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Stage B: What is the Evidence for Treatment of Asymptomatic Left Ventricular Dysfunction?

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Abstract: Although patients with American College of Cardiology / American Heart Association (ACC/AHA) Stage B heart failure, or asymptomatic left ventricular dysfunction (ALVD) are at high risk for developing symptomatic heart failure, few management strategies have been shown to slow disease state progression or improve long-term morbidity and mortality. Of the pharmacologic therapies utilized in patients with symptomatic disease, only angiotensin converting enzyme (ACE) inhibitors (and to a lesser extent, angiotensin receptor blockers, or ARBs) have been shown to improve clinical outcomes among patients with ALVD. Although evidence to support the use of beta blockers in this setting has been primarily derived from retrospective studies or subgroup analyses, they are generally recommended in most patients with ALVD, especially those with ischemic etiology. Statins are associated with improvements in both major adverse cardiovascular events and heart failure events among patients with a history of acute myocardial infarction. Finally, in eligible patients, placement of an automatic implantable cardioverter defibrillator (ICD) has been associated with reduced mortality rates among those with ALVD due to ischemic cardiomyopathy, and some subgroups may derive benefit from cardiac resynchronization therapy or biventricular pacing.

Keywords: ACE inhibitors, asymptomatic left ventricular dysfunction, beta blockers, device therapy, heart failure, stage B.

INTRODUCTION

Patients with American College of Cardiology / American Heart Association (ACC/AHA) Stage B heart failure, also known as asymptomatic left ventricular dysfunction (ALVD), are characterized as having evidence of structural heart disease (i.e., left ventricular dysfunction, left ventricular hypertrophy) without overt clinical signs or symptoms of heart failure. Although the reported prevalence of ALVD varies widely in the literature, some studies estimate that it may exceed the number of patients with symptomatic heart failure [1]. Moreover, patients with ALVD are at five times greater risk for developing symptomatic heart failure when compared to those with normal left ventricular function [2]. In an effort to slow the projected 25% increase in the prevalence of heart failure over the next two decades [3], strategies for appropriately screening for patients with ALVD and preventing progression to symptomatic heart failure are strongly advocated in clinical practice guidelines [1]. However, given that most of the trials to support pharmacologic therapy in heart failure enrolled symptomatic patients, very little information exists to guide clinicians in the appropriate management of patients with Stage B heart failure.

Although some patients may progress immediately to symptomatic heart failure following an acute event, most are recognized as progressing through Stage A and B prior to the development of symptoms. As a result, the preventive strategies discussed for Stage A patients (i.e., control of cardiovascular risk factors such as blood pressure and diabetes, use of statins in patients with ischemic disease, moderation of alcohol consumption, smoking cessation) should also be applied to those with ALVD (*see article on Prevention*). A summary of the evidence to date for pharmacologic and device therapy in Stage B patients is summarized in Table **1**, including details related to the population enrolled in each trial (i.e., chronic heart failure versus acute myocardial infarction, left ventricular ejection fraction) as well as the number needed to treat (NNT) for expected benefit with each individual intervention.

ACE INHIBITORS

As one of the few pharmacologic therapies supported by evidence from prospective randomized controlled clinical trials, angiotensin-converting enzyme (ACE) inhibitors are the foundation of management for patients with Stage B heart failure. Likely a result of their impact on the pathophysiologic remodeling process that characterizes progressive heart failure, ACE inhibitors have been shown to improve cardiovascular morbidity and mortality, including progression to symptomatic heart failure. In the prevention arm of the Studies of Left Ventricular Dysfunction (SOLVD) trial, a decrease in the incidence of heart failure and hospitalizations for heart failure was observed among patients with ALVD and left ventricular ejection fraction (LVEF) $\leq$ 35% who received enalapril [4], and a 12-year follow-up demonstrated an improvement in mortality among enalapril-treated

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Table 1. Summary of trials in patients with asymptomatic left ventricular dysfunction.

Drug Class	Trial	Population (% with ALVD)	LVEF	Comparison	Outcome	NNT	Duration (years)
ACE Inhibitors	SOLVD Prevention [4]	Chronic (100%)	< 35%	Enalapril vs. placebo	Progression to HF	11	3.1
					First hospitalization for HF	24	
					Multiple hospitalizations for HF	48	
	SOLVD Prevention Follow-up [5]	Chronic (100%)	< 35%	Enalapril vs. placebo	All-cause mortality	19	11.2
					Cardiovascular mortality	20	
	SAVE [6]	AMI (100%)	≤ 40%	Captopril vs. placebo	Total mortality	20	3.5
					Cardiovascular mortality	25	
					Hospitalization for HF	34	
	TRACE [7]	AMI (41%)	≤ 35%	Trandolapril vs. placebo	All-cause mortality	14	2-4.2
					Cardiovascular mortality	14	
					Progression to severe HF	19	
ARBs	OPTIMAAL [16]	AMI (33%)	-	Losartan vs. captopril	No statistically significant differences for total and cardiovascular mortality	-	2.7
	VALIANT [18]	AMI (28%)	≤ 40%	Valsartan vs. captopril vs. both	Non-inferior to captopril for total and cardiovascular mortality	-	2.3
Beta Blockers	SAVE Retrospective Analysis [19]	AMI (100%)	≤ 40%	Beta blocker vs. no beta blocker	Relative risk reduction in cardiovascular mortality and progression to severe HF of 30% and 21%, respectively	-	3.5
	SOLVD Retrospective Analysis [20]	Chronic (100%)	< 35%	Beta blocker vs. no beta blocker	Relative risk reduction in cardiovascular mortality of 34%, and all-cause mortality of 26% in combination with enalapril	-	3.1
	ANZ [21]	Chronic HF due to ischemic etiology (30%)	< 45%	Carvedilol vs. placebo	Composite of death or hospitalization	8	1.6
					Hospitalization	11	
	CAPRICORN [22]	AMI (53%)	≤ 40%	Carvedilol vs. placebo	All-cause mortality	34	1.3
					Cardiovascular mortality	34	
	REVERT [24]	Chronic (100%)	< 40%	Metoprolol succinate vs. placebo	Improved measures of left ventricular function, including EF	-	1
Statins	4S [25]	Previous MI (79%)	NR	Simvastatin vs. placebo	Incidence of HF	50	5.4
					HF-associated mortality	16	
	CARE [26]	Previous MI (100%)	> 25%	Pravastatin vs. placebo	Composite of fatal coronary events, nonfatal MI, CABG, or PTCA	13	5.0
	IDEAL [28]	Previous MI (100%)	NR	Atorvastatin vs. simvastatin	New or recurrent hospitalization for HF	167	4.8
Devices	MADIT-II [29]	History of MI (37%)	≤ 30%	ICD vs. medical therapy	All-cause mortality	18	1.7
	MADIT-CRT [31]	Chronic (15%)	≤ 30%	ICD-CRT vs. ICD alone	Composite of all-cause mortality or nonfatal HF events	13	2.4
					Nonfatal HF events	12	
	BLOCK HF [34]	Chronic and AV block (16%)	≤ 50%	Biventricular vs. right ventricular pacing	Composite of all-cause mortality, heart failure events requiring urgent care, or a ≥15% increase in LV end-systolic volume index	11	3.1
					Hospitalization for HF	28	

Abbreviations: ACE angiotensin-converting enzyme, ALVD asymptomatic left ventricular dysfunction, AMI acute myocardial infarction, ARB angiotensin receptor blocker, AV atrioventricular, CABG coronary artery bypass grafting, CRT cardiac resynchronization therapy, HF heart failure, ICD automatic implantable cardioverter defibrillator, LV left ventricular, LVEF left ventricular ejection fraction, MI myocardial infarction, NNT number-needed-to-treat, NR not reported, PTCA percutaneous transluminal coronary angioplasty.

patients [5]. Two trials investigated the effects of ACE inhibitor therapy in patients with acute myocardial infarction (AMI). In both the Survival And Ventricular Enlargement (SAVE) trial and TRAndolapril Cardiac Evaluation (TRACE) trial, ACE inhibitors were associated with improvements in all-cause mortality, recurrent cardiovascular events, and progression to heart failure compared to placebo [6, 7].

Whether similar improvements may be expected among patients with preserved ejection fraction remains controversial. Although improved outcomes (e.g., all-cause mortality, sudden death, recurrent cardiovascular events, and/or progression to heart failure) have been observed with the use of ACE inhibitors among AMI survivors without documented left ventricular systolic dysfunction [8-10] and in patients at high risk for recurrent events [11, 12], these results have not been replicated among lower-risk patients, such as those who have been revascularized or in whom cardiovascular risk factors are well-controlled [13]. In the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) study, trandolapril failed to improve the composite endpoint of cardiovascular death, myocardial infarction, or revascularization among patients with stable coronary artery disease, although post-hoc analysis demonstrated a reduction in heart failure as the primary cause for hospitalization or death. As the authors note in their discussion, patients in PEACE were at much lower risk for recurrent events compared to those enrolled in previous trials, as evidenced by fewer cardiovascular risk factors and more widespread use of revascularization and other evidence-based pharmacologic therapies (e.g., lipid-lowering agents) [13].

On the basis of these investigations, ACE inhibitors should be administered to all patients with ALVD, an intervention now recognized as a national quality measure in the setting of both AMI and heart failure. Furthermore, ACE inhibitors should be considered in all AMI patients irrespective of ejection fraction, although continued use beyond the initial recovery period (i.e., weeks to months) should be based on patient-specific risk factors and other clinical considerations (e.g., whether or not revascularization was performed, presence or absence of compelling indications such as diabetes mellitus or hypertension, or use of other evidence-based therapies, such as antiplatelet drugs or statins).

ANGIOTENSIN RECEPTOR BLOCKERS

No clinical trials have specifically evaluated angiotensin receptor blockers (ARBs) in patients with ALVD. Among patients with symptomatic heart failure, a number of large randomized controlled clinical trials have demonstrated that ARBs may serve as an acceptable substitute in patients with a history of intolerance to ACE inhibitors, based on comparable reductions in cardiovascular morbidity and mortality [14, 15]. However, evidence to support their use in patients with ALVD has been derived primarily from subgroup analysis of two trials in AMI patients with heart failure. In the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL), losartan was not superior to captopril among AMI patients with heart failure, of whom about one-third had ALVD [16]. Notably, the dose of losartan used in OPTIMAAL (50 mg daily) was significantly lower than the recommended target dose (150 mg daily). Given more recent evidence to indicate additional improvement associated with higher losartan doses among symptomatic patients [17], the low dose used in OPTIMAAL may have been responsible for its apparent lack of benefit. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), valsartan was non-inferior to captopril in terms of total and cardiovascular mortality, including among the subgroup of asymptomatic patients [18]. Therefore, while ACE inhibitors should be preferred as first line therapy in patients with ALVD, ARBs may be considered in those with a history of intolerance to ACE inhibitors.

BETA BLOCKERS

Similar to inhibitors of the renin-angiotensin-aldosterone system, beta blockers may benefit patients with ALVD by way of their inhibition of the remodeling effects mediated by the sympathetic nervous system. Despite overwhelming evidence to support their use in symptomatic heart failure with or without concomitant ischemic heart disease, a dearth of literature exists to support their use in asymptomatic patients, especially those without a history of ischemic heart disease.

Some of the evidence to support the use of beta blockers in the setting of ALVD has been derived from retrospective analyses of the SAVE and SOLVD trials. In the SAVE trial, concomitant use of beta blocker therapy was associated with additive reductions in cardiovascular death and progression to heart failure among asymptomatic patients with an LVEF $\leq$ 40% who sustained an AMI [19]. The combination of ACE inhibitors and beta blockers in SOLVD was associated with a synergistic decrease in mortality in addition to improvements in other clinical outcomes among asymptomatic patients with chronic systolic dysfunction [20]. In the Australia/New Zealand (ANZ) trial, an improvement in ejection fraction and reduction in the combined endpoint of death or hospital admission was observed among patients randomized to carvedilol [21]. Similarly, in the Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) trial, which enrolled AMI patients with an LVEF $\leq$ 40%, the administration of carvedilol was associated with significant reductions in all-cause mortality, cardiovascular mortality, and recurrent cardiovascular events [22, 23].

Evidence to support the role of beta blockers in reversing left ventricular remodeling has been supported in a more recent analysis, the REversal of VEntricular Remodeling with Toprol-XL (REVERT) trial, where metoprolol succinate was associated with improvements in measures of left ventricular function, including ejection fraction, compared to placebo [24]. In contrast to previous investigations, where study populations have been comprised primarily of patients with ischemic etiology, half of the patients enrolled in REVERT had non-ischemic disease. Altogether, while these trials do not provide conclusive evidence of benefit among this population, the addition of beta blockers to ACE inhibitors should be strongly considered among patients with ALVD, even in the absence of ischemic disease.

STATINS

Statins are a cornerstone for the prevention of major adverse cardiovascular events in patients with coronary artery disease (CAD), and several trials have also reported their impact on heart failure endpoints. In the Scandinavian Simvastatin Survival Study (4S), a reduction in the incidence of heart failure and heart failure-associated mortality was observed with simvastatin in patients with previous AMI or angina but without symptoms of heart failure [25]. In the Cholesterol and Recurrent Events (CARE) trial, pravastatin was associated with an improvement in the composite primary endpoint of fatal coronary events and nonfatal myocardial infarction among patients with previous AMI and average plasma cholesterol concentrations (i.e., total cholesterol < 240 mg/dL and low-density lipoprotein < 115-174 mg/dL) [26]. Patients with symptoms of heart failure were excluded from the trial, but an improvement in major coronary events (i.e., composite of the primary endpoint and patients receiving coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty) was observed among the subgroup of patients with LVEF ≤ 40%.

Compared to usual doses, intensive statin therapy appears to confer additional improvements in heart failure outcomes. A meta-analysis of six trials (n=110,271) evaluated intensive versus moderate statin therapy in patients with recent acute coronary syndrome (ACS) or stable CAD, and found that intensive statin therapy reduced all-cause mortality among patients with ACS but not stable CAD [27]. Among the overall cohort, intensive statin therapy was associated with a reduction in major adverse cardiovascular events (cardiovascular death, ACS, stroke, need for revascularization, or resuscitated cardiac arrest) and hospitalization for heart failure. Additionally, in the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial, patients with a history of AMI (94% had no history of heart failure) were randomized to usual dose simvastatin (20-40 mg) or high-dose atorvastatin (80 mg); after accounting for differences in baseline characteristics (e.g., age, gender, differences in baseline lipid concentrations) among the 222 patients hospitalized for heart failure, a reduction in new or recurrent heart failure events was observed in the atorvastatin group [28].

Although most of the trials investigating the use of statins in patients with ACS or CAD have not specifically evaluated their impact in patients with ALVD, they should be administered to all patients with a history of AMI in order to prevent recurrent cardiovascular events and progression to symptomatic heart failure. Additionally, given evidence to support a dose-related impact on outcomes following AMI, intensive statin therapy should be favored in patients able to tolerate it.

OTHER PHARMACOLOGIC THERAPIES

No evidence currently exists to support other pharmacologic therapies (i.e., aldosterone antagonists, digoxin, isosorbide dinitrate, hydralazine) commonly employed in patients with asymptomatic heart failure.

DEVICE THERAPIES

Although a more detailed discussion of device therapy is provided in a later chapter, a brief summary of its impact on Stage B patients will be provided here. Among survivors of AMI (> 1 month) with LVEF < 30%, the prophylactic use of an automatic implantable cardioverter defibrillator (ICD) in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) resulted in a significant reduction in all-cause mortality compared to optimal medical therapy, irrespective of NYHA Class, including among the nearly 40% of patients who were asymptomatic [29]. Similar improvements have also been observed with the combined use of an ICD and cardiac resynchronization therapy (CRT). Both the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study [30] and Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) Trial [31] showed reversed left ventricular remodeling and a reduction in heart failure hospitalizations among patients receiving CRT-D therapy. Additionally, MADIT-CRT also demonstrated reductions in all-cause mortality and nonfatal heart failure events [31]; however, a significant difference was not observed among the subgroup of patients with NYHA Class I heart failure, although this only comprised approximately 15% of the patient population.

Evidence indicates that chronic right ventricular (RV) pacing can result in adverse cardiac remodeling. The Pacing to Avoid Cardiac Enlargement (PACE) trial randomized 177 patients with EF ≥ 45% and indications for pacing to atrial synchronized biventricular pacing or RV pacing. After one year, mean EF was significantly lower and was accompanied by an increase in end-systolic volume in the RV pacing group [32]. Two year follow-up results demonstrated a further decline in EF and increase in end-systolic volume in the RV pacing group [33]. The more recent Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) trial consisted of patients with indications for pacing due to atrioventricular block, who were NYHA class I-III and had LVEF ≤ 50%. Patients randomized to biventricular pacing demonstrated an improvement in the composite end point of all-cause mortality, heart failure events requiring urgent care, or a ≥15% increase in LV end-systolic volume index compared to patients randomized to RV pacing. Hospitalizations were also significantly reduced among patients randomized to biventricular pacing. Approximately 16% of the population was asymptomatic, although results for this subgroup were not provided [34].

CONCLUSIONS

Patients with ALVD represent a population that is at considerable risk for the development of symptomatic heart failure. Given the morbidity and mortality associated with this condition, efforts should be made to identify patients with ALVD in order to monitor and potentially slow disease state progression. Despite the growing number of pharmacologic and non-pharmacologic strategies for managing symptomatic heart failure, only limited evidence exists to support their use in patients with ALVD. Based on the available evidence to date, ACE inhibitors (or ARBs in those with a history of intolerance to ACE inhibitors) should be administered to all patients with ALVD in the absence of contraindications. Beta blockers should also be considered in the vast majority of patients, although evidence to support their use is less robust, especially among patients without a history of ischemic disease. Statins should be considered for all patients with a history of AMI irrespective of ejection fraction.

Finally, an ICD should be considered for all eligible patients (e.g., those with a history of AMI and ALVD). Biventricular pacemakers should be considered in patients who have indications for pacing for AV block. Further studies are needed to identify therapies aimed at preventing the progression of ALVD to symptomatic heart failure.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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