Management of ACCF/AHA Stage A and B Patients

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KEYWORDS

• Stage A heart failure • Stage B heart failure • Screening • Management • Asymptomatic

KEY POINTS

- Patients with Stage A heart failure (HF) are at high risk for development of HF without any evidence of structural heart disease.
- Patients with Stage B HF have structural heart disease without any current or previous symptoms.
- Early detection of patients with Stage A and B with subsequent early intervention can lead to long-term reduction in morbidity and mortality of HF.
- Coronary artery disease, hypertension, and diabetes are the three major risk factors for development of HF.
- Neurohormonal blockade with angiotensin-converting enzyme inhibitors and β-blockers is the foundation of medical treatment in Stage B HF.

INTRODUCTION

Heart failure (HF) remains a major health problem in the United States, affecting 5.8 million Americans.[1] The prevalence of HF continues to rise due to the improved survival of patients. Despite advances in treatment, morbidity and mortality remains very high, with a median survival of about 5 years after the first clinical symptoms.[2] Hence, there has been a paradigm shift toward prevention of HF and identifying patients before the development of the first clinical episode. HF is a progressive disorder that is characterized by cardiac remodeling, typically a change in chamber size and geometry leading to increased hemodynamic stress and ventricular dysfunction. These changes further exacerbate the remodeling process and lead to a vicious cycle culminating in progressive deterioration. In 2001, American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines identified four stages of progressive development of HF[3]:

1. Stage A: patients at high risk for HF, but without evidence of structural heart disease
2. Stage B: patients with structural heart disease, but without signs or symptoms of HF
3. Stage C: patients with previous or current signs or symptoms of HF
4. Stage D: refractory HF requiring special interventions.

This classification complements the New York Heart Association (NYHA) functional classification, which primarily assesses the severity of clinical symptoms in Stage C or D. It identifies patients at high risk for developing HF and, hence, allows early therapeutic interventions. It is hoped this approach will reduce long-term morbidity and mortality of HF.

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STAGE A HF

Stage A patients have high-risk factors for developing HF but do not have any evidence of cardiac structural abnormalities and have normal ventricular function. The prevalence of Stage A HF was 22% in a population-based cross-sectional study of 45-year-old adults.[4] Coronary artery disease (CAD), hypertension, and diabetes are the three major risk factors for development of HF (**Box 1**).[5,6] Early detection and risk reduction are the two most important components of management of Stage A HF. It is important for health care providers to identify patients in Stage A, implement early interventions to delay progression to advanced stages of HF, and reverse the potentially treatable causes. Routine periodic evaluation should be done for signs and symptoms of HF. See later discussion of management strategies for specific risk factors.

CAD

CAD is the most common risk factor for development of HF, especially in male patients.[5] Population-attributable risk (PAR) for CAD was 62% in the National Health and Nutrition Examination Survey (NHANES). In the Framingham Study, combined PAR for angina and myocardial infarction was 39% for men and 18% for women. Secondary prevention of CAD in patients without any structural heart disease reduces the incidence, as well as delays the development, of HF.[7] Treatment with β-blockers, statins,[8] angiotensin-converting enzyme (ACE) inhibitors,[9] clopidogrel,[10] and revascularization (when appropriate) has reduced the incidence of HF. Most of the benefits are due to the prevention of further coronary syndromes; however, there are other secondary effects leading to reduction of HF. β-blockers can have unfavorable effects on lipid profile and glycemic control; however, benefits outweigh the minor increase in risk. In addition, combined α-blockers and β-blockers do not have these adverse effects.[11] Aggressive primary and secondary prevention of CAD remains the cornerstone of management of Stage A HF.

Box 1
Risk factors for developing HF

Common Risk Factors	Other Risk Factors
CAD	Sleep apnea
Hypertension	Tachycardia induced cardiomyopathy
Diabetes	Cardiotoxins (eg, anthracyclines, cocaine, Ephedra, amphetamines, trastuzumab, cyclophosphamide)
Metabolic syndrome	Right ventricular pacing
Smoking	Physical inactivity
Dyslipidemia	Endocrine disorders (hypothyroidism or hyperthyroidism, pheochromocytoma, acromegaly)
Obesity	HIV
Alcohol use	Mediastinal irradiation
Family history	Connective tissue disorders
Renal disease	Genetic disorders
	Sarcoidosis

HYPERTENSION

Hypertension is one of the most important risk factors for development of HF, especially in women and African Americans.[5] Aggressive treatment of systolic, as well as diastolic, hypertension reduces the incidence of HF, with an average risk reduction of 40% to 50%.[12] Diuretics, ACE inhibitors, angiotensin receptor blockers (ARBs), and β-blockers have all decreased the risk of HF with no significant difference among the various agents.[13] However, trials have shown increased incidence of HF with use of doxazosin and nifedipine.[14,15] These medications should be avoided as first-line therapy for treatment of hypertension. Detailed recommendations of blood pressure goals and choice of antihypertensive drugs are provided in guidelines by Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure.[16]

DIABETES

Diabetes can lead to HF either by development of coronary heart disease or diabetic cardiomyopathy. The risk of developing HF is two times higher in male patients and three to four times higher in female patients with diabetes.[17] Poor glycemic control and duration of diabetes are directly related to the development of HF.[18] Increase in hemoglobin A1c by 1% leads to 8% to 15% increase in risk of developing HF.[19] Tight glycemic control remains the most important goal in management of diabetes and prevention of HF. Blockade of the renin-angiotension system is equally important and provides additional benefit in reduction of microvascular complications, progression of diabetic nephropathy, and the incidence of HF.[11]

DYSLIPIDEMIA

Dyslipidemia is another important risk factor for development of HF.[20] Low high-density lipoprotein (HDL), elevated non-HDL, high total cholesterol to HDL ratio, and high triglyceride level have all been implicated as risk factors for the development of HF. Despite mixed results from various studies, appropriate management of dyslipidemia is an essential component of reducing risk of HF. Management of dyslipidemia should be done in accordance with guidelines recommended by the National Cholesterol Education Program.[21]

METABOLIC SYNDROME, OBESITY, AND PHYSICAL INACTIVITY

Metabolic syndrome, obesity, and physical inactivity are independent risk factors for the development of HF after adjustment for other established risks factors.[22–24] Multiple mechanisms have been hypothesized in metabolic syndrome, including increased myocardial mass by direct effects of insulin, sympathetic activation, potentiation of effects of angiotension II on myocytes, and increased collagen cross-linking due to increased glycosylation end-products.[22] It is also an inflammatory state, which may be a potential mechanism for increased risk of development of HF. Approximately 11% of HF cases in male patients and 14% in female patients are associated with obesity alone.[23] Physical inactivity leads to increased left ventricular stiffness and decreased compliance with aging.[25] Lifestyle modification, weight loss, and regular exercise are highly recommended for all patients. Although no prospective studies have shown that these interventions lead to reduction in HF, it is a reasonable assumption to make. Further studies are required to prove and quantify the benefits from these interventions.

SLEEP APNEA

Obstructive sleep apnea (OSA) is an independent predictor for development of HF. One study showed an odds ratio of 2.38 for risk of developing HF with OSA.[26] Potential mechanisms include hypoxia, exaggerated negative intrathoracic pressure, sympathetic activation, and systemic hypertension.[27] Effective treatment of sleep apnea by continuous positive airway pressure and weight loss can potentially reduce the risk of developing HF. However, the data for the benefit of these therapies in ameliorating the progression of HF is lacking.

RENAL DISEASE

Prevalence of HF is 10 to 30 times higher in dialysis patients.[28] Myocardial dysfunction is common with renal disease and it worsens with initiation of dialysis.[29] The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend that all patients undergo baseline echocardiogram at initiation of dialysis, repeated every 3 years.[30] Echocardiogram should be obtained after the dry weight is obtained. Aggressive blood pressure control, optimizing calcium phosphate homeostasis, and correction of anemia can potentially reduce the risk of developing HF. ACE inhibitors and calcium channel blockers (CCBs) are the antihypertensives of choice in these patients. Some studies have also shown that risk of HF reduces with renal transplantation.[31] Microalbuminuria is also strongly associated with an increased incidence of HF in diabetics as well as nondiabetics.[32] However, treatment with ACE inhibitors has not been shown to reduce risk of HF in these patients.

SMOKING

Smoking is one of the strongest risk factors for developing HF. The effect of smoking is generally mediated through its role in the development of CAD. It is associated with 60% increased risk of HF after adjusting for all the other risk factors.[33] Although smoking cessation has not been shown to reduce risk of developing HF, it has been shown to reduce mortality in patients with established HF.[34] Smoking cessation and abstinence should be advised to all the patients, irrespective of the stage of HF.

ALCOHOL

Mild-to-moderate alcohol use has been associated with reduced risk of HF, probably related to reduced risk of CAD.[35] However, heavy alcohol use is a leading cause of HF, especially in men.[36] Various studies have reported alcohol consumption as the cause for dilated cardiomyopathy in the range of 21% to 50%.[37] Increased apoptosis, direct cardiotoxic effects, activation of the renin-angiotensin system, and nutritional deficiencies have been hypothesized as the potential mechanisms. Avoiding excessive alcohol consumption can be highly successful in reducing the risk of development of HF, apart from other potential health benefits.

CARDIOTOXINS

Cardiotoxic potential of many substances and drugs, such as amphetamines, cocaine, Ephedra,

anthracyclines, trastuzumab, cyclophosphamide, has been very well described. Complete abstinence from use of offending illicit drugs and termination of use of therapeutic agents is essential.

Trastuzumab, a monoclonal antibody, is used to treat breast tumors, which overexpress the epidermal growth factor, HER2. It is associated with an increased incidence of HF in all age groups.[38] Cardiac dysfunction from trastuzumab is thought to be due to blocking the ErbB2 signaling pathway and abnormalities in expression of Bcl-2, Bcl-cS, and BAX proteins.[39] The National Comprehensive Cancer Network guidelines recommend assessment of left ventricle (LV) systolic function at baseline, 3, 6, and 9 months after initiation of therapy.[40] Imatinib, a tyrosine kinase inhibitor used to treat Philadelphia chromosome–positive chronic myelogenous leukemia and other malignancies, can rarely be associated with congestive HF.[41]

Cardiac dysfunction from anthracycline therapy occurs because of free radical injury leading to permanent myocyte loss.[42] In patients receiving anthracyclines, evaluation of LV systolic function is recommended at baseline and after administration of cumulative dosage of 300 mg/m^2.[42] Screening is recommended at relatively low cumulative dosage for patients younger than 15 years of age and older than 60 years of age.

Cocaine-induced cardiomyopathy is an underrecognized entity. One small study showed 7% incidence of LV systolic dysfunction 2 weeks after cocaine use in asymptomatic young adults.[43] Sympathomimetic effects of cocaine, increased oxidative stress, and increased risk of thrombosis have been proposed as the potential mechanisms.[44] Complete abstinence from cocaine is essential in the prevention and management of cocaine-induced cardiomyopathy.

RIGHT VENTRICULAR PACING

There has been growing evidence over the last decade that right ventricular pacing leads to increased risk of HF and hospitalization.[45] Patients with chronic right ventricular pacing, such as patients with high-degree AV block, should be regularly examined for the development of HF symptoms. Serial echocardiograms are also recommended to detect asymptomatic left ventricular dysfunction. Some trials have shown the benefit of implantation of biventricular pacemakers, instead of dual chamber pacemakers, in subjects who will require pacing the right ventricle more than 50% of the time.[46]

TACHYCARDIA-INDUCED CARDIOMYOPATHY

Tachycardia-induced cardiomyopathy is also a well-recognized reversible cause of HF. Almost all supraventricular arrhythmias have been associated with tachycardia-induced cardiomyopathy, atrial fibrillation, atrial tachycardia, atrioventricular nodal reentry tachycardia, and atrioventricular reciprocating tachycardia.[47] Frequent ventricular ectopy can also lead to development of left ventricular systolic dysfunction.[48] Restoration of sinus rhythm is the main goal and pharmacologic, electrical cardioversion, or ablative strategies can be used. Rate control can also be effective in refractory arrhythmias using drugs or AV node ablation, if required.

HIV

Left ventricular systolic dysfunction is a well-known complication of HIV, with incidence ranging from 4% to 28% without highly active antiretroviral therapy (HAART).[49,50] There is some evidence that HAART reduces incidence of HF in HIV patients, but this cardioprotective effect decreases over time and, eventually, the incidence of HF becomes similar in patients who are exposed or not exposed to HAART.[51] However, robust data are lacking and further studies are needed. Regardless, HAART therapy should be recommended to all HIV patients and it seems to provide at least some benefit in reduction of incidence of HF. For patients at high risk for cardiovascular disease, some panels have recommended a baseline screening echocardiogram, then every 1 to 2 years or as clinically indicated.[52]

ENDOCRINE DISORDERS

Hyperthyroidism has been associated with development of HF. It was thought to be a high output cardiac failure; however, increased heart rate, atrial fibrillation, systemic hypertension, changes in systemic vascular resistance, and so forth, have been implicated as potential mechanisms.[53] Hypothyroidism, pheochromocytoma, and acromegaly have also been associated with increased risk of HF. Management of underlying endocrine disorder is the mainstay of management and reduction in incidence of HF.

DIAGNOSTIC MODALITIES

Echocardiography is the imaging modality of choice, which can differentiate between Stage A and B HF. The prevalence of systolic and diastolic dysfunction was found to be 8% and 32%, respectively, in patients with Stage A HF and one

risk factor. Prevalence increased to 9% and 38%, respectively, with two risk factors and to 15% and 38%, respectively, with three or more risk factors.[54] These numbers may be expected to increase with development of more sensitive techniques of detecting systolic and diastolic dysfunction. Routine echocardiography is strongly recommended for patients with two or more risk factors for development of HF. Brain natriuretic peptide levels in patients older than 60 years of age could provide a cost-effective screening tool.[55]

STAGE B HF

Stage B HF patients are defined as those with evidence of structural heart disease but without current or previous symptoms. Once patients start to manifest symptoms of HF, they advance to stage C HF in the spectrum of this progressive disease. Examples of such patients include those who have recently had a myocardial infarction and have developed LV systolic dysfunction without any symptoms of HF or patients with hypertension and LV remodeling, such as hypertrophy demonstrated by routine echocardiography.

The prevalence of Stage B HF is approximately fourfold greater than patients who have Stage C or D combined.[56] Unless a vigorous screening program is in place, most of these patients go unnoticed until they advance to Stage C. It is also possible that patients minimize their symptoms because of the gradual onset of HF symptoms. In addition, and patients might unconsciously reduce their activity levels to compensate for the decreased exercise tolerance and underreport their symptoms.

MANAGEMENT GOALS

The biggest challenge in managing Stage B patients is identification. Although it is well established that treating these patients early will decrease their morbidity and mortality, a definitive cost-effective screening program has not been developed.[57,58] Screening tools such as echocardiography or plasma brain natriuretic peptide levels are a reasonable approach to these patients.[55,59]

Most of the clinical trials identify CAD as the predominant cause of Stage B HF. The nonischemic causes include, but are not limited to, valvular heart disease, postviral myocarditis, familial dilated cardiomyopathy, and hypertension. It is important to identify the cause of myocardial dysfunction because it guides the therapeutic options (see **Box 1**).

The proportion of patients with Stage B increases when diastolic dysfunction is included. Recent studies have shown that diastolic dysfunction identified by echocardiography has a substantial prognostic significance for those with and without preserved ejection fraction (EF).[60,61] Serial echocardiography for these select individuals is a promising approach for screening and follow-up.[62]

PHARMACOLOGIC TREATMENT

β-Blockers

LV dysfunction activates counteracting mechanisms through the neurohormonal system, including renin-angiotensin and norepinephrine. These mechanisms are initiated much before the development of symptoms.[63]

β-blockers reduce the LV chamber volume and improve EF. The REversal of VEntricular Remodeling with Metoprolol Succinate (REVERT) Trial randomized subjects to receive metoprolol succinate or placebo. Over the course of 12 months, EF, as well as end systolic volumes, significantly decreased compared with baseline or placebo in a dose-dependent fashion. This is the only trial that looked only at Stage B subjects and the effect of β-blockers.[64]

In the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial, the long-term effects of carvedilol on ischemic cardiomyopathy were shown to be beneficial. Of the 1959 randomized subjects, 53% were asymptomatic. Over the course of 2 years, carvedilol had a 31% risk reduction in all cause mortality compared with placebo.[65] A further echocardiography substudy showed significant improvements in LV EF and a reduction in LV chamber volumes when compared with placebo.[66]

β-blockers should be introduced early to prevent any further remodeling in an already structurally abnormal LV. The ACCF/AHA guidelines recommend the use of β-blockers in Stage B HF patients, regardless of the cause, as a Class I recommendation.[59]

ACE Inhibitors and ARBs

As previously discussed, the neurohormonal system activation occurs early in the spectrum of this clinical syndrome, which influences the rationale of blocking the renin-angiotensin-aldosterone system (RAAS). The benefit of ACE inhibitors is that they inhibit the formation of angiotensin II, promoting antihypertensive, antifibrotic, and vasodilatory properties to the cardiovascular system.[67] ARBs work in a similar fashion, inhibiting the effects by blocking angiotensin II receptor.

The Studies of Left Ventricular Dysfunction (SOLVD) prevention trial demonstrated the effects of enalapril versus placebo on 4228 Stage B HF subjects with an EF lower than 35%. There were significant reductions in progression of disease, as well as hospitalizations related to HF. There was also a trend toward fewer deaths in the enalapril group, although this difference did not reach statistical significance.[68] ARBs have been shown to have no mortality difference compared with ACE inhibitors in ischemic cardiomyopathy and they are recommended for patients who are intolerant of ACE inhibitors.[69,70]

RAAS blockade is also beneficial in nonischemic causes of HF such as hypertensive heart disease.[67] ACE inhibitors and ARBs have been shown to prevent and reverse hypertrophy and fibrosis. ACCF/AHA guidelines recommend the use of ACE inhibitors in those patients with Stage B HF (Class I) and ARBs can be used in patients intolerant to ACE inhibitors.[59]

CCBs, Digoxin, and Aldosterone Antagonists

The use of CCBs has clinical benefit in the asymptomatic patient with LV systolic dysfunction. Although there have been no studies showing adverse effects, CCBs with negative inotropic effects should not be used in asymptomatic patients with an EF lower than 40%, especially after a myocardial infarction.[71]

Digoxin is also a Class III recommendation in asymptomatic patients with low EF because there is no proven benefit and a high risk of harm.[72]

Most of the data for aldosterone antagonists is available in stage C and D HF. In the Randomized Aldactone Evaluation Study (RALES) and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), there were significant reductions in mortality and morbidity when compared with placebo.[73,74] The effect of aldosterone inhibition on LV remodeling has also been shown to affect patients with HF with preserved EF.[75] Currently, these drugs are not recommended in the ACCF/AHA guidelines for management of asymptomatic patients.[59]

NONPHARMACOLOGICAL TREATMENT

Patients with asymptomatic LV systolic dysfunction are at increased risk for sudden cardiac death. In the Framingham Study population, 43% deaths in subjects with ischemic cardiomyopathy occurred suddenly without overt signs of HF.[58] One trial, which looked at asymptomatic subjects with LV systolic dysfunction and primary prevention of sudden cardiac death, was the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II). In this trial, 1232 subjects with a previous myocardial infarction and an EF less than 30% were randomized to receive an implantable cardioverter-defibrillator (ICD) or conventional medical therapy. One-third of both groups were asymptomatic. Over the follow-up of 20 months, there was a 31% reduction in death in the ICD arm compared with conventional medical therapy.[76] The data for primary prevention in nonischemic patients are derived from the Defibrillators in Non-Ishcemic Cardiomyopathy Treatment Evaluation (DEFINITE) study, which evaluated 458 subjects with EF higher than 36% over a 29-month period (22% were asymptomatic). Overall, there was an insignificant reduction in mortality of 35% and most of the mortality benefit was in the symptomatic subjects.[77] ACCF/AHA guidelines recommend ICD placement in selected, asymptomatic patients with ischemic cardiomyopathy (Class IIa) as well as nonischemic cardiomyopathy (Class IIb).[59]

Some other causes of Stage B HF are valvular heart disease and tachyarrhythmias. Although the patients may not exhibit symptoms, valvular stenosis or regurgitation may be classified as severe by echocardiography. Repair or replacement should be considered for these patients.[78] If tachyarrhythmia has been diagnosed as the primary cause of LV dysfunction, such as supraventricular tachycardia with rapid ventricle response or a high burden of isolated PVCS, efforts should be made to keep the patient in sinus rhythm or control the ventricular response rates as much as possible with either ablation therapy or medications.

SUMMARY

Patients at high risk for developing HF are classified as stage A HF. CAD, diabetes, and hypertension are the three major risk factors. There are various other modifiable, as well as nonmodifiable, risk factors. These patients may advance to stage B HF; however, diagnosis may be difficult because the patients are asymptomatic. Early detection of stage A and B patients with early therapeutic interventions and close monitoring is critically important to slow the progression to advanced stages of HF, and to decrease morbidity and mortality. Left ventricular remodeling and dysfunction are mediated through neurohormonal activation. ACE inhibitors and β-blockers remain the mainstay of medical management of stage B patients. Implantation of ICD may be considered in selected patients to reduce mortality. Routine use of echocardiography in high-risk patients is highly recommended for early detection of stage A and B patients.

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