

## Stage B Heart Failure

### Management of Asymptomatic Left Ventricular Systolic Dysfunction

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Heart failure (HF) is a clinical syndrome characterized by symptoms of effort intolerance (eg, dyspnea and fatigue) and/or signs of fluid retention (eg, pulmonary congestion and peripheral edema) due to a variety of pathological processes that perturb normal cardiac function. Approximately 50% of HF patients present with evidence of left ventricular systolic dysfunction (LVSD) manifested as a low left ventricular ejection fraction (LVEF); the remaining half are found to have preserved left ventricular (LV) function.<sup>1</sup> HF with either low or normal LVEF represents a significant contemporary medical problem that affects an estimated 5 million people in the United States, with an annual mortality rate approaching 20%.<sup>2</sup>

HF is considered a progressive disorder that can be represented as a clinical continuum. The American College of Cardiology/American Heart Association (ACC/AHA) updated 2005 guidelines for the management of chronic HF identify 4 stages in this continuum (Figure 1)<sup>3</sup> and link the stages in the natural history of HF to therapeutic recommendations for each stage. Previously, the New York Heart Association (NYHA) functional classification, based solely on the severity of symptoms (primarily of patients in ACC/AHA stage C or D), was used as a criteria to initiate or change HF therapy. NYHA classification can change over a relatively short period of time even in the absence of medication changes. Nearly every patient who presents to an emergency department for care has at least NYHA class III or IV symptoms; however, at discharge after treatment, many patients are minimally symptomatic. Clinicians must then decide whether to apply NYHA class IV therapies or only class II therapies, which leads to some uncertainty. This approach may result in the undertreatment of some patients with severe LV dysfunction who might be only mildly symptomatic.

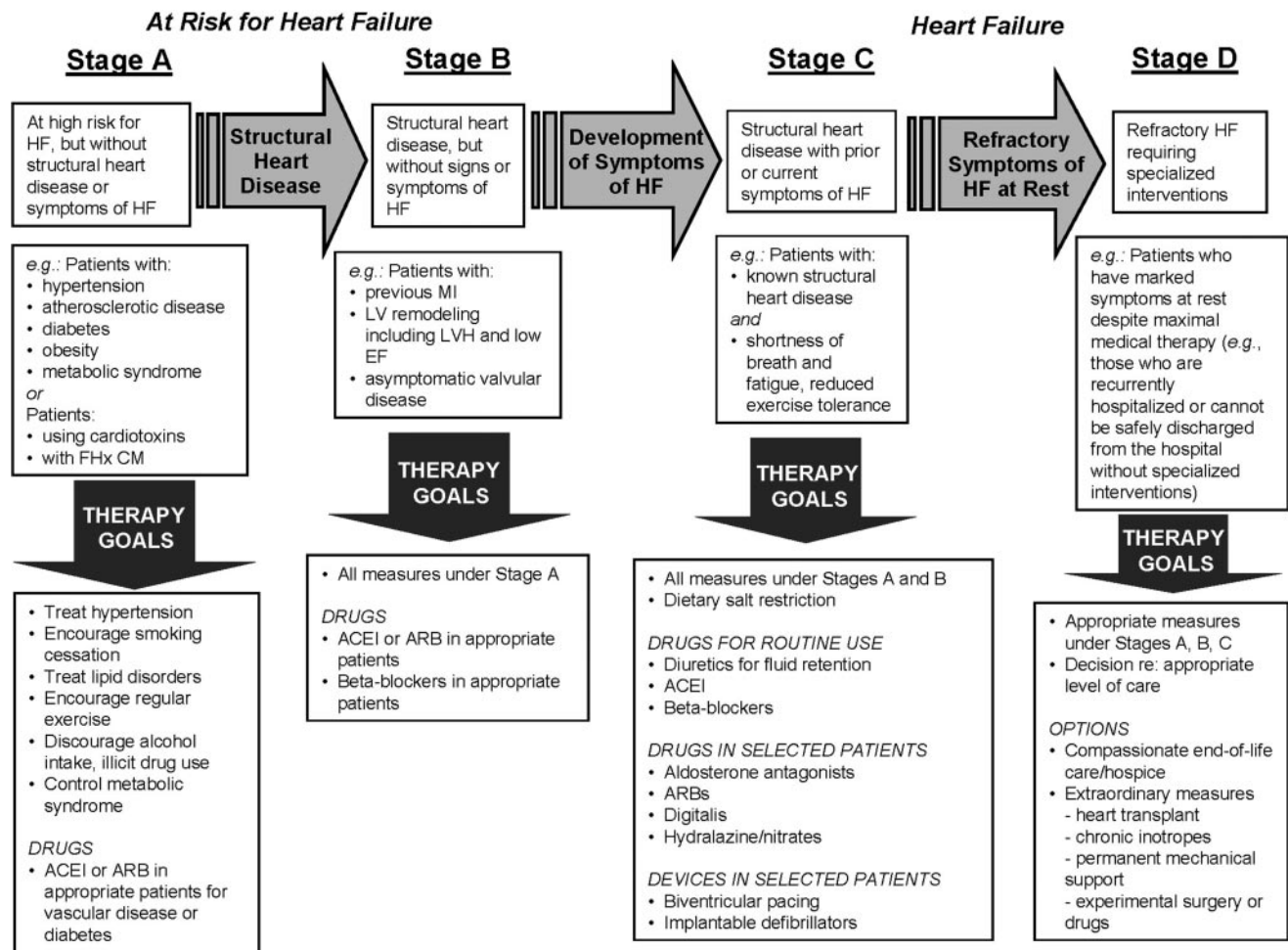
Stage B HF, as defined by the ACC/AHA guidelines, includes patients with structural heart disease but no current or prior symptoms of HF. Once a patient experiences symptoms of HF, they advance to stage C even if they later become asymptomatic. The current guidelines stipulate that patients may only move forward through the stages and not regress. Not every patient with symptomatic HF (stage C or D) has progressed through the stage of reduced LVEF without symptoms of HF (stage B). For example, an asymptomatic

individual with known hypertension, diabetes mellitus, and abnormal lipids (stage A) may experience a large anterior wall myocardial infarction (MI) and develop severe LVSD and markedly symptomatic HF. This patient would now be classified as stage C. Conversely, a second patient might suffer a small inferior wall MI but never develop effort intolerance or fluid retention, despite a structural abnormality of the LV as a residual from the MI. This patient, therefore, would be classified as stage B.

The number of patients with LVSD in stage B is estimated to be 4 times greater than in stages C and D combined.<sup>4</sup> These patients remain at risk for significant morbidity and mortality and the subsequent development of symptomatic HF.<sup>5</sup> Despite the high risk associated with asymptomatic LVSD, these patients often go undetected and untreated. As one example, the utilization of angiotensin-converting enzyme (ACE) inhibitors in patients with asymptomatic LVSD was evaluated using the medical records of a consecutive series of hospitalized patients with objective findings of LVSD but no evidence of current or prior HF.<sup>6</sup> In 68% of the cases reviewed, the initial diagnosis of LVSD was made with an echocardiogram performed during the index admission. Other sources of evidence of LVSD included a prior echocardiogram and cardiac catheterization either during or before the index admission. During the index hospitalization, 51 patients (48%) did not receive ACE inhibitor treatment, 34 (32%) were newly initiated on an ACE inhibitor regimen, and 20 (19%) were continued on a previously established ACE inhibitor regimen. Patients with a history of hypertension or MI were more likely to be prescribed an ACE inhibitor at the time of hospital discharge. These findings indicate that despite a large body of data and the recommendation of several practice guidelines, approximately half of patients who were admitted and found to have asymptomatic LVSD did not receive ACE inhibitors at the time of discharge.<sup>6</sup> The rate of 50% ACE inhibitor treatment was seen in the hospital, when patients are most likely to be started on therapy. Patients with asymptomatic LVSD who are not admitted to the hospital are undoubtedly even less likely to be recognized and treated.

This review primarily examines the available data on the demographics of stage B patients with systolic dysfunction and summarizes relevant clinical trials that might provide

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**Figure 1.** ACC/AHA guidelines for the evaluation and management of chronic HF: evolution of HF and recommended therapy by stage. ACEI indicates ACE inhibitors; EF, ejection fraction; FHx CM, family history of cardiomyopathy; IV, intravenous; LVH, LV hypertrophy. Adapted from Hunt et al,<sup>3</sup> with permission from the American College of Cardiology Foundation.

insight into appropriate management of these patients. Patients with LV hypertrophy but who have not experienced HF are also classified as stage B HF but will not be reviewed here. Several studies, however, have evaluated the regression of LV hypertrophy in the setting of hypertension (eg, Losartan Intervention for Endpoint Reduction [LIFE] in hypertension) that would incorporate this group of patients.

It is important to recognize that the largest proportion of patients with stage B LVSD evaluated in clinical trials have had an ischemic origin, either from a recognized MI or subclinical myocardial necrosis, often exacerbated by hypertension and/or diabetes mellitus. Ischemia in the form of angina or infarction is often the trigger to evaluate an otherwise asymptomatic patient and discover the LV dysfunction. In addition, a smaller but still sizable number of stage B LVSD patients present with a nonischemic cause, including those with hypertensive or valvular heart disease, cardiotoxin exposure, post-viral infection/myocarditis, or familial idiopathic dilated cardiomyopathy.

Results of large, randomized clinical trials conducted in patients with asymptomatic LVSD have demonstrated that several pharmacological therapies significantly reduce the risk of progression to symptomatic HF and associated death,

as well as sudden cardiac death. It is critical, therefore, that physicians understand the prevalence, diagnosis, and optimal treatment of asymptomatic LVSD.

## Prevalence

Stage B includes patients with asymptomatic abnormalities of cardiac structure. It is possible, of course, that many patients with these myocardial disorders minimize or deny their symptoms, despite demonstrable exercise intolerance. The onset of HF symptoms is gradual and may not be appreciated or acknowledged by patients. These patients may remain apparently symptom-free by unconsciously reducing activity levels to compensate for worsening exertional symptoms. Therefore, clinicians may need objective testing, including formal exercise testing, to truly differentiate stage B from stage C patients. This makes the identification of stage B patients in epidemiological or treatment trials more challenging.

Wang et al<sup>7</sup> performed a comprehensive search of studies that estimated the prevalence of asymptomatic LVSD. Prevalence reports vary according to the methods used to measure ventricular function, the categorical cutoff used to define low LVEF (which ranges from 30% to 54%), the clinical criteria

used to define “asymptomatic,” and the population characteristics studied. Although the prevalence of stage B patients in individual studies varied from 0.9% to 12.9% in the community, adjustment for the above factors yielded 3% to 6% as a reasonable estimate for the presence of asymptomatic LVSD in the adult population. Therefore, asymptomatic LVSD, or stage B, is at least as common as symptomatic HF (stages C and D). In addition, Wang and colleagues concluded that more than half of all patients with impaired systolic function (34% to 92% of patients) had been reported to be asymptomatic.

Other investigations have also assessed the prevalence of asymptomatic LVSD. In a study of 2042 randomly selected men and women aged  $\geq 45$  years, 65% of subjects with a low LVEF (defined as 2 SDs less than normal) were free from HF symptoms.<sup>8</sup> A previous study included patients with an LVEF  $< 35\%$  and reported that 77% of that population subset were asymptomatic.<sup>9</sup> The prevalence of asymptomatic LVSD has been reported to be 2- to 8-fold greater in men than in women. In the Framingham population, the prevalence of asymptomatic LVSD was 6.0% in men and 0.8% in women and increased significantly with age: Only 2.1% of women aged 40 to 59 years with LVSD were asymptomatic compared with 14.3% of men aged 80 years and older.<sup>5</sup>

### Etiology

The assumption has been that most LVSD progresses gradually, beginning with myocardial injury of various causes, most commonly due to the loss of functioning myocytes from an acute infarction, often exacerbated by hypertension or diabetes mellitus. Depending on the extent of acute injury to the myocardium, clinical evidence of HF occurs in only 2% to 20% of patients within the first 4 weeks after an MI.<sup>10</sup> The initial loss of cardiac function results in the activation of compensatory mechanisms, such as peripheral vasoconstriction, salt and water retention, or enhanced contractility of noninfarcted myocardium, to maintain homeostatic levels of systemic blood flow and pressure. In the ensuing weeks and months, structural changes (remodeling) result in an increased LV chamber size (dilatation) and wall thickness (hypertrophy), accompanied by myocardial fibrosis. The resultant changes in LV shape toward a more spherical, less efficient chamber (increased sphericity) are accompanied by an increased end-diastolic volume, reduced systolic function (low LVEF), and a decrease in ventricular compliance. These remodeling forces are mediated in part by the neurohormones of the sympathetic nervous system and the renin-angiotensin-aldosterone system. The remodeling process can persist despite the absence of any further myocardial injury, producing progressive increases in LV volume and concomitant diminution of contractility. This progression of structural deterioration leads to the eventual emergence of HF symptoms in an increasing proportion of patients.

Hypertension and coronary artery disease (CAD) have been identified as the most important underlying causes of HF in the United States and accounted for  $> 80\%$  of all HF events in a 34-year follow-up of the Framingham Heart Study population.<sup>11</sup> The Framingham Study found that 65% of patients with asymptomatic LVSD had a prior history of

hypertension, and 49% had suffered a previous MI.<sup>7</sup> Concomitant hypertension can decrease the threshold for the emergence of post-MI HF, due to LV hypertrophy-associated decreases in diastolic compliance and structural and functional abnormalities of the coronary microcirculation.<sup>12</sup> Of all HF cases from the original Framingham data, 91% were antedated by the presence of hypertension; this was particularly evident for HF in the elderly, women, and blacks.<sup>13</sup>

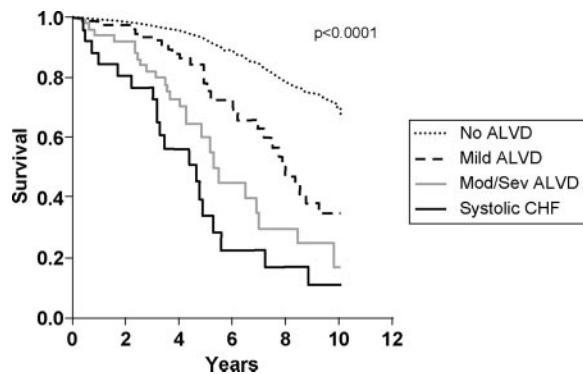
The National Health and Nutrition Evaluation Survey (NHANES) I Epidemiologic Follow-up Study of  $> 13\,000$  men and women without HF at baseline found that after an average of 19 years,  $> 60\%$  of all HF cases were attributable to CAD.<sup>14</sup> CAD is present in nearly 70% of all patients enrolled in multicenter HF treatment trials. Nevertheless, CAD may still be underestimated as the cause of HF, because ischemic cardiomyopathy may be present without a history of MI, angina, or other distinct ischemic events.<sup>15</sup> Autopsy results of the Assessment of Treatment With Lisinopril and Survival (ATLAS) trial revealed that nearly one third of subjects with HF who died suddenly had clinically unrecognized CAD.<sup>16</sup> In the Studies of Left Ventricular Dysfunction (SOLVD) prevention trial of 4228 patients with asymptomatic LVSD, 83% had a history of ischemic CAD, and 37% had a history of hypertension.<sup>17</sup> The SOLVD trials also identified the role of race with respect to the risk conferred by coexistent hypertension or CAD. In the SOLVD registry, only 36% of black patients had an ischemic origin for their HF compared with the much higher percentage (65%) in the general population.<sup>17a</sup> The role of hypertension as a precedent for HF was similar in the white and black study patients.<sup>13</sup> Populations other than predominantly white, middle-aged men are less often studied, which highlights the importance of race when one assesses risk factors for asymptomatic LVSD.

There are other factors that appear to determine which patient will develop clinical HF once myocardial injury has occurred. Diabetes may contribute to systolic dysfunction through a unique type of both structural and functional abnormalities related to increased fibrosis and irreversible collagen glycation. In addition, diabetes serves to promote coronary atherosclerosis through effects on lipid metabolism and endothelial function.<sup>18</sup> LV performance, as measured with standard echocardiography and dobutamine stress echocardiography, is impaired in a higher percentage of diabetic patients without clinically apparent heart disease. The abnormalities have been inversely associated with the degree of glycemic control.<sup>19</sup>

A study by Redfield et al<sup>20</sup> evaluated 222 patients with idiopathic dilated cardiomyopathy with LVEF  $< 50\%$ . In this group, 14% never had symptoms of HF, which suggests that an asymptomatic state may precede HF in patients with idiopathic dilated cardiomyopathy.<sup>20</sup> Other clinical characteristics that have been identified as independent risk factors for the future development of clinical, and therefore presumably preclinical, HF in the NHANES I Epidemiologic Follow-Up Study include physical inactivity, cigarette smoking, obesity, and valvular heart disease.<sup>14</sup>

From the above data, it is clear that many patients with significant abnormalities of cardiac function are apparently asymptomatic. If intervention in these patients is indeed





**Figure 2.** Kaplan-Meier curves for survival. Reference group (No ALVD) consists of subjects with normal LV systolic function (LVEF >50%) and no history of congestive HF. Mild ALVD indicates mild asymptomatic LVSD (LVEF 40% to 50%); Mod/Sev ALVD, moderate-to-severe asymptomatic LVSD (LVEF <40%); and Systolic CHF, congestive heart failure with LVEF ≤50%. Adapted from Wang et al,<sup>5</sup> with permission from the American Heart Association.

beneficial, it implies that screening programs will need to be implemented to detect these individuals. Thus, it is important to review the evidence concerning the natural history of stage B patients with LVSD.

### Outcomes

Perhaps the most compelling prognostic data come from the Framingham Study on 4257 participants and an assessment of their risk of progression from asymptomatic LVSD to clinical HF. Subjects ( $n=129$ ) with asymptomatic LVSD at entry had a nearly 5-fold increase in the risk of developing HF compared with those with normal LV function.<sup>5</sup> Forty-nine percent of the patients categorized with asymptomatic LVSD had a previous MI, whereas only 2% of patients with normal LV function had a previous MI. During an average follow-up of only 5 years, 26% of subjects with asymptomatic LVSD developed HF; 40% of subjects with asymptomatic LVSD died compared with 12% of subjects with normal baseline LV function. The mean age at baseline was 61 years for those with normal LVEF and 69 years for those with LVSD. The median survival for subjects with asymptomatic LVSD was only 7.1 years (Figure 2).<sup>5</sup>

The SOLVD prevention trial followed 2117 placebo-treated patients with asymptomatic LVSD and an LVEF below 35%.<sup>17</sup> In this study, “asymptomatic” was used to describe patients who were not being treated for HF; 67% of patients were classified as being in NYHA class I, and the remaining patients were class II. The mean LVEF was 28%, which suggests a severe degree of systolic impairment in this large cohort despite the absence of HF symptoms. Over an average follow-up period of 3 years, the placebo group experienced a 16% mortality rate, with 5% dying within the first year, and nearly one third progressed to symptomatic HF. Mortality and HF risk were associated with the degree of baseline systolic dysfunction.<sup>17</sup> In the Survival and Ventricular Enlargement Study (SAVE) of 2231 post-MI patients with reduced LV function (LVEF <40%) but without overt HF, 13% developed progressive HF, with 14% (active treat-

ment) compared with 17% (placebo treatment) requiring hospitalization for worsening HF.<sup>21</sup>

Patients with asymptomatic LVSD are at increased risk for sudden death. In the SOLVD prevention trial, 5% of participants suffered sudden cardiac death that was not preceded by worsening HF.<sup>17</sup> In SAVE, 7% of placebo-treated and 6% of captopril-treated patients with asymptomatic LVSD died suddenly without prior worsening HF, and another 5% and 4%, respectively, died suddenly after worsening HF.<sup>21</sup> In the Framingham Study population, 43% of patients with asymptomatic LVSD who died of CAD did so suddenly.<sup>5</sup>

### Management

There are 2 primary challenges for clinicians in attempting to manage this group of patients: treatment compliance and a paucity of evidence-based recommendations. Patients with asymptomatic LVSD feel good and may be unwilling to take medications for an extended period of time, especially if they lead to side effects or increased healthcare costs. Also, data supporting the use of specific therapies are limited. Without a structured screening program, identification of asymptomatic patients is difficult, because they are unlikely to present for care. Unfortunately, no cost-effective screening program has been developed. In this population, most of the existing studies are in patients presenting with coronary ischemia who, in the course of their evaluation, are identified as having LVSD without symptoms of HF. Only limited data are available for patients with nonischemic cardiomyopathies, who in clinical practice are most commonly identified incidentally from an abnormal ECG or chest radiograph.

Large-scale, randomized clinical trials of patients with HF due to LVSD have demonstrated that pharmacological treatment significantly improves clinical outcomes by interrupting the neurohormonal systems responsible for cardiac remodeling. Many of the patients in these trials might be correctly classified as stage B, because LVSD was commonly a primary determinant for enrollment, often without a concomitant need for HF symptoms. A review of these studies provides important insights into the role of medical therapy for patients with asymptomatic LVSD. Likewise, Table 1 provides a summary of recent trials that have included patients with asymptomatic LVSD.

### ACE Inhibitors

The SOLVD prevention trial demonstrated significantly better mortality and morbidity outcomes with the ACE inhibitor enalapril than with placebo in patients with asymptomatic LVSD.<sup>17</sup> Although treatment during the 3-month follow-up showed an insignificant 8% mortality reduction, an extended 12-year follow-up of these patients found a 14% reduction of risk for mortality in the enalapril-treated patients, a highly statistically and clinically significant result.<sup>32</sup>

The SAVE trial specifically enrolled only patients ( $n=2231$ ) with asymptomatic LVSD who had survived the first 3 days after an acute MI and randomly assigned them to treatment with captopril or placebo.<sup>21</sup> The mean baseline LVEF was 31%; when LV function was reassessed near the end of the follow-up period, 16% of placebo-treated patients demonstrated further deterioration of LV function, as indi-

TABLE 1. Clinical Trials in Patients With Asymptomatic LVSD

Study	Patient Population (n)	Treatment	Average Duration, mo	Relative Mortality Risk Reduction	Sudden Death Risk Reduction	Death Due to Worsening HF Risk Reduction
<b>ACE inhibitors</b>						
SAVE <sup>21</sup>	AMI and asymptomatic LVSD (2231)	Captopril vs placebo	42	19% ( $P=0.019$ )	No difference ( $P=NS$ )	36% ( $P=0.032$ )
SOLVD Prevention <sup>17</sup>	Asymptomatic LVSD (4228)	Enalapril vs placebo	37.4	8% ( $P=NS$ )	No difference ( $P=NS$ )	20%* ( $P<0.001$ )
TRACE <sup>22,23</sup>	MI and LVSD (6676; 1749 randomized); Asymptomatic LVSD (542)	Trandolapril vs placebo	24–50	22% ( $P=0.001$ )	24% ( $P=0.03$ )	29%† ( $P=0.003$ )
<b><math>\beta</math>-Blockers</b>						
Retrospective analysis of SOLVD Prevention <sup>24</sup>	Asymptomatic LVSD (4228; 1015 patients taking $\beta$ -blockers)	$\beta$ -Blockers vs no $\beta$ -blockers plus enalapril	37.4	23% ( $P<0.01$ )	28%‡ ( $P<0.05$ )	29% ( $P<0.05$ )
Post hoc analysis of SAVE <sup>25</sup>	Asymptomatic LVSD (2231; 789 patients taking $\beta$ -blockers)	$\beta$ -Blockers vs no $\beta$ -blockers plus captopril	42	43% ( $P<0.001$ )	NR	32%† ( $P<0.001$ )
ANZ <sup>26</sup>	HF (415); asymptomatic LVSD (124)	Carvedilol vs placebo	19	36%* ( $P=0.02$ )	10% ( $P=NS$ )	8% ( $P=NS$ )
CAPRICORN <sup>27</sup>	Post-AMI LVSD (1959); asymptomatic LVSD (1023)	Carvedilol vs placebo (including ACE inhibitor)	15.6	23% ( $P=0.03$ )	26% ( $P=0.098$ )	40% ( $P=0.083$ )
<b>ARBs</b>						
VALIANT <sup>28</sup>	MI and LVSD, HF, or both (14 703) Asymptomatic LVSD (4099)	Valsartan, captopril, or both	24.7	No difference ( $P=NS$ )	NR	No difference ( $P=NS$ )
OPTIMAAL <sup>29</sup>	AMI and symptomatic HF (5477); asymptomatic LVSD (1735)	Losartan vs captopril	32.4	13% Increase in risk with losartan ( $P=0.069$ )	19% Increase in risk with losartan ( $P=0.072$ )	NR
<b>ICDs</b>						
MADIT-II <sup>30</sup>	MI and LVEF $\leq 30\%$ (1232); asymptomatic LVSD (461)	ICD vs CMT	20	31% ( $P=0.016$ )	NR	NR
DEFINITE <sup>31</sup>	Nonischemic dilated cardiomyopathy, LVEF $< 36\%$ (458); asymptomatic LVSD (99)	ICD vs CMT	29	35% ( $P=NS$ )	80%§ ( $P=0.006$ )	NR

AMI indicates acute MI; CMT, conventional medical therapy; and NR, not reported.

\*Death or hospitalization for HF.

†Severe HF.

‡Arrhythmic death.

§Sudden death due to arrhythmia.

cated by a reduction of  $\geq 9$  LVEF units. The emergence of symptomatic HF also occurred in 16% of the placebo-treated patients, severe enough in 17% of these patients to require hospitalization; half of this group subsequently died. Overall, total mortality was 25% for the placebo arm of asymptomatic LVSD patients after MI; 12% died within 1 year. Compared with placebo, captopril treatment resulted in a 19% reduction in all-cause mortality ( $P<0.019$ ), a 22% reduction in HF hospitalization ( $P<0.019$ ), and a 36% reduction in death due to worsening HF ( $P<0.032$ ).<sup>21</sup>

The Trandolapril Cardiac Evaluation (TRACE) randomized 1749 patients with acute MI and an LVEF  $< 35\%$ , 31% of whom had asymptomatic LVSD, to treatment with trandolapril or placebo for up to 50 months.<sup>22,23</sup> Compared with placebo, ACE inhibitor therapy resulted in a 30% mortality risk reduction in patients with asymptomatic LVSD. Thus, these 3 studies, in which almost all of the patients could be classified as stage B with LVSD, unequivocally demonstrate the marked beneficial effect of ACE inhibitor therapy on morbidity and mortality.

There are few data on the impact of treatment of asymptomatic LVSD in women or different racial groups. The only trial to show the effect of therapy on a group of black patients with asymptomatic LVSD is a post hoc analysis of the SOLVD trial. Randomization to enalapril was associated with

a comparable reduction in the relative risk of the development of symptomatic HF in black (relative risk 0.67, 95% confidence interval [CI] 0.49 to 0.92,  $P=0.01$ ) and white (relative risk 0.61, 95% CI 0.53 to 0.70,  $P<0.001$ ) patients. Treatment with enalapril was also associated with a comparable reduction in the risk of the development of HF requiring medical therapy and the composite end point of death or development of HF in black and white patients.<sup>33</sup> The ACC/AHA guideline recommendations for the use of ACE inhibitors in stage B patients are summarized in Table 2.<sup>3</sup>

### $\beta$ -Adrenergic Blockers

Maladaptive sympathetic nervous system activity continues in patients with asymptomatic LVSD despite treatment with ACE inhibitors, which leads to negative remodeling and clinical events. In a post hoc analysis of the SOLVD prevention trial, the benefit of adding  $\beta$ -blockers to ACE inhibitors in asymptomatic patients with LVSD was observed; the 25% of patients who were receiving both  $\beta$ -blockers and ACE inhibitors had significantly lower rates of mortality and hospitalization for HF than those not receiving  $\beta$ -blockers.<sup>24</sup> Retrospective data analysis of the SAVE trial also found that the 35% of patients who were concomitantly receiving  $\beta$ -blockers had a 30% lower risk of death and a 21% lower rate of progression to overt HF, independent of captopril use.<sup>25</sup>

**TABLE 2. ACC/AHA Guideline Recommendations and Levels of Evidence for Stage B Patients With Systolic Dysfunction****ACE inhibitors**

## Class I

Use of ACE inhibitors in all patients with a recent or remote history of MI regardless of the presence of HF (Level of Evidence: A)

Use of ACE inhibitors in patients with a reduced LVEF and no symptoms of HF, even if they have not experienced MI (Level of Evidence: A)

 **$\beta$ -Blockers**

## Class I

Use of  $\beta$ -blockers in all patients with a recent or remote history of MI regardless of the presence of HF (Level of Evidence: A)

$\beta$ -Blockers are indicated in all patients without a history of MI who have a reduced LVEF with no HF symptoms (Level of Evidence: C)

**ARBs**

## Class I

An ARB should be administered to post-MI patients without HF who are intolerant of ACE inhibitors and have a low LVEF (Level of Evidence: B)

## Class IIa

ARBs can be beneficial in patients with low LVEF and no symptoms of HF who are intolerant of ACE inhibitors (Level of Evidence: C)

**Digoxin**

## Class III

Digoxin should not be used in patients with low LVEF, sinus rhythm, and no history of HF symptoms, because in this population, the risk of harm is not balanced by any known benefit (Level of Evidence: C)

**ICDs**

## Class IIa

Placement of an ICD is reasonable in patients with ischemic cardiomyopathy who are at least 40 days post-MI, have an LVEF of 30% or less, are NYHA functional class I on chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year (Level of Evidence: B)

## Class IIb

Placement of an ICD might be considered in patients without HF who have nonischemic cardiomyopathy and an LVEF less than or equal to 30% who are in NYHA functional class I with chronic optimal medical therapy and have a reasonable expectation of survival with good functional status for more than 1 year (Level of Evidence: C)

Data derived from Hunt et al.<sup>3</sup>

The Australia–New Zealand Heart Failure trial randomized 415 patients with LVSD (LVEF  $\leq 45\%$ ), 30% of whom were asymptomatic, to carvedilol or placebo. Most patients received concurrent ACE inhibitor therapy (86%). After 1 year, carvedilol-treated patients had a significant improvement in LVEF compared with placebo-treated patients.<sup>26</sup>

In the Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) trial, 53% of the 1959 post-MI patients with a reduced LVEF (mean 33%) were asymptomatic.<sup>27,34</sup> Nearly all patients were receiving ACE inhibitors, and 46% underwent thrombolysis or percutaneous transluminal coronary angioplasty. In a subgroup analysis of the asymptomatic or stage B patients from CAPRICORN, the use of carvedilol resulted in a risk reduction of 31% in all-cause mortality.<sup>35</sup>

$\beta$ -Blockers may reverse LV remodeling and slow its progression. An echocardiographic substudy of 127 patients in CAPRICORN found that carvedilol resulted in statistically greater reductions in LV volumes and superior improvements in LVEF compared with placebo after 6 months of treatment.<sup>36</sup> The effect of ACE inhibitors and  $\beta$ -blockers on cardiac remodeling were tested in the Carvedilol ACE Inhibitor Remodeling Mild CHF Evaluation (CARMEN), an 18-month trial in NYHA class I (8%), II (63%), and III (29%) patients.<sup>37</sup> Treatment with carvedilol resulted in reduced LV size and increased cardiac function. Patients who were treated with ACE inhibition alone (enalapril) had no decrease in LV

size and a small, late increase in LVEF. The combined treatment of carvedilol and enalapril resulted in more substantial cardiac remodeling reversal and increase in LVEF than with either monotherapy. A study of the effect of ACE inhibitors alone,  $\beta$ -blockers alone, or their combination in elderly patients with asymptomatic LVSD showed that although each drug alone significantly reduced the incidence of HF, combination therapy resulted in the lowest percentage of patients with new coronary events and HF.<sup>38</sup> For these reasons,  $\beta$ -blockers appear to be indicated in patients with asymptomatic LVSD to prevent progression to symptomatic HF, promote positive remodeling of the ventricle, and reduce mortality. The ACC/AHA guideline recommendations for the use of  $\beta$ -blockers in stage B patients are summarized in Table 2.<sup>3</sup>

**Angiotensin Receptor Blockers**

Although angiotensin receptor blockers (ARBs) have been studied in several large, randomized clinical trials of patients with chronic HF, these studies included only patients with symptomatic LVSD, or stage C patients. Two recent large trials investigating ARBs in post-MI LVSD included a significant proportion of stage B patients with no clinical HF. The Valsartan in Acute Myocardial Infarction (VALIANT) trial compared the ARB valsartan, the ACE inhibitor captopril, and a combination of both in a total of 14 703 patients with LVSD (mean LVEF 35%) up to 10 days after MI;  $\approx 28\%$

had no symptoms of HF.<sup>28</sup> During a median follow-up period of 25 months, treatment with valsartan resulted in mortality benefits comparable to captopril in all groups, including those without clinical HF. The combination of both drugs added no extra benefit while increasing the risk of adverse events. The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL)<sup>29</sup> randomized 5477 patients who had either clinical HF or echocardiographic evidence of LVSD to losartan or captopril within 10 days of acute MI; approximately one third had no symptoms of HF. Those patients with or without symptoms of HF who received treatment with captopril showed a trend toward better clinical outcomes, including all-cause mortality ( $P=0.069$ ), than those given losartan. These somewhat discordant results suggest that the impact of an ARB either varies by the specific agent used or by how the ARB was dosed. Although 50 mg of losartan was the target dose in the OPTIMAAL trial, doses of losartan ranging from 5 to 150 mg in patients with HF resulted in a stepwise increase in plasma renin activity and angiotensin II concentrations, which indicates more potent negative feedback at the highest doses. The substantial event rate during the early post-MI phase in the OPTIMAAL trial emphasizes the importance of rapid titration and adequate dosage. The relatively slow dose up-titration of losartan in OPTIMAAL might have resulted in a suboptimal effect compared with captopril. In contrast, VALIANT used a more rapidly titrated and higher dose of valsartan and reported equivalent reductions in events compared with captopril.

The current ACC/AHA recommendations accordingly advocate using an ACE inhibitor first and an ARB as second-line therapy for those with ACE intolerance (Table 2). There are no data for combining an ACE inhibitor and ARB in this population unless needed to control blood pressure despite maximal ACE inhibitor and  $\beta$ -blocker doses.

### Digoxin

The Digitalis Investigation Group (DIG) trial randomized 6800 patients to digoxin or placebo and showed no difference in mortality overall but significant reductions in hospitalizations and symptoms in those patients taking digoxin.<sup>39</sup> Because patients with stage B HF are asymptomatic by definition, there appears to be no role for the use of digoxin in this population. In addition, digoxin has been associated with an increased risk of arrhythmias and mortality, especially in women.<sup>40</sup> For these reasons, asymptomatic patients may not benefit from digoxin but may be exposed to risk (Table 2).

### Aldosterone Antagonists

The role of aldosterone antagonists in patients with asymptomatic LVSD has not been studied. The Randomized Aldosterone Evaluation Study (RALES) showed a significant reduction in mortality with spironolactone versus placebo but was limited to patients with advanced symptomatic HF of NYHA class III or IV that defined a class C or D population.<sup>41</sup>

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) randomized patients after MI with LVEF  $\leq 40\%$  and symptomatic HF to the selective aldosterone antagonist eplerenone or placebo.<sup>42</sup> There was a significant reduction in both morbidity and

mortality in the eplerenone group; however, this study was also limited to patients with symptomatic stage C HF due to an ischemic cause. It is unknown whether extrapolating these results to patients who have asymptomatic LVSD or other etiologies would lead to similar results. There is no ACC/AHA recommendation for the use of aldosterone antagonists in stage B patients.<sup>3</sup>

### Nonpharmacological Therapy

Although optimal pharmacological therapy as reviewed above, including both ACE inhibitors and  $\beta$ -blockers, significantly reduces the risk of death in patients with LVSD, the mortality rate remains unacceptably high. For example, MI survivors with LVSD have a 4- to 5-year mortality rate  $\geq 20\%$ , and approximately one third of these deaths are sudden.<sup>43</sup> This has led to the investigation of implantable cardioverter defibrillators (ICDs) as adjunctive therapy in patients with HF and LVSD. Early studies selecting high-risk patients on the basis of invasive electrophysiological testing confirmed a reduction in mortality risk after placement of ICDs in this population.<sup>44</sup> Subsequent studies investigated ICD use without electrophysiological testing in LVSD patients, both in ischemic and nonischemic LVSD.<sup>30,31</sup> Each of these studies included a sizable proportion of asymptomatic patients (NYHA class I).

In the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II), 1232 patients with past MI (at least 1 month) and LVEF  $<30\%$  were randomized to conventional medical therapy plus ICD implantation or medical therapy alone and followed up for an average of 20 months. Approximately one third of each group was asymptomatic. ICD therapy was associated with an overall 31% reduction in death compared with medical therapy alone. NYHA class I patients benefited to the same degree as those with symptomatic HF.<sup>30</sup> The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) study investigated ICD versus medical therapy in 458 patients with nonischemic dilated cardiomyopathy (LVEF  $<36\%$ ) over a mean of 29 months.<sup>31</sup> Twenty-two percent of these patients were asymptomatic (NYHA class I). Overall, there was a 35% greater reduction in deaths in the ICD group, a statistically insignificant difference ( $P=0.08$ ). Unlike the results of MADIT-II, however, only patients in NYHA class III experienced a significant mortality benefit from ICD, not those in NYHA class I or II. The results of these 2 trials suggest that ICD implantation may be a reasonable intervention to improve overall survival in patients with HF and LVSD after MI.

Although the role of ICDs in stage C HF was investigated by the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) and extended the potential benefit of ICD therapy to patients with nonischemic cardiomyopathy, these results are not necessarily applicable to an asymptomatic population.<sup>45</sup> Despite this, the SCD-HeFT trial has raised the issue that those patients with LVSD and the fewest symptoms have the best chance of survival from an HF perspective and the best quality of life and may therefore derive the most benefit from an ICD. Because stage B patients have no symptoms but are at a continual risk of sudden death, it may be reasonable to consider an ICD in this population on a case-by-case basis.



Additional studies in nonischemic stage B patients will be necessary to further define the benefit and risk of ICD therapy in this population.<sup>45</sup> The ACC/AHA guideline recommendations for the use of ICDs in stage B patients are summarized in Table 2.<sup>3</sup>

The data on biventricular pacemakers are also difficult to apply to the stage B patient. All of the clinical trials to date have focused on stage C patients with NYHA class III HF. Biventricular pacemakers have been shown to promote significant positive remodeling of the ventricle, which in theory could be beneficial to stage B patients.<sup>46</sup> Unfortunately, there are inadequate data at this time to recommend a biventricular pacemaker for patients with asymptomatic LVSD.

### Screening

The clinical trial results reviewed above detail risk reduction of up to 42% with neurohormonal inhibitor therapy. Although not studied in a trial, it would be reasonable to infer that the earliest possible identification of patients with asymptomatic LVSD might enable early treatment that could confer the highest benefit. Because substantial evidence indicates that pharmacological intervention may have an effect on the risk of progression to HF and death, identification of patients who are asymptomatic would then appear to be a priority. However, recognition of asymptomatic LVSD is a challenge that our present diagnostic methods have yet to answer completely. Although echocardiography represents the “gold standard” in the assessment of LVSD, its use as a general screening tool is impractical and prohibitively expensive. Owing to high cost and the need for skilled technicians, routine comprehensive echocardiography cannot be recommended currently in the absence of some other clinical indication, such as a recent MI, abnormal ECG or chest radiograph, family history of cardiomyopathy, or HF symptoms. Ideally, an effective screening program should be able to identify those patients likely to have asymptomatic LVSD using an inexpensive questionnaire, risk profile, or blood test, which could then be confirmed by echocardiography or radionuclide scanning. It may also be possible to develop a limited screening echocardiogram that would be rapid and less expensive that could be used to evaluate ventricular function and could be used alone as screening or in combination with other screening tools. This would need to be combined with a prospective treatment trial that would evaluate the impact of treatment after positive screening.

The current ACC/AHA guidelines discuss early detection of structural cardiac abnormalities and acknowledge that there is no definitive screening method. Instead, the guidelines advocate identifying high-risk patients either by comorbid illness, family history, or exposure to cardiotoxic medications.<sup>3</sup> Given the data from population studies, asymptomatic LVSD most often occurs in patients who are elderly or who have CAD, hypertension, diabetes mellitus, an abnormal ECG, family history of dilated cardiomyopathy, cardiotoxic drug exposure, atrial fibrillation, or valvular heart disease. Asymptomatic LVSD should also be suspected in post-MI patients despite the absence of HF. Kannel et al<sup>47</sup> devised a risk model from the Framingham cohort to identify high-risk candidates for the subsequent occurrence of HF. On

the basis of 486 HF cases during 38 years of follow-up, 4-year probabilities of developing clinical HF were computed with pooled data such as age, presence of CAD, and blood pressure. With this multivariate risk assessment, it was possible to identify persons at high risk for HF in whom asymptomatic LVSD was likely to be present and in whom preventative measures might be instituted.

The measurement of plasma brain natriuretic peptide (BNP) levels has become a potential tool to identify asymptomatic LVSD and is discussed as a promising, although not yet recommended, modality in the guidelines. BNP is a member of the family of vasodilating natriuretic proteins synthesized in the heart and released in response to increased atrial or ventricular filling pressures or load. BNP may also be predictive of post-MI LVSD and remodeling. In studies comparing various natriuretic peptide markers, BNP was found to be superior to carboxy-terminal atrial natriuretic peptide or amino-terminal atrial natriuretic peptide as an indicator of LV systolic or diastolic dysfunction in patients suspected of having cardiac disease.<sup>48</sup> In a study of patients with asymptomatic LVSD or newly symptomatic HF (mean LVEF 37%) who were followed up for a mean of 1071 days, plasma BNP levels but not other neurohormone levels, such as norepinephrine, were independent predictors of mortality.<sup>49</sup> In a study of 75 MI survivors without HF, plasma BNP levels had 84% sensitivity in identifying the presence of asymptomatic LVSD.<sup>50</sup> Another study in 1252 randomly selected individuals, aged 25 to 74 years, found that plasma BNP levels had a 77% sensitivity and 87% specificity in identifying 19 asymptomatic and 18 symptomatic individuals with LVEF <30%; when the population was limited to patients older than 55 years with a history of CAD, BNP sensitivity rose to 92%, and specificity was reduced to 72%.<sup>51</sup> The accuracy of BNP in identifying patients with impaired LV function in this study was similar to other commonly used screening tests, such as prostate-specific antigen for prostate cancer or mammography for breast cancer.<sup>52,53</sup> Recently, the use of N-terminal proBNP, rather than BNP, has been advocated because of its longer half-life and higher sensitivity to lesser degrees of LVSD, although low specificity limits its clinical utility as a general screening tool.<sup>54</sup>

The issue of cost-effective LVSD screening in an asymptomatic population was analyzed with prevalence data from community cohort studies and treatment benefits from randomized trials.<sup>55</sup> To detect patients with LVEF <40%, a strategy of using plasma BNP levels followed by echocardiography was evaluated in a population of 2000 asymptomatic 60-year-olds. This strategy was predicted to cost \$22 300 per quality-adjusted life year (QALY) gained for men and \$77 700 per QALY for women. For an at-risk population with at least a 1% prevalence of LVSD, BNP followed by echocardiography would cost less than \$50 000 per QALY gained for men and women, comparable to many other commonly used medical interventions.<sup>55</sup> In the absence of a comprehensive or limited echocardiogram, BNP may be a reasonable marker to screen for asymptomatic LVSD in high-risk patients. The ACC/AHA guidelines acknowledge that BNP may be a useful screening tool; however, there is no consensus, and there are limited data to support this approach



in general clinical practice. No specific recommendations apart from screening high-risk patients are made in the guidelines. Clearly, there is a need for more data and the development of a consensus approach to screening for asymptomatic LV dysfunction. Currently, a gap exists between the evidence-based treatment recommendations for the patient with asymptomatic LVSD and what is currently practiced. The challenge to clinicians is not only to develop screening strategies to identify patients who have asymptomatic LVSD but also to use the recent clinical trial evidence to institute appropriate therapy and improve outcomes in those who ultimately are diagnosed with asymptomatic LVSD.

### Conclusions

Asymptomatic LVSD, as a precursor to HF and cardiovascular death, is an important contemporary health problem. The elderly, men, and those with CAD, hypertension, and diabetes mellitus are at greatest risk for developing asymptomatic LVSD. Those with a family history of nonischemic cardiomyopathy may also be at risk for the development of asymptomatic LVSD. Because HF represents the product of a progressive continuum of LVSD, initiated by myocardial injury and perpetuated by neurohormonally mediated remodeling, both ACE inhibitors and  $\beta$ -blockers can limit the progression of asymptomatic LVSD to HF and reduce the risk of death and hospitalization. There is no role for the use of digoxin, and the role of aldosterone antagonists remains unknown. ICD prophylactic therapy may be appropriate in post-MI patients. Treatment of underlying factors or comorbidities, such as hypertension and diabetes, may also slow HF progression. Populations at risk for the development of asymptomatic LVSD should be screened to identify those patients who might benefit from pharmacological interventions. More effort should be focused on finding appropriate treatment for populations such as women and blacks, because these groups have been underrepresented in trials that include asymptomatic LVSD. One potential, although not validated, screening strategy is measurement of plasma BNP in the high-risk population, followed by echocardiography in those patients with elevated BNP. A clinical trial to provide data leading to a consensus recommendation for screening is needed. Through diagnosis and screening, an increased identification of patients with asymptomatic LVSD may lead to the early initiation of appropriate pharmacological therapy. Appropriate therapy, in turn, can improve outcomes and decrease morbidity, mortality, and progression to clinical HF.

### Disclosures

Dr Goldberg is on the speakers' bureau and advisory board of and has received honoraria from GlaxoSmithKline. Dr Jessup is on the speakers' bureau of and has received honoraria from GlaxoSmithKline, AstraZeneca, and Medtronic; she is on the advisory boards of Medtronic and GlaxoSmithKline. Editorial assistance was provided by Accel Health, New York, NY, which was supported by GlaxoSmithKline. Drs Goldberg and Jessup have received research funding from Medtronic, Novartis, GlaxoSmithKline, and Pfizer.

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KEY WORDS: heart failure ■ diagnosis ■ risk factors

## Stage B Heart Failure: Management of Asymptomatic Left Ventricular Systolic Dysfunction

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