Section 11: Evaluation and Management of Patients with Heart Failure and Preserved Left Ventricular Ejection Fraction

Overview

A substantial number of patients with heart failure (HF) have preserved left ventricular ejection fraction (LVEF), variably defined as an LVEF $>40\%$, $>45\%$, or $>50\%$.[1,2] When these patients have invasive or non-invasive evidence of abnormal diastolic function (either abnormal relaxation, filling or stiffness) they are said to have "diastolic HF".[3] Although the term "HF with normal LVEF" is often used to denote this group, because "normal" is variously defined, "HF with preserved LVEF" will be the active definition in this document. Few randomized clinical trials have been performed in this patient group, but appropriate treatment strategies have been proposed by the American College of Cardiology, American Heart Association, Canadian Society of Cardiology, and the European Society of Cardiology, and are proposed in this document by the Heart Failure Society of America.[4–10] Patients with a previously reduced LVEF whose LVEF has returned to normal with medical and/or device therapy should not be included in the classification of HF with preserved LVEF, but they should be treated as outlined in Section 7.

Pathophysiology. The left ventricle in HF with preserved LVEF may be characterized by LV hypertrophy,[11] concentric remodeling, increased extracellular matrix,[12] abnormal calcium handling, abnormal relaxation and filling and decreased diastolic distensibility.[6,13] Activation of the neurohormonal milieu, including the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, is common in HF with and without preserved LVEF.[6]

Prevalence. In prospective studies, approximately 50% of the population of patients with HF has normal or near normal resting LVEF.[2,5,14–16] HF with preserved LVEF is particularly prevalent among the elderly, females, and patients with hypertension.[2,15,17,18] Among 4 prospective studies of HF with preserved LVEF, the average age range of patients was 73 to 79 years, and the percentage of females ranged from 61% to 76%.[2,14,19] However, neither age <70 years nor male gender excludes the diagnosis of HF with preserved LVEF.

Mortality and Morbidity. The mortality of patients with HF with preserved LVEF is considerable, and in the general population of unselected patients it may be comparable to mortality in patients with HF and reduced LVEF.[2,14,16] An analysis from the Framingham Heart Study showed that HF patients with preserved LVEF had lower 5 year mortality compared with those with reduced LVEF.[16] This difference was even more pronounced in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study. However, in a study from Olmsted County, survival was similar for patients with HF and either reduced or preserved LVEF.[15]

This variability in relative clinical outcomes may reflect differences in criteria for the diagnosis of HF, the number of co-morbidities present, and the demographic and clinical composition of the populations studied. In the Olmstead County report, the mean age of the patients with HF with preserved LVEF was 77 $\pm$ 12 years.[15] In a recent review by the same investigators, mortality in HF with preserved LVEF was similar to that in patients with HF and reduced LVEF when patients were older than 65; among patients younger than 65, mortality was lower in those with preserved LVEF.[18]

HF with preserved LVEF is also associated with considerable morbidity. There is a 50% chance of re-hospitalization for HF in 6 months in patients with HF with preserved LVEF. A recent study comparing patients with preserved or reduced LVEF found similar rates of hospital readmissions, HF readmissions, and functional decline.[2]

Women make up a majority of patients with HF with preserved LVEF.[14,16,20] Most studies have shown no difference in survival by gender, but in the Digitalis Investigation Group (DIG) study [21] and one other study,[16] female gender was associated with improved survival.

An analysis of the Coronary Artery Surgery Study registry showed that the presence of coronary artery disease (CAD) was an adverse factor for survival in patients with HF and LVEF $>45\%$.[22] A review of the available literature in 2002 showed that the prevalence of CAD in patients with HF and preserved LVEF ranged widely from 0% to 67%, but is clearly less than the prevalence in HF and a reduced LVEF.[6]

Recommendation

11.1 Careful attention to differential diagnosis is recommended in patients with HF and preserved LVEF to distinguish among a variety of cardiac disorders, because treatments may differ. These various entities may be distinguished based on echocardiography, electrocardiography, and stress imaging (via exercise or pharmacologic means, using myocardial perfusion or echocardiographic imaging) and cardiac catheterization. See Figures 11.1, 11.2, and 11.3 for guidance to a differential diagnosis. (Strength of Evidence = C)

Background

Diagnosis. The clinical diagnosis of HF depends on the presence of commonly accepted signs and symptoms (Fig. 11.1). Preserved LVEF may be shown by quantifying LVEF and LV volumes or dimensions through imaging techniques such as echocardiography, radionuclide ventriculography, contrast ventriculography, or cardiac

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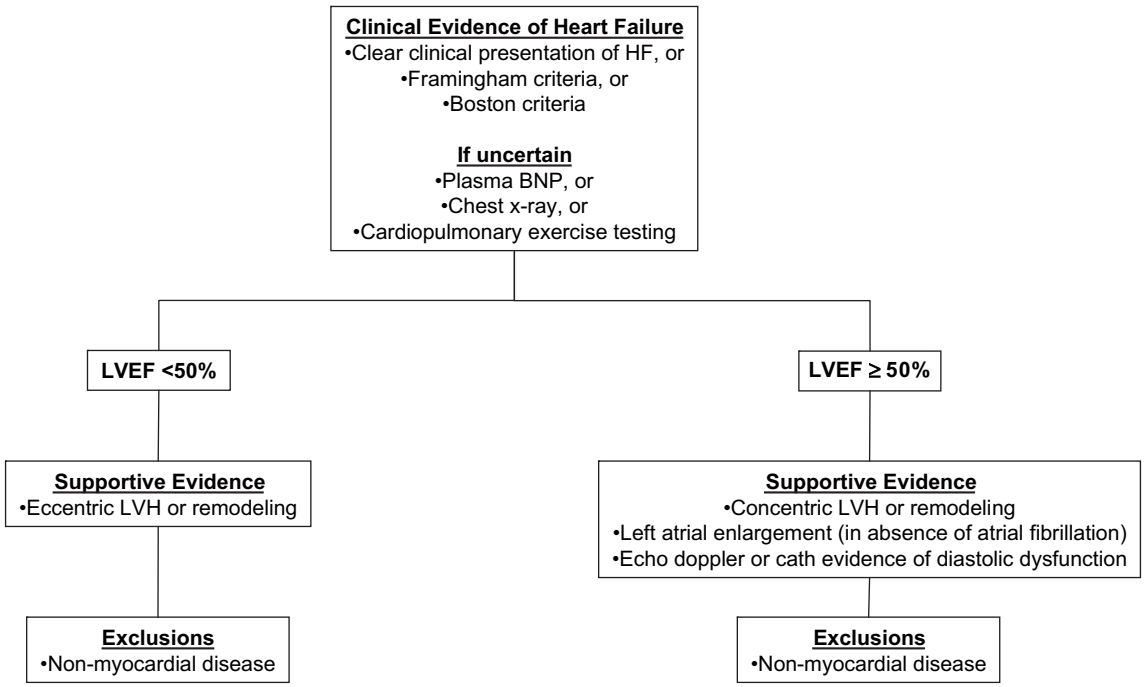


Adapted from Yturralde FR et al. *Prog Cardiovasc Dis* 2005;47:314-319.

Fig. 11.1. Diagnostic Criteria: HF with Reduced Versus HF with Preserved EF.

magnetic resonance imaging. Among these, echocardiography is the most commonly used and has several advantages, including availability and the ability to provide information about LV wall thickness, filling patterns, cardiac anatomy, and valvular function.

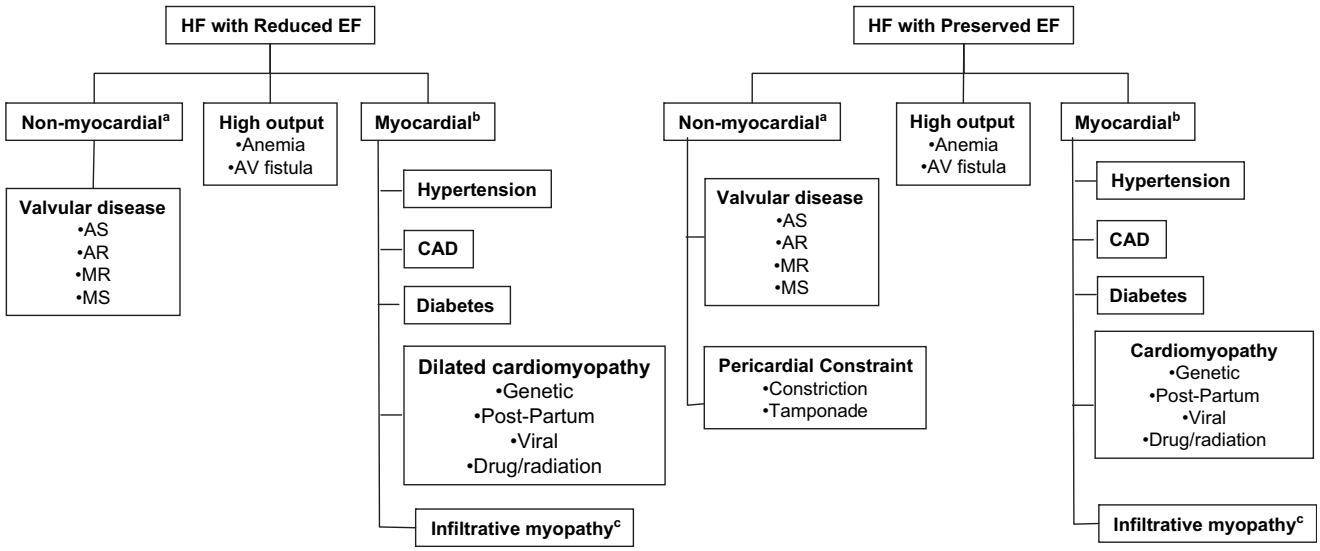
Confirmation of increased LV diastolic filling pressure by documenting elevation of B-type natriuretic peptide (BNP or NT-proBNP) may be useful when dyspnea may be due to noncardiac causes.[23] Increased BNP or NT-proBNP may identify patients with elevation of the LV diastolic pressures, but does not differentiate patients with preserved versus reduced LVEF.[24] HF with reduced LVEF tends to be associated with greater elevation of BNP than does HF with preserved LVEF, but BNP is above normal in both categories of HF, except in the obese patient, where BNP or NT-proBNP may be falsely low.[25] In HF with preserved LVEF, there is some overlap with the normal range.[23,24,26]

Differential Diagnosis. The causes of HF with either preserved or reduced LVEF are similar as shown in Figure 11.2. A diagnostic algorithm for patients with HF and preserved LVEF is outlined in Figure 11.3. LV hypertrophy (LVH) or concentric remodeling diagnosed by echocardiography or electrocardiography, is commonly present in patients with HF with preserved LVEF. Doppler echocardiography frequently demonstrates abnormalities in LV diastolic function.

The echocardiogram is more sensitive than the electrocardiogram for the diagnosis of LVH.[27] In addition to chronic systemic hypertension, LVH may be due to other causes of LV pressure overload, such as aortic stenosis or aortic coarctation. Detecting LVH in the absence of an obvious cause for LV pressure overload supports the diagnosis of hypertrophic cardiomyopathy. This condition is usually regional (eg, septal, apical), but may be global. It is usually familial and genetically mediated.[28,29] Increased wall thickness by echocardiography, coupled with low voltage on the electrocardiogram, strongly supports the diagnosis of an infiltrative cardiomyopathy. Among the most common infiltrative disorders is amyloidosis,[30] a disorder with a very poor prognosis.[31] In addition to low voltage, pseudo-infarction Q waves may be present. In the absence of hypertrophy, other infiltrative processes include sarcoidosis and Gaucher's disease. Sarcoid nodules in the myocardium rarely cause LV restrictive physiology, but pulmonary sarcoidosis may commonly cause pulmonary hypertension and right-sided HF.[32]

Less common storage disorders include hemochromatosis. Rare disorders include Fabry disease and glycogen storage diseases. Hemochromatosis has several etiologies (familial, idiopathic, and acquired) and is manifested primarily as a dilated cardiomyopathy with reduced systolic performance, but occasionally as a non-dilated, restrictive cardiomyopathy.[33] Fabry disease may be associated initially with normal LV mass, but later with hypertrophy. Restrictive disorders are rare, and may be associated with either LVH or normal LV mass.[34] Endomyocardial disorders include endomyocardial fibrosis (usually in tropical climates); the hypereosinophilic syndrome, which may or may not be related to endomyocardial fibrosis; and carcinoid.

In the absence of aortic or mitral regurgitation, LV volume overload denotes a high cardiac output because of ventricular



[a]Cause of HF or specific target for therapy
[b]Disease process that may lead to HF
[c]May have stage in which EF is normal but often declines

Fig. 11.2. Etiology of HF with Reduced Versus HF with Preserved EF.

septal defect, patent ductus arteriosus or other arteriovenous shunt, chronic anemia, thyrotoxicosis, or chronic liver disease.

It is essential to clarify the diagnosis of pericardial disorders with constrictive physiology versus restrictive disorders. In the absence of substantial pericardial fluid, the diagnosis of pericardial disease may require invasive hemodynamics, computerized tomography, or magnetic resonance imaging to identify pericardial thickening.[35]

In contrast to restrictive and infiltrative cardiomyopathies and to pericardial disease, ischemic heart disease with transient LV dysfunction is much more common. It is considered here and in other sections, particularly Section 13.

Right ventricular (RV) dysfunction is most commonly caused by LV dysfunction. In such conditions, there is pulmonary hypertension. Other causes of pulmonary hypertension, such as pulmonary thromboembolic disorders and intrinsic lung disease, may also precipitate RV dysfunction. Occasionally severe RV dysfunction may follow RV infarction. Occasionally chronic RV dysfunction can cause LV dysfunction resulting from ventricular interaction, a situation in which RV pressure-volume overload may deform and displace the interventricular septum toward the LV, increasing LV diastolic pressure even as LV volume remains constant or decreases. Such conditions reduce LV compliance.

In summary, there is a broad differential diagnosis of all HF patients. This is also true in HF with preserved LVEF and must be kept in mind during the initial evaluation of such patients. Hypertensive LVH is the most common cause of HF with preserved LVEF. However, CAD and diabetes mellitus are also common disease processes associated with the development of HF with preserved LVEF. In analyzing HF in such patients, most emphasis has centered on assessment of LV and LA structural changes and changes in LV diastolic function.

Recommendation

11.2 Evaluation for ischemic heart disease and inducible myocardial ischemia is recommended in patients with HF and preserved LVEF (see Section 13). (Strength of Evidence = C)

Background

Section 13 provides a detailed approach to the diagnosis of ischemic heart disease in patients with HF by noninvasive stress imaging and by cardiac catheterization. Ischemic mitral regurgitation, acute or chronic, may aggravate HF with normal systolic performance.

Recommendations

11.3 Blood pressure monitoring is recommended in patients with HF and preserved LVEF (Section 14, Recommendation 14.1). (Strength of Evidence = C)

11.4 Counseling on the use of a low-sodium diet (Section 6) is recommended for all patients with HF, including those with preserved LVEF. (Strength of Evidence = C)

11.5 Diuretic treatment is recommended in all patients with HF and clinical evidence of volume overload, including those with preserved LVEF. Treatment may begin with either a thiazide or loop diuretic.

In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided. (Strength of Evidence = C)

Background

In conditions with LVH, restrictive or constrictive physiology, a small decrease in intravascular volume may be associated with significant reduction in LV preload, resulting in decreased cardiac output. Orthostatic changes and prerenal azotemia provide evidence for excessive preload reduction.[6] Acutely, in addition to diuretics, nitrates may have a role in diminishing pulmonary venous pressure and clinical congestion. Chronically, the effects may be similar, but one must be alert to the possibility of excess reduction in LV preload.

Recommendation

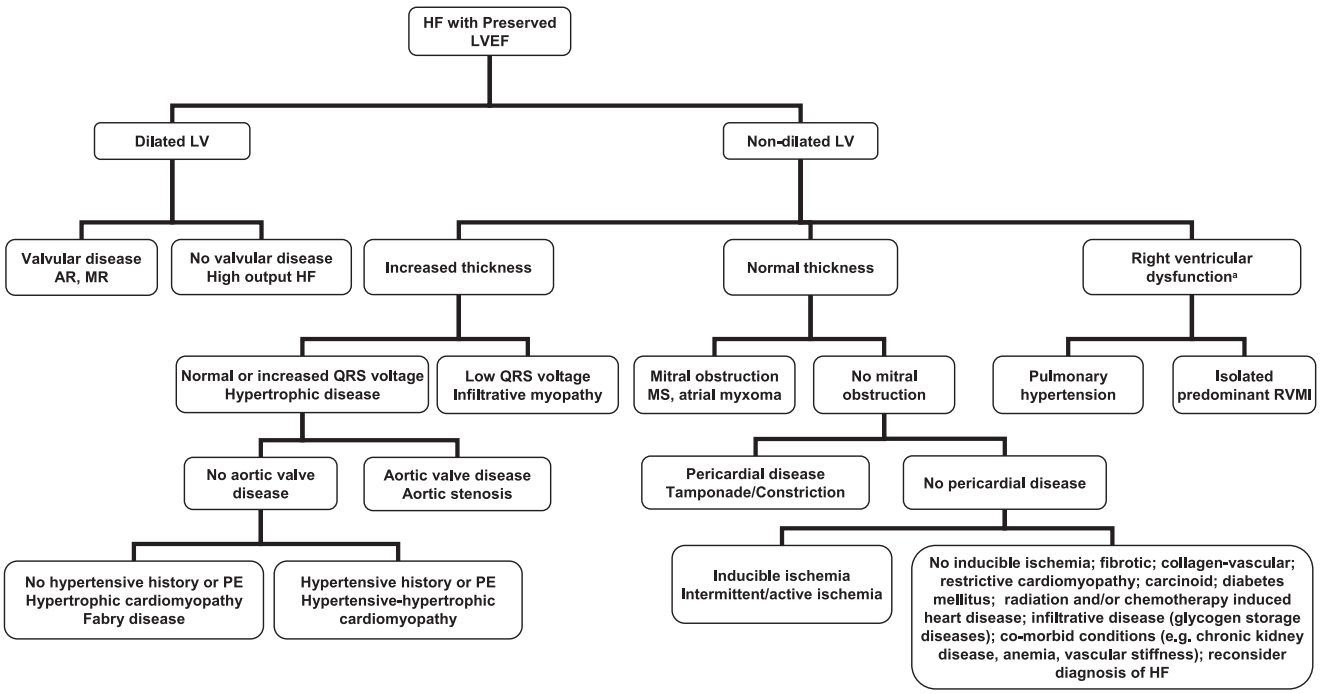
11.6 In the absence of other specific indications for these drugs, angiotensin receptor blockers (ARBs) or angiotensin converting enzyme (ACE) inhibitors may be considered in patients with HF and preserved LVEF.

- **ARBs (Strength of Evidence = C)**
- **ACE inhibitors (Strength of Evidence = C)**

Background

A trial of the ARB, candesartan, in patients with HF and preserved LVEF showed a trend toward reduction in the primary endpoint of cardiovascular death or hospitalization (unadjusted hazard ratio 0.89, CI 0.77-1.03, $P = .118$; adjusted hazard ratio 0.86, CI 0.74-1.00, $P = .051$).[36] At enrollment, approximately 20% of patients were receiving ACE inhibitors and 55% were receiving beta adrenergic blocking drugs. There was no subset analysis of the combination of these drugs in these specific patients, but the candesartan group showed a reduction in both hospitalizations and blood pressure.

The Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) study enrolled 4128 patients who were at least 60 years of age and had New York Heart Association class II, III, or IV HF and a LVEF of at least 45% and randomly assigned them to receive 300 mg of irbesartan or placebo per day.[37] The primary composite outcome was death from any cause or hospitalization for a cardiovascular cause (HF, myocardial infarction, unstable angina, arrhythmia, or stroke). Secondary outcomes included death from HF or hospitalization for HF, death from any cause and from cardiovascular causes, and quality of life. During a mean follow-up of 49.5 months, the primary outcome occurred in 742 patients in the irbesartan group and 763 in the placebo group. Primary event rates in the irbesartan and placebo groups were 100.4 and 105.4 per 1000 patient-



LVEF = left ventricular ejection fraction; HF = heart failure; QRS = electrocardiographic ventricular depolarization; AR = aortic Regurgitation; MR = mitral regurgitation; MS = mitral stenosis; RVMI = right ventricular myocardial infarction; PE = pulmonary embolism

[a]Some patients with right ventricular dysfunction have LV dysfunction due to ventricular interaction

Fig. 11.3. Diagnostic Algorithm for Heart Failure with Preserved LVEF.

years, respectively (hazard ratio, 0.95; 95% confidence interval [CI], 0.86 to 1.05; P = 0.35).Overall rates of death were 52.6 and 52.3 per 1000 patient-years, respectively (hazard ratio, 1.00; 95% CI, 0.88 to 1.14; P = 0.98). Rates of hospitalization for cardiovascular causes that contributed to the primary outcome were 70.6 and 74.3 per 1000 patient-years, respectively (hazard ratio, 0.95; 95% CI, 0.85 to 1.08; P = 0.44). There were no significant differences in the other prespecified outcomes. Irbesartan did not improve the outcomes of patients with HF and preserved LVEF.

Recommendation

11.7 ACE inhibitors should be considered in all patients with HF and preserved LVEF who have symptomatic atherosclerotic cardiovascular disease or diabetes and one additional risk factor. (Strength of Evidence = C)

In patients who meet these criteria but are intolerant to ACE inhibitors, ARBs should be considered. (Strength of Evidence = C)

Studies supporting the use of ACE inhibitors in patients with HF and preserved LVEF did not enroll patients with known HF. A secondary endpoint of the Heart Outcomes Prevention Evaluation (HOPE) trial was progression to HF in the following high risk patients: those older than age 55 years with either documented vascular disease or multiple cardiac risk factors, one of which was diabetes.[38] In this randomized study, 9297 patients received double-blind placebo or ramipril 10 mg daily and were followed for 4.5 years. The annual risk for development of HF was approximately 2.5%, which was reduced by 23% with the ACE inhibitor. The risk reduction was independent of multiple covariates. The presence of a subsequent MI during the study increased the risk of developing HF more than eightfold. Treatment with ramipril was associated with a 33% reduction in the development of HF in those with a baseline systolic pressure above the median of 139 mm Hg versus only 9% in those whose systolic blood pressure was below the median *(P = .024)*.

The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) studied high dose ACE inhibitor therapy versus placebo in patients older than age 18 with documented CAD.[39] A mean follow-up of 4.2 years showed that perindopril reduced total mortality by 14% (from 6.9% to 6.1%), recurrent MI by 22% (6.2% to 4.8%), and hospital admission for HF by 39%. All findings were statistically significant, were consistent in all predefined subgroups, were independent of coexistent beta blocker therapy, and were seen in the setting of aggressive treatment of vascular disease, as determined by the high rate of antiplatelet (92%), antilipid (58%), and beta blocker (62%) usage.

Recommendation

11.8 Beta blocker treatment is recommended in patients with HF and preserved LVEF who have:

- **Prior myocardial infarction (Strength of Evidence = A)**
- **Hypertension (see Section 14) (Strength of Evidence = B)**
- **Atrial fibrillation requiring control of ventricular rate (Strength of Evidence = B)**

Background

No large-scale studies to date have demonstrated improvement in clinical outcomes from beta blockers specifically in patients with HF and preserved LVEF. However, as with ACE inhibitors, large subsets of this population fall into one or another category for which beta blockers have either proven beneficial or are highly likely to achieve clinical benefit.

In failing hearts, rapid rates are associated with progressively reduced contractile force and increased resting tension. The increased resting tension is related to incomplete relaxation due to incomplete reuptake of calcium to storage sites in the sarcoplasmic reticulum.[13] In a noninvasive study of hypertrophic cardiomyopathy, beta adrenergic blocking drugs prolonged diastolic filling time, suggesting better LV filling.[40] In the presence of CAD, tachycardia is associated with a prompt increase in LV diastolic pressure when associated with ischemia.[41] Thus reducing the heart rate with beta adrenergic blocking drugs should be beneficial for LV filling and a reduction in the LV end-diastolic pressure. Furthermore, retrospective studies have suggested substantial benefit of adequate rate control on systolic function in patients with atrial fibrillation with a rapid ventricular response.[42,43] Patients with sinus tachycardia may benefit from a reduction in heart rate; however, because the tachycardia may reflect an inability to increase stroke volume, care must be taken when using beta blockade.

The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) study was a randomized trial in 2128 patients ≥70 years with a history of HF (a hospitalization for HF in the last year or an LVEF ≤35%). The primary endpoint of all-cause mortality or cardiovascular hospitalizations was reduced with nebivolol from 35.3% to 31.1% (HR = 0.86, 95% CI = 0.74-0.99, p = 0.039).[44] Thirty-five percent of patients in SENIORS had an LVEF of >35% and there was no significant difference in the effect of nebivolol between the group with an LVEF >35% and that with an LVEF ≤35%.[45] However, more than half of subjects with an LVEF >35% had an LVEF of 35-50%, leaving a small number of subjects with preserved LVEF. [44] In a study of ventricular remodeling comparing Chinese patients with HF and an LVEF <40%, 40-55%, or > 55%, the cohort with a mildly decreased LVEF had eccentrically enlarged ventricles with evidence of remodeling (rightward shifted end-diastolic pressure-volume relation) and decreased chamber contractility (downward shifted end-systolic pressure-volume relation) most comparable to subjects with overt systolic HF.[46] Studies comparing patients with HF and mildly reduced LVEF also suggest

that clinical features of patients with mildly reduced LVEF are more comparable to patients with an LVEF < 40 than in those with a preserved LVEF.[47,48] Thus, data are inadequate to recommend beta-blockers for most patients with HF and a preserved LVEF (LVEF >55%) in the absence of prior MI, hypertension, or atrial fibrillation requiring adequate rate control.

Recommendation

11.9 Calcium channel blockers should be considered in patients with HF and preserved LVEF and:
- **Atrial fibrillation requiring control of ventricular rate and intolerance to beta blockers. In these patients, diltiazem or verapamil should be considered. (Strength of Evidence = C)**
- **Symptom-limiting angina. (Strength of Evidence = A)**
- **Hypertension. (Strength of Evidence = C)**

Background

Although controlled clinical trial data are lacking, several properties of the calcium channel blocking drugs (eg, verapamil, diltiazem), suggest they may benefit patients with HF and preserved LVEF. Beyond these circumstances, calcium channel blockers are not routinely recommended, despite small studies showing hemodynamic benefit in select patients.

An important effect of these drugs is slowing heart rate. This effect should enhance calcium removal from the myocyte and calcium reuptake in the sarcoplasmic reticulum.[6,13,49] This should lower end-diastolic pressure[49] and improve passive ventricular filling.[50] Improved passive ventricular filling is associated with long-term improvement in exercise capacity in patients with hypertrophic obstructive cardiomyopathy, a clinical condition which, like HF with preserved LVEF, may be associated with significant abnormalities in myocardial relaxation.[50] Numerous studies have shown benefit from verapamil or diltiazem in chronic stable angina pectoris, although the patients likely did not have HF with preserved LVEF.[51] Verapamil has been shown to acutely reduce arterial stiffness in elderly normal subjects. The improvement is due to improved arterioventricular interaction, and this reduction in arterial stiffness has been related to improved exercise performance.[52]

Recommendation

11.10 Measures to restore and maintain sinus rhythm may be considered in patients who have symptomatic atrial flutter-fibrillation and preserved LVEF, but this decision should be individualized. (Strength of Evidence = C)

Background

In patients with atrial fibrillation or flutter who remain symptomatic after adequate rate control, it is reasonable to consider restoration of sinus rhythm. Because studies comparing rhythm control to rate control in patients with atrial fibrillation have generally excluded symptomatic patients, there are no randomized clinical trials for guidance. Nevertheless, retrospective evaluation of studies of patients with HF suggest that in the subset of patients with atrial fibrillation both amiodarone and dofetilide increased conversion to sinus rhythm and maintenance of sinus rhythm.[53–55]

These trials also demonstrated the safety of these drugs in patients with HF. Early experience suggests that catheter ablation of atrial fibrillation may also be considered in patients with HF to improve symptoms.[56]

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