M, Taylor J, Marinchak R, Rials S, Rubin A, Kowey P.** Outcome of patients with nonsustained ventricular tachycardia and severely impaired ventricular function who have negative electrophysiologic studies. Am Heart J. 1995;129:492-6. [PMID: 7872177]

19. **Aronow WS, Ahn C, Kronzon I.** Effect of beta blockers alone, of angiotensin-converting enzyme inhibitors alone, and of beta blockers plus angiotensin-converting enzyme inhibitors on new coronary events and on congestive heart failure in older persons with healed myocardial infarcts and asymptomatic left ventricular systolic dysfunction. Am J Cardiol. 2001;88:1298-300. [PMID: 11728359]

20. **Redfield MM, Gersh BJ, Bailey KR, Ballard DJ, Rodeheffer RJ.** Natural history of idiopathic dilated cardiomyopathy: effect of referral bias and secular trend. J Am Coll Cardiol. 1993;22:1921-6. [PMID: 8245350]

21. **Redfield MM, Gersh BJ, Bailey KR, Rodeheffer RJ.** Natural history of incidentally discovered, asymptomatic idiopathic dilated cardiomyopathy. Am J Cardiol. 1994;74:737-9. [PMID: 7942539]

22. **Tsutamoto T, Wada A, Maeda K, Hisanaga T, Mabuchi N, Hayashi M, et**

al. Plasma brain natriuretic peptide level as a biochemical marker of morbidity and mortality in patients with asymptomatic or minimally symptomatic left ventricular dysfunction. Comparison with plasma angiotensin II and endothelin-1. Eur Heart J. 1999;20:1799-807. [PMID: 10581138]

23. **Seidman JG, Seidman C.** The genetic basis for cardiomyopathy: from mutation identification to mechanistic paradigms. Cell. 2001;104:557-67. [PMID: 11239412]

24. **Towbin JA, Bowles NE.** Molecular genetics of left ventricular dysfunction. Curr Mol Med. 2001;1:81-90. [PMID: 11899244]

25. **Nicol RL, Frey N, Olson EN.** From the sarcomere to the nucleus: role of genetics and signaling in structural heart disease. Annu Rev Genomics Hum Genet. 2000;1:179-223. [PMID: 11701629]

26. **Devereux RB, Roman MJ, Paranicas M, Lee ET, Welty TK, Fabsitz RR, et al.** A population-based assessment of left ventricular systolic dysfunction in middle-aged and older adults: the Strong Heart Study. Am Heart J. 2001;141:439-46. [PMID: 11231443]

27. **Devereux RB, Bella JN, Palmieri V, Oberman A, Kitzman DW, Hopkins PN, et al.** Left ventricular systolic dysfunction in a biracial sample of hypertensive adults: The Hypertension Genetic Epidemiology Network (HyperGEN) Study. Hypertension. 2001;38:417-23. [PMID: 11566915]

28. **Davies M, Hobbs F, Davis R, Kenkre J, Roalfe AK, Hare R, et al.** Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. Lancet. 2001;358:439-44. [PMID: 11513906]

29. **Schunkert H, Broeckel U, Hense HW, Keil U, Riegger GA.** Left-ventricular dysfunction [Letter]. Lancet. 1998;351:372. [PMID: 9652648]

30. **Hedberg P, Lönnberg I, Jonason T, Nilsson G, Pehrsson K, Ringqvist I.** Left ventricular systolic dysfunction in 75-year-old men and women; a population-based study. Eur Heart J. 2001;22:676-83. [PMID: 11286525]

31. **Nielsen OW, Hilden J, Larsen CT, Hansen JF.** Cross sectional study estimating prevalence of heart failure and left ventricular systolic dysfunction in community patients at risk. Heart. 2001;86:172-8. [PMID: 11454835]

32. **Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A, et al.** Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. Eur Heart J. 1999;20:447-55. [PMID: 10213348]

33. **Kupari M, Lindroos M, Iivanainen AM, Heikkilä J, Tilvis R.** Congestive heart failure in old age: prevalence, mechanisms and 4-year prognosis in the Helsinki Ageing Study. J Intern Med. 1997;241:387-94. [PMID: 9183306]

34. **McDonagh TA, Morrison CE, Lawrence A, Ford I, Tunstall-Pedoe H, McMurray JJ, et al.** Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. Lancet. 1997;350:829-33. [PMID: 9310600]

35. **Gottdiener JS, McClelland RL, Marshall R, Shemanski L, Furberg CD, Kitzman DW, et al.** Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. Ann Intern Med. 2002;137:631-9. [PMID: 12379062]

36. **Morgan S, Smith H, Simpson I, Liddiard GS, Raphael H, Pickering RM, et al.** Prevalence and clinical characteristics of left ventricular dysfunction among elderly patients in general practice setting: cross sectional survey. BMJ. 1999;318:368-72. [PMID: 9933201]

37. **Remme WJ, Swedberg K.** Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J. 2001;22:1527-60. [PMID: 11492984]

38. **McDonagh TA.** Screening for left ventricular dysfunction: a step too far? Heart. 2002;88 Suppl 2:ii12-4. [PMID: 12213794]

39. **Struthers AD, Morris AD.** Screening for and treating left-ventricular abnormalities in diabetes mellitus: a new way of reducing cardiac deaths. Lancet. 2002;359:1430-2. [PMID: 11978359]

40. **McDonagh TA, Cunningham AD, Morrison CE, McMurray JJ, Ford I, Morton JJ, et al.** Left ventricular dysfunction, natriuretic peptides, and mortality in an urban population. Heart. 2001;86:21-6. [PMID: 11410555]

41. **Lauer MS, Evans JC, Levy D.** Prognostic implications of subclinical left ventricular dilatation and systolic dysfunction in men free of overt cardiovascular disease (the Framingham Heart Study). Am J Cardiol. 1992;70:1180-4. [PMID: 1414943]

42. **Sharpe N, Murphy J, Smith H, Hannan S.** Preventive treatment of asymptomatic left ventricular dysfunction following myocardial infarction. Eur Heart J. 1990;11 Suppl B:147-56. [PMID: 2142081]

43. **Køber L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, et al.** A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med. 1995;333:1670-6. [PMID: 7477219]

44. **Køber L, Bloch Thomsen PE, Møller M, Torp-Pedersen C, Carlsen J, Sandøe E, et al.** Effect of dofetilide in patients with recent myocardial infarction and left-ventricular dysfunction: a randomised trial. Lancet. 2000;356:2052-8. [PMID: 11145491]

45. **Aurigemma GP, Gottdiener JS, Shemanski L, Gardin J, Kitzman D.** Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the cardiovascular health study. J Am Coll Cardiol. 2001;37:1042-8. [PMID: 11263606]

46. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med. 1991;325:293-302. [PMID: 2057034]

47. **Flather MD, Yusuf S, Køber L, Pfeffer M, Hall A, Murray G, et al.** Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet. 2000;355:1575-81. [PMID: 10821360]

48. **Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW.** The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol. 2000;35:681-9.

49. **Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW.** Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. J Am Coll Cardiol. 1998;32:695-703. [PMID: 9741514]

50. **Dries DL, Sweitzer NK, Drazner MH, Stevenson LW, Gersh BJ.** Prognostic impact of diabetes mellitus in patients with heart failure according to the etiology of left ventricular systolic dysfunction. J Am Coll Cardiol. 2001;38:421-8. [PMID: 11499733]

51. **Vasan RS, Benjamin EJ, Levy D.** Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol. 1995;26:1565-74. [PMID: 7594087]

52. **Redfield MM, Burnett JC, Jacobsen SJ, Mahoney DW, Rodeheffer RJ.** Prevalence of left ventricular systolic and diastolic dysfunction in Olmsted county, MN: a population-based, cross-sectional Doppler-echocardiographic survey [Abstract]. J Am Coll Cardiol. 2001;37:145A.

53. **Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, et al.** Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation. 1998;98:2282-9. [PMID: 9826315]

54. **Zile MR, Brutsaert DL.** New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. Circulation. 2002;105:1387-93. [PMID: 11901053]

55. **Boyko EJ.** Ruling out or ruling in disease with the most sensitive or specific diagnostic test: short cut or wrong turn? Med Decis Making. 1994;14:175-9. [PMID: 8028470]

56. **Krishnaswamy P, Lubien E, Clopton P, Koon J, Kazanegra R, Wanner E, et al.** Utility of B-natriuretic peptide levels in identifying patients with left ventricular systolic or diastolic dysfunction. Am J Med. 2001;111:274-9. [PMID: 11566457]

57. **Yamamoto K, Burnett JC Jr, Jougasaki M, Nishimura RA, Bailey KR, Saito Y, et al.** Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. Hypertension. 1996;28:988-94. [PMID: 8952587]

58. **Yamamoto K, Burnett JC Jr, Bermudez EA, Jougasaki M, Bailey KR, Redfield MM.** Clinical criteria and biochemical markers for the detection of systolic dysfunction. J Card Fail. 2000;6:194-200. [PMID: 10997744]

59. **Lerman A, Gibbons RJ, Rodeheffer RJ, Bailey KR, McKinley LJ, Heublein DM, et al.** Circulating N-terminal atrial natriuretic peptide as a marker for symptomless left-ventricular dysfunction. Lancet. 1993;341:1105-9. [PMID: 8097801]

60. **Omland T, Aakvaag A, Vik-Mo H.** Plasma cardiac natriuretic peptide de-

termination as a screening test for the detection of patients with mild left ventricular impairment. Heart. 1996;76:232-7. [PMID: 8868981]

61. **Davidson NC, Naas AA, Hanson JK, Kennedy NS, Coutie WJ, Struthers AD.** Comparison of atrial natriuretic peptide B-type natriuretic peptide, and N-terminal proatrial natriuretic peptide as indicators of left ventricular systolic dysfunction. Am J Cardiol. 1996;77:828-31. [PMID: 8623734]

62. **Vasan RS, Levy D, Larson MG, Benjamin EJ.** Interpretation of echocardiographic measurements: a call for standardization. Am Heart J. 2000;139:412-22. [PMID: 10689255]

63. **Nielsen OW, Hansen JF, Hilden J, Larsen CT, Svanegaard J.** Risk assessment of left ventricular systolic dysfunction in primary care: cross sectional study evaluating a range of diagnostic tests. BMJ. 2000;320:220-4. [PMID: 10642232]

64. **Davie AP, Francis CM, Love MP, Caruana L, Starkey IR, Shaw TR, et al.** Value of the electrocardiogram in identifying heart failure due to left ventricular systolic dysfunction. BMJ. 1996;312:222. [PMID: 8563589]

65. **Rihal CS, Davis KB, Kennedy JW, Gersh BJ.** The utility of clinical, electrocardiographic, and roentgenographic variables in the prediction of left ventricular function. Am J Cardiol. 1995;75:220-3. [PMID: 7832126]

66. **Kelly R, Struthers AD.** Screening for left ventricular systolic dysfunction in patients with stroke, transient ischaemic attacks, and peripheral vascular disease [Editorial]. QJM. 1999;92:295-7. [PMID: 10616704]

67. **Luchner A, Burnett JC Jr, Jougasaki M, Hense HW, Heid IM, Muders F, et al.** Evaluation of brain natriuretic peptide as marker of left ventricular dysfunction and hypertrophy in the population. J Hypertens. 2000;18:1121-8. [PMID: 10954005]

68. **Arnlöv J, Lind L, Stridsberg M, Andrén B, Lithell H.** N-terminal atrial natriuretic peptide and left ventricular geometry and function in a population sample of elderly males. J Intern Med. 2000;247:699-708. [PMID: 10886492]

69. **Vasan RS, Benjamin EJ, Larson MG, Leip EP, Wang TJ, Wilson PW, et al.** Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. JAMA. 2002;288: 1252-9. [PMID: 12215132]

70. **Friedl W, Mair J, Thomas S, Pichler M, Puschendorf B.** Natriuretic peptides and cyclic guanosine 3′,5′-monophosphate in asymptomatic and symptomatic left ventricular dysfunction. Heart. 1996;76:129-36. [PMID: 8795474]

71. **Muders F, Kromer EP, Griese DP, Pfeifer M, Hense HW, Riegger GA, et al.** Evaluation of plasma natriuretic peptides as markers for left ventricular dysfunction. Am Heart J. 1997;134:442-9. [PMID: 9327700]

72. **Smith H, Pickering RM, Struthers A, Simpson I, Mant D.** Biochemical diagnosis of ventricular dysfunction in elderly patients in general practice: observational study. BMJ. 2000;320:906-8. [PMID: 10741999]

73. **Landray MJ, Lehman R, Arnold I.** Measuring brain natriuretic peptide in suspected left ventricular systolic dysfunction in general practice: cross-sectional study. BMJ. 2000;320:985-6. [PMID: 10753153]

74. **Hetmanski DJ, Sparrow NJ, Curtis S, Cowley AJ.** Failure of plasma brain natriuretic peptide to identify left ventricular systolic dysfunction in the community. Heart. 2000;84:440-1. [PMID: 10995422]

75. **Vantrimpont P, Rouleau JL, Wun CC, Ciampi A, Klein M, Sussex B, et al.** Additive beneficial effects of beta-blockers to angiotensin-converting enzyme inhibitors in the Survival and Ventricular Enlargement (SAVE) Study. SAVE Investigators. J Am Coll Cardiol. 1997;29:229-36. [PMID: 9014971]

76. **Doughty RN, Whalley GA, Gamble G, MacMahon S, Sharpe N.** Left ventricular remodeling with carvedilol in patients with congestive heart failure due to ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group. J Am Coll Cardiol. 1997;29:1060-6. [PMID: 9120160]

77. **Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G.** Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000;342:145-53. [PMID: 10639539]

78. **Soumerai SB, McLaughlin TJ, Spiegelman D, Hertzmark E, Thibault G, Goldman L.** Adverse outcomes of underuse of beta-blockers in elderly survivors of acute myocardial infarction. JAMA. 1997;277:115-21. [PMID: 8990335]

79. **Richards AM, Nicholls MG, Yandle TG, Frampton C, Espiner EA, Turner JG, et al.** Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: new neurohormonal predictors of left ventricular function and prognosis after myocardial infarction. Circulation. 1998;97:1921-9. [PMID: 9609085]

80. **Talwar S, Squire IB, O'Brien RJ, Downie PF, Davies JE, Ng LL.** Plasma cardiotrophin-1 following acute myocardial infarction: relationship with left ventricular systolic dysfunction. Clin Sci (Lond). 2002;102:9-14. [PMID: 11749655]

81. **Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ.** Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003; 289:194-202. [PMID: 12517230]

82. **Nielsen OW, McDonagh TA, Robb SD, Dargie HJ.** Retrospective analysis of the cost-effectiveness of using plasma brain natriuretic peptide in screening for left ventricular systolic dysfunction in the general population. J Am Coll Cardiol. 2003;41:113-20. [PMID: 12570953]

Current Author Addresses: Drs. Wang, Levy, Benjamin, and Vasan: Framingham Heart Study, 73 Mt. Wayte Avenue, Suite 2, Framingham, MA 01702-5827.