Section 15: Management of Heart Failure in Special Populations

Overview

Heart failure (HF) is a prevalent condition in women, African Americans, and the elderly of both sexes and any race. In the absence of contradictory data, the clinical recommendations based on trial data derived from predominately younger white male study populations have generally been applied equally to these groups. However, there are etiologic and pathophysiologic considerations specific to these groups that warrant attention if care and outcomes are to be optimized. Discussion in this section is based primarily on available data from subgroup analyses of randomized HF trials and the results of cohort studies. A substantial amount of the data on drug efficacy comes from studies of patients treated after a recent acute myocardial infarction (MI).

Although a significant number of women and elderly patients with HF have preserved left ventricular ejection fraction (LVEF) there are few evidence-based data to guide therapy in this group. Other special populations, ethnic groups such as Hispanics, Asians, American Indians, or Pacific Islanders, are important special populations but there are inadequate data currently available about HF management to discuss these groups individually. Asian, particularly Chinese, patients have been reported to have a high incidence of cough with angiotensin converting enzyme (ACE) inhibitors, although this finding was not confirmed in a larger study of perindopril.[1−3] Mitochondrial aldehyde dehydrogenase-2 is responsible for the bioactivation of nitroglycerin as well as the clearance of acetaldehyde.[4] A polymorphism of this enzyme is present in 30-50% of Asians, and it is associated with decreased efficacy of the anti-anginal effects of nitroglycerin and an inability to clear acetaldehyde resulting in flushing after alcohol ingestion. Thus, it is possible, though not tested, that the combination of hydralazine and isosorbide dinitrate may not be effective in a significant number of Asians with HF. No HF treatment data is currently available in Hispanics, although epidemiologic factors such as diabetes may be particularly important in this subgroup.

The recommendations that follow are specific for the elderly, African-Americans, and women with HF and abnormal systolic function, as there are substantial data concerning HF management in these subgroups.

Elderly Patients with HF

Clinical Characteristics and Prognosis. HF represents a significant and growing public health problem for the elderly. The progressive aging of the US population is well established[5] and has profound implications for the prevalence of cardiovascular disease-particularly HF. A number of studies have documented the substantial increase in the prevalence of this syndrome as age increases.[6] As with most illnesses in the elderly, HF is associated with higher rates of morbidity and mortality than in younger patients.[7,8] Among elderly patients hospitalized with HF, median survival is approximately 2.5 years, with 25% of patients dying within 1 year.[9]

Pathophysiology of HF in the Elderly. There are a number of well described changes in cardiovascular physiology which occur with aging. Resting systolic left ventricular (LV) function appears to be preserved, but perhaps at the expense of some LV enlargement.[10] A diminution of diastolic function has been documented in otherwise normal elderly individuals.[11] Exercise capacity declines with age, most likely from a combination of changes in cardiac and peripheral vascular factors, ventricular-vascular coupling and aortic distensibility.[12,13] With age, diastolic filling of the ventricle becomes more dependent on atrial contraction and ventricular volume changes with increasing cardiac output are significantly different than those seen in younger subjects.[14] Though these diverse cardiovascular changes tend to reduce exercise capacity, their impact on health and quality of life remains modest in most individuals compared to the detrimental effects of HF.

The presentation of HF may differ in elderly patients with HF. Although they commonly present with the classic symptoms of dyspnea and fatigue, the elderly are more likely than younger patients to present with atypical symptoms such as poor executive functioning, altered mental status, or depression.[15,16]

Recommendations

15.1 **As with younger patients, it is recommended that elderly patients, particularly those age >80 years, be evaluated for HF when presenting with symptoms of dyspnea and fatigue. (Strength of Evidence = C)**

15.2 **Beta blocker and ACE inhibitor therapy is recommended as standard therapy in all elderly patients with HF due to LV systolic dysfunction. (Strength of Evidence = B) In the absence of contraindications, these agents are also recommended in the very elderly (age >80 years). (Strength of Evidence = C)**

15.3 **As in all patients, but especially in the elderly, careful attention to volume status, the possibility of symptomatic cerebrovascular disease, and the presence of postural hypotension is recommended during therapy with ACE inhibitors, beta blockers and diuretics. (Strength of Evidence = C)**

Background

Beta Blockers. Diminished response to catecholamine stimulation in elderly individuals has been shown by several investigators[17] and appears related to diminished number and activity of both beta$_1$ and beta$_2$ receptors.[18] However, the changes in response to the sympathetic nervous system do not mitigate the need for beta receptor antagonism in the elderly. The striking risk in the elderly of major morbidity and early mortality, combined with the substantial benefit derived from beta blockade, strongly supports the use of these agents as tolerated in elderly patients with symptomatic LV systolic dysfunction.

Conclusions from randomized placebo-controlled trials are limited concerning the efficacy of beta blockade in the elderly. However, a retrospective analysis of a study of metoprolol CR/XL, which enrolled patients up to age 80 and included a substantial subgroup of elderly patients, found a similar degree of morbidity and mortality reduction in patients 69 or older versus those younger than 69.[19,20] Observational studies of the outcome of elderly patients after MI have consistently shown substantial reductions in mortality when beta blockers are prescribed at discharge.[21-23] These studies have included octogenarians. The one randomized trial of beta blockers in an elderly population with HF (mean age 76) demonstrated a reduction of 14% in the combined endpoint of all-cause mortality or primary cardiovascular admission for the group on nebivolol.[24]

ACE Inhibitors. No randomized controlled trial has been conducted specifically to investigate the benefit of ACE inhibition in elderly patients. However, convincing evidence of the effectiveness of ACE inhibition in elderly patients is provided by the results of a trial in which the mean age was 70 and the reduction in mortality was 31% at 2 year and 27% at the end of the study for patients with LV dysfunction following MI treated with ACE inhibition.[23] Observational studies and a meta-analysis of post-MI patients with HF reinforce these findings,[25-27] though caution is necessary in extrapolating the results of post-MI studies to chronic HF.

Other Medications. In the absence of data to the contrary, other HF medications, including angiotensin receptor blockers (ARBs), aldosterone antagonists, and the combination of hydralazine/isosorbide dinitrate, should be considered as options for elderly patients with HF, keeping in mind the complications of polypharmacy in a population characterized by multiple comorbidities. In particular, older age is an independent risk factor for hyperkalemia when inhibitors of the renin-angiotensin aldosterone system (RAAS) are used alone or in combination.[28]

HF in Women

Clinical Characteristics and Prognosis. HF is common in women, and among the elderly the prevalence of HF is greater in women than in men.[29] A growing body of evidence has demonstrated significant differences in the clinical characteristics and prognosis of HF in women and men. Early results from the Framingham Heart Study pointed to a difference in prognosis between men and women with HF, with men having worse survival than women.[30–32] Subsequent findings from some HF databases have confirmed this observation in both a broad population of patients with HF and those at a very advanced stage.[31,33–35] These studies have suggested that women's survival advantage is etiology-dependent, with better outcomes noted when the primary cause is non-ischemic. Hypertension and diabetes carry with them significantly greater risk of subsequent HF in women compared to men.[36] For women with coronary artery disease but no symptoms of HF, diabetes confers particular risk for the subsequent development of HF.[37] Diabetes and coronary disease are also associated with excess mortality in women with HF and systolic dysfunction compared to men.[38]

Sex and Cardiovascular Pathophysiology. A number of experimental studies point to fundamental, sex-related differences in the nature and extent of myocardial hypertrophy and adaptation, which might account for the survival advantage for females.[39,40] Early studies of spontaneously hypertensive rats suggested that the adverse influence of hypertrophy on cardiac function was greater in male than in female rats.[41] A number of animal studies suggest sex-related differences in myocardial remodeling in response to a pressure load and after MI.[41–46]

Treatment Response. Recognition of the pathophysiologic and clinical differences between men and women with HF has raised concern that treatment response might differ as well. Results of individual controlled clinical trials, even of standard therapeutic agents for HF from systolic dysfunction, generally are inconclusive, because of the small number of women enrolled. Data from pooled analyses are equally sparse. Recommendations are made in the context of this limited database.

Recommendation

15.4 Beta blocker therapy is recommended for women with HF from:
- **symptomatic LV systolic dysfunction (Strength of Evidence = B)**
- **asymptomatic LV systolic dysfunction (Strength of Evidence = C)**

Background

Women are underrepresented in HF clinical trials, as they are in clinical studies of other cardiovascular diseases.[47] However, a review of the experience of women in several of the large-scale prospective mortality trials of beta blockade in patients with symptomatic LV dysfunction does suggest that women and men benefit to a similar degree.[48]

Similarly, a pooling of the mortality results from several other large trials showed strong evidence of a similar beneficial effect in women and men.[48,49] Given the absence of contrary data, the most prudent course is to recommend the routine use of beta blockade for HF in both women and men.

Recommendation

15.5 ACE inhibitor therapy is recommended as standard therapy in all women with symptomatic or asymptomatic LV systolic dysfunction. (Strength of Evidence = B)

Background

As with beta blockers, the available data on ACE inhibition suggest comparable effects in women and men with HF. A meta-analysis of large-scale HF and post-MI randomized trials demonstrated evidence of a mortality benefit of ACE inhibition in women. A more convincing effect was seen on the composite end point of death, reinfarction, or admission for HF. Comparable findings related to sex were also noted in the meta-analysis of mostly small-scale, short-term studies of ACE inhibition, which found similar favorable point estimates for reduction in mortality and for mortality plus hospitalization in women.[25,50]

Recommendation

15.6 ARBs are recommended for administration to symptomatic and asymptomatic women with an LVEF ≤40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency. (Strength of Evidence = A)

Background

Investigators in both the Valsartan Heart Failure Trial (Val-Heft) and the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trials have analyzed the benefits of valsartan and candesartan, respectively, in women with HF and systolic dysfunction. In Val-HeFT significant reductions in both morbidity and mortality and HF hospitalizations were reported for women and were the same as benefits reported in men.[51] In CHARM there was a significant reduction in all-cause mortality and HF hospitalization that was the same as in men.[38] Subgroup analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT) study also showed no difference in the effects of ARB vs. ACE inhibitor in men and women status post MI complicated by HF, LV dysfunction or both.[52] Thus the recommendations for ARBs in women have a level of evidence similar to those for men. Cough due to ACE inhibitors is more than twice as common in women compared to men and thus substitution of ARBs for ACE inhibitors is also likely to be more common in women compared to men.[53]

Evidence for Other Medical Therapy in Women

Although digoxin therapy has been demonstrated to decrease HF hospitalization,[54] it has not been demonstrated to improve survival. In a retrospective analysis of the Digitalis Investigation Group (DIG) trial, digoxin was associated with an increased risk of death from any cause among women, but not men, with HF and reduced LVEF.[55] However, that analysis did not account for serum potassium concentration and serum digoxin concentration differences. Another analysis of the same trial reported no excess mortality in either women or men with digoxin at serum concentrations between 0.5 and 0.9 mg/ml.[56] This report demonstrated that digoxin levels are higher in women compared to men at any given dose presumably due to decreased lean body mass and renal function. Analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trials also did not demonstrate an increase in mortality in women with digoxin.[57]

Although sex-specific data is not available from prospective trials on the benefits of aldosterone antagonists for women with LV systolic dysfunction and symptoms of HF, adequate numbers of women were included in the large randomized, controlled trials of these agents and subgroup analyses were shown to demonstrate benefit in women.[58,59]

Recommendation

15.7 The combination of hydralazine/isosorbide dinitrate is recommended as standard therapy for African American women with moderate to severe HF symptoms who are on background neurohormonal inhibition. (Strength of Evidence = B)

Background

The A-HeFT (African-American Heart Failure Trial) confirmed the benefit of hydralazine/isosorbide dinitrate in black HF patients.[60] Importantly, 40% of the A-HeFT cohort were women. An analysis of outcomes by gender in A-HeFT showed that fixed-dose combined hydralazine/isosorbide dinitrate improved HF outcomes in both men and women. There were no gender differences between men and women in the benefit of hydralazine/isosorbide dinitrate on the primary composite score, time to first HF hospitalization, and event-free survival.[61]

HF in African Americans

Clinical Characteristics and Prognosis. Cardiovascular disease is a major health issue for African Americans.[30,62] Traditionally, concern has focused on hypertension and stroke as key components of the burden of cardiovascular disease in this population. However, HF represents a major source of cardiovascular morbidity and mortality for African Americans. Epidemiologic data suggests that they are

at greater risk for HF than Caucasians, with approximately 3% of all African-American adults affected.

A number of clinical studies have documented substantial differences between the baseline clinical characteristics of African Americans and Caucasians with HF.[33,34,49] Age of onset is significantly younger in blacks than in whites, and HF is less likely to be due to ischemic heart disease. Incident HF before 50 years of age is substantially more common among blacks than among whites. Hypertension, obesity, and systolic dysfunction that are present before a person is 35 years of age are important antecedents.[63]

Analysis of outcome data from the SOLVD trials has shown higher mortality and morbidity rates in blacks compared to whites with HF.[64] Whether these differences reflect differences in baseline characteristics, delivery of care or socioeconomic factors has not been resolved. Other studies point to problems with access to care and unfavorable clinical characteristics independent of HF as factors increasing the risk of African Americans for worse outcomes.[65−67]

Aggressive, early treatment of hypertension has been proposed as a major strategy for the prevention of HF in this racial group. Persistent hypertension is not uncommon in African-American patients with HF and systolic dysfunction.

Treatment Response. Although a number of clinical characteristics have been shown to differ significantly between African Americans and other races afflicted with HF, the implications of these differences for therapy remain to be determined.

Recommendation

15.8 Beta blockers are recommended as part of standard therapy for African Americans with HF due to:
- **symptomatic LV systolic dysfunction (Strength of Evidence = B)**
- **asymptomatic LV systolic dysfunction (Strength of Evidence = C)**

Background

Although 1 trial with bucindolol did not find a beneficial effect of beta blockade in African Americans with HF,[68] subgroup analysis of data from the US Carvedilol Trials suggests that the beneficial effect of beta blockers on outcomes in African Americans with HF from systolic dysfunction is similar to the effects in the larger population.[69] Other studies demonstrate similar findings.[21,50,70] The totality of the data supports substantial benefit from these agents, regardless of race.

Recommendations

15.9 ACE inhibitors are recommended as part of standard therapy for African-American patients with HF from symptomatic or asymptomatic LV systolic dysfunction. (Strength of Evidence = C)

15.10 ARBs are recommended as substitute therapy for HF in African Americans intolerant of ACE inhibitors. (Strength of Evidence = B)

Background

ACE Inhibition. Long-standing clinical experience suggests that African Americans with hypertension respond less well than Caucasians to ACE inhibitors.[71] Concern has persisted that differences in the effectiveness of blockade of the RAAS in HF might be present between the 2 races as well. Recently, retrospective subgroup analysis of data from 2 randomized clinical trials has added support to the concept that the response of blacks and whites with HF and LV systolic dysfunction to ACE inhibition may differ. A reanalysis of the SOLVD Prevention and Treatment trials investigated the influence of race on the response to enalapril.[72] Unadjusted analysis in the matched-cohort indicated that enalapril reduced the risk of hospitalization for HF in white patients by 44%, whereas no significant benefit was seen in black patients. Adjusted analysis confirmed a beneficial effect on hospitalization risk for Caucasians, but not for African Americans. At 1 year, enalapril therapy was associated with a significant reduction in both systolic blood pressure and diastolic blood pressure in Caucasian patients, whereas no significant reduction was observed in African-American patients.

It must be remembered that this study was a post-hoc subgroup analyses of randomized studies that were not stratified based on race. The SOLVD data raise the possibility that treatment response to ACE inhibition may vary between the races. However, they do not provide sufficient data to support a strategy other than routine use of ACE inhibitors in African Americans with HF.

Clinical studies have also shown that the risk of angioedema is greater in African American patients compared to Caucasians.[73]

Angiotensin-Receptor Blockade. The use of ARBs in African Americans with HF has not been well characterized in clinical trials. It would thus be reasonable in this population to follow the general recommendations for the use of ARBs (see Section 7).

Recommendation

15.11 A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to beta blockers and ACE-inhibitors for African Americans with LV systolic dysfunction and:
- **New York Heart Association (NYHA) class III or IV HF (Strength of Evidence = A)**
- **NYHA class II HF (Strength of Evidence = B)**

Background

A strong recommendation now exists for the addition of the fixed combination of isosorbide dinitrate and

hydralazine to the standard medical regimen for African Americans with HF. Data from the Vasodilator-Heart Failure Trial (VHeFT) I and II suggested that a racial difference in treatment response existed between white and black patients with symptomatic LV dysfunction treated with hydralazine-isosorbide dinitrate versus placebo or enalapril, respectively.[74] The A-HeFT enrolled 1050 self-identified black patients who had NYHA class III or IV HF with dilated ventricles and systolic dysfunction.[60] In this placebo-controlled, blinded, and randomized trial, subjects were randomly assigned to receive a fixed combination of isosorbide dinitrate plus hydralazine or placebo in addition to standard therapy for HF. The primary end point was a composite score made up of weighted values for death from any cause, a first hospitalization for HF, and change in the quality of life. The study was terminated early owing to a significantly higher mortality rate in the placebo group than in the group given the fixed combination of isosorbide dinitrate plus hydralazine. The mean primary composite score was significantly better in the group given isosorbide dinitrate plus hydralazine than in the placebo group, as were its individual components: 43% reduction in the rate of death from any cause, 33% relative reduction in the rate of first hospitalization for HF, and an improvement in the quality of life. A provocative retrospective analysis of the A-HeFT study suggests that fixed dose isorsorbide dinitrate and hydralazine have a mortality benefit in African-Americans in the absence of beta-blockers and ACE inhibitors, and that beta-blockers but not ACE inhibitors add significant additional mortality benefit.[75]

Other Medications. In the absence of data to the contrary, other HF medications, including diuretics, digoxin, and aldosterone antagonists should be considered as options for the African-American patient with HF.

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