## Section 5: Management of Asymptomatic Patients with Reduced Left Ventricular Ejection Fraction

### Overview

Left ventricular (LV) remodeling and reduced ejection fraction (EF) should be distinguished from the syndrome of clinical heart failure (HF). When LVEF is reduced (<40%), but there are no signs and symptoms of HF, the condition frequently is referred to as asymptomatic LV dysfunction (ALVD). It is important to distinguish between ALVD and patients categorized as New York Heart Association (NYHA) Class I HF. Although patients with NYHA Class I HF do not currently have HF symptoms, they may have ALVD currently, or they may have clinical systolic HF with symptoms in the past. In contrast, patients with ALVD have no past history of HF symptoms. It is now well recognized that there may be a latency period when the LVEF is reduced before the development of symptomatic HF. Although most attention in the HF literature has centered on patients with symptoms, evidence now indicates that ALVD is more common than previously assumed. The recent realization that therapies aimed at symptomatic HF may improve outcomes in patients with ALVD has increased the importance of recognizing and treating patients with this condition.

**Prevalence.** The prevalence of systolic ALVD ranges from 6% to 16% in population-based studies.[1–4] The prevalence of ALVD was 16.7% among a cohort of 1046 asymptomatic diabetic patients without known coronary artery disease.[5] Some studies suggest that patients with ALVD equal or outnumber those with overt HF. The First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHANES I) reported only a 2% prevalence of overt HF in individuals ages 25 to 74 years, though this value likely is an underestimate.[6] The prevalence of both ALVD and overt HF dramatically increase with age. The lifetime risk of developing HF is approximately 20% in octogenarians.[7–9] In specific populations, such as those who have received cardiotoxic agents and those screened due to a family history of dilated cardiomyopathy, the incidence of ALVD is likely much higher.

**Prognosis.** Patients with ALVD have approximately half the mortality rate (5% annualized) of those with overt symptoms of HF, but their risk of death is 5 to 8 times higher than a normal age-matched population. In the Study of Left Ventricular Dysfunction (SOLVD) prevention study, patients with untreated ALVD developed overt HF at a 10% annual rate, with a further 8% annual risk of death or hospitalization for HF.[10] These data indicate patients with ALVD are at high risk for developing HF. The majority of data regarding outcomes in patients with ALVD come from the SOLVD-prevention study; it would be valuable to have more recent data to fully understand the mortality risk of ALVD in the current era.

One trial that can be used to evaluate ALVD outcomes in the current era is the Occluded Artery Trial (OAT).[11] The study enrolled 2216 subjects 3−28 days post-myocardial infarction (MI) with mean LVEF 48% (LVEF <40% in 21% of the study population). The large majority of subjects (83%) were asymptomatic. A high proportion of subjects received multiple drug therapies including >80% treated with beta blockers, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), statins, and aspirin. Subjects were randomly assigned to a percutaneous coronary intervention (PCI) strategy to open the infarct-related artery or medical management. During a mean follow-up period of 1059 days, adverse cardiac event rates (all-cause mortality, non-fatal MI, and HF hospitalization) were much lower than that reported in the SOLVD study population (301 events with calculated crude event rate 4.8 per 100 patient-years). There were no significant differences in rates of adverse outcome events in the two treatment groups. Lower cardiac event rates in the OAT study population may be attributable to less severe systolic dysfunction and more widespread use of post-MI medical therapies.

**Managing Patients With ALVD.** The management of patients with ALVD focuses on cardiovascular risk factors and on preventing, controlling, or reducing progressive ventricular remodeling.

A number of risk factors have the potential to promote progression of ventricular remodeling and adverse outcomes in patients with ALVD. These include systemic hypertension, coronary artery disease, diabetes, obesity, and metabolic syndrome.[6,12–15] Population-attributable risk for hypertension and MI may be as high as 60% to 70%, underscoring the importance of preventing and managing these two conditions.[12,13,16–18] The 30% or more of patients with ALVD who do not have ischemic heart disease may suffer from hypertension, diabetes mellitus, alcohol overuse, or familial or idiopathic dilated cardiomyopathy. Surveillance studies suggest that relatives of those with idiopathic dilated cardiomyopathy often have asymptomatic LV dilatation and may be at increased risk for developing HF.[19,20] In addition, those exposed to toxins through alcohol overuse, ionizing radiation, or chemotherapy with anthracyclines may develop ALVD, which may progress to HF in the absence of intervention.[21]

### Recommendations

**5.1 It is recommended that all patients with ALVD exercise regularly according to a physician-directed prescription to avoid general deconditioning; to optimize weight, blood pressure, and diabetes control; and to reduce cardiovascular risk. (Strength of Evidence = C)**

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**5.2 Smoking cessation is recommended in all patients including those with ALVD. (Strength of Evidence = B)**

**5.3 Alcohol abstinence is recommended if there is current or previous history of excessive alcohol intake. (Strength of Evidence = C)**

**5.4 It is recommended that all patients with ALVD with hypertension achieve optimal blood pressure control. (Strength of Evidence = B)**

### Background

**Therapeutic Approaches.** Cardiovascular risk factor reduction is advocated in patients with ALVD to decrease the risk of developing overt HF. Control of blood pressure and treatments that slow the progression of ischemic heart disease may have substantial benefit. (See Section 3 for more on the control of cardiovascular risk factors.)

### Recommendation

**5.5 ACE inhibitor therapy is recommended for asymptomatic patients with reduced LVEF (<40%). (Strength of Evidence = A)**

### Background

A twelve-year follow up in SOLVD demonstrated that the initial benefit of enalapril was maintained.[10] Survival curve analysis has confirmed an absolute 9.2-month benefit in life expectancy conferred by 40 months of treatment with an ACE inhibitor, a benefit conferred despite the fact that nearly all patients enrolled in SOLVD went on to receive ACE inhibitors after termination of the randomized portion of the trial. The likelihood of death after 12 years in the treatment group remained fairly constant at approximately 5% annually.

A substudy of the SOLVD trial found that administration of enalapril reduced the tendency to progressive LV enlargement in patients with ALVD.[22] This beneficial effect on LV remodeling, in combination with prevention of MI, most likely explains the mechanism of reduction of both cardiovascular mortality and progression to HF observed in the SOLVD Prevention trial.[23–25] Thus ACE inhibitors are indicated in patients with reduced LVEF, regardless of symptoms.

### Recommendation

**5.6 ARBs are recommended for asymptomatic patients with reduced LVEF who are intolerant of ACE inhibitors from cough or angioedema. (Strength of Evidence = C)**

**Routine use of the combination of ACE inhibitors and ARBs for prevention of HF is not recommended in this population. (Strength of Evidence = C)**

### Background

Randomized clinical trials of ARBs in asymptomatic patients with LV systolic dysfunction who are intolerant of ACE inhibitors have not been conducted. Despite the absence of definitive data, based on the results of the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Alternative and the Valsartan Heart Failure Trial (Val-HeFT) and a variety of pathophysiologic and clinical considerations, it is reasonable to use an ARB in a patient with ALVD if the patient is intolerant to an ACE inhibitor.[26,27] The addition of an ARB to an ACE inhibitor in asymptomatic patients with reduced LVEF has not been investigated.

### Recommendation

**5.7 Beta blocker therapy should be considered in asymptomatic patients with reduced LVEF. (post-MI, Strength of Evidence = B; non post-MI, Strength of Evidence = C)**

### Background

**Ischemic Heart Disease With ALVD.** A strong rationale exists for the use of beta blocker therapy in the management of patients with ALVD from ischemic heart disease, based on the benefits seen in patients with cardiac dysfunction and no overt HF after acute MI. The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) study examined the effects of carvedilol in asymptomatic patients with reduced LVEF after MI, with concomitant use of ACE inhibitors, aspirin, and statins in the majority of patients. Although there was no difference between the carvedilol and placebo groups in the number of patients meeting the primary endpoint of all-cause mortality or hospital admission, carvedilol use was associated with fewer deaths, as well as a reduction in the combined endpoint of death or recurrent MI, classical end points in previous studies of beta blockade after MI.[28]

Beta blockade has been shown to attenuate LV remodeling in patients with ALVD. The Reversal of Ventricular Remodeling with Toprol-XL (REVERT) Trial randomized 149 patients to metoprolol succinate 50 mg, 200 mg, or placebo for 12 months. LV end-systolic volume, end-diastolic volume, and LVEF were measured at baseline and 6 and 12 months. Patients randomized to metoprolol succinate 200 mg had a significant decrease in LV end-systolic volume index and a significant increase in LVEF as compared to baseline and placebo at 12 months.[29] Approximately half of the patients in REVERT had a non-ischemic HF etiology.

**Nonischemic Heart Disease With ALVD.** No trial has specifically examined the effect of beta blockers on mortality in asymptomatic patients with reduced LVEF but no recent MI. Given the consistency of benefit observed with beta blockers across symptomatic populations, with and without ischemic heart disease, and in patients with prior MI, regardless of HF symptoms, it is reasonable to recommend use of these agents in asymptomatic patients with reduced LVEF in the absence of identifiable ischemic heart disease. See more about beta blockers in Section 7.

**Aldosterone Antagonists in Patients With ALVD.** Although aldosterone antagonists have been demonstrated to decrease morbidity and mortality in patients with moderate to severe symptoms of HF and reduced LVEF, there are currently no substantial data to suggest that these agents should be recommended as treatment for patients with ALVD. Studies are ongoing to determine the potential of aldosterone antagonists to impact the process of remodeling.

## Device Therapies in Patients With ALVD

Cardiac resynchronization therapy (CRT) in patients with ALVD has not been investigated in a large clinical trial. Two trials, the Resynchronization Reverses Remodeling in systolic Left Ventricular Dysfunction (REVERSE)[30] and the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT)[31] have studied CRT in patients with NYHA class I and II HF. Further research in a true ALVD population is needed to evaluate the efficacy of CRT in this setting.

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