Section 3: Prevention of Ventricular Remodeling, Cardiac Dysfunction, and Heart Failure

Overview

Heart failure (HF) is an all-too-frequent outcome of hypertension and arterial vascular disease, making it a major public health concern.[1,2] Epidemiologic, clinical, and basic research have identified a number of antecedent conditions that predispose individuals to HF and its predecessors, left ventricular (LV) remodeling and dysfunction.[3–11] Recognition that many of these risk factors can be modified and that treating HF is difficult and costly has focused attention on preventive strategies for HF.

Development of both systolic and diastolic dysfunction related to adverse ventricular remodeling may take years to produce significant ill effects.[12–18] Although the precise mechanisms for the transition to symptomatic HF are not clear, many modifiable factors have been identified that predispose or aggravate the remodeling process and the development of cardiac dysfunction. Treatment of systemic hypertension, with or without LV hypertrophy, reduces the development of HF.[19–27] Prevention of myocardial infarction (MI) in patients with atherosclerotic cardiovascular disease is a critical intervention, since occurrence of MI confers an 8- to 10-fold increased risk for subsequent HF.[20] Other modifiable risk factors include anemia, diabetes, hyperlipidemia, obesity, valvular abnormalities, alcohol, certain illicit drugs, some cardiotoxic medications, and diet.[28,29] Consumption of one or more breakfast cereals per week and four or more servings of fruits and vegetables per day, as well as frequent exercise and moderate alcohol use have been individually and jointly associated with lower lifetime risk of HF in men.[29]

Patients with Risk Factors for Ventricular Remodeling, Cardiac Dysfunction, and HF

Recommendations

3.1 A careful and thorough clinical assessment, with appropriate investigation for known or potential risk factors, is recommended in an effort to prevent development of LV remodeling, cardiac dysfunction, and HF. These risk factors include, but are not limited to, hypertension, hyperlipidemia, atherosclerosis, diabetes mellitus, valvular disease, obesity, physical inactivity, excessive alcohol intake, dietary choices, and smoking. (Strength of Evidence = A)

3.2 The recommended goals for the management of specific risk factors for the development of cardiac dysfunction and HF are shown in Table 3.1.

These recommendations are based are well-documented data.[17,20,30–39]

Background

Hypertension. It is estimated that 74% of patients with HF have a history of blood pressure >140/90 mmHg.[40] A history of hypertension has been associated with a higher risk of HF hospitalization among post-MI patients without a prior HF history enrolled in the EPHESUS study.[41] Hypertension is a particularly significant risk factor for the development of HF in women.[9] Results from numerous randomized controlled clinical trials have proven antihypertensive therapy can reduce the incidence of symptomatic HF by 50% to 80%. The risk reduction (both absolute and relative) is greatest in severe hypertension (>160/110 mm Hg) and least in those with mild hypertension (>145/95 mm Hg). Optimal blood pressure for the prevention of HF is not known. Data from recent trials suggest that 130/80 mm Hg or lower is the optimal blood pressure for patients with documented end-organ disease (diabetes with nephropathy, patients with proteinuria).[31] The World Health Organization has suggested an optimal blood pressure of 115/75 mm Hg for individuals with no documented end-organ disease. It is uncertain whether additional therapy to lower blood pressure further will confer additional benefit.

Reducing blood pressure is a critical component of HF prevention. The choice of antihypertensive agent should be made in the context of the patient's cardiovascular risks and comorbidities or other compelling indications.[31] In general, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta blockers, and diuretics when used as anti-hypertensives all decrease the risk of developing HF, while amlodipine is associated with increased risk.[42–50] However, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), amlodipine was associated with a lower overall risk of cardiovascular events as compared to lisinopril or chlorthalidone.[48–50] Meta- analyses have confirmed these findings.[51,52] In the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, a combination of benazepril and amlodipine decreased time to cardiovascular death or cardiovascular events by 20% compared to the combination of benazepril-hydrochlorthiazide without an increase in HF hospitalizations.[53]

Restriction of dietary sodium intake has been associated with blood pressure reduction similar to single drug therapy. The Dietary Approaches to Stop Hypertension (ie, DASH) diet, rich in potassium and calcium, has been associated with a reduced incidence of hypertension requiring drug therapy.[54] Lower rates of HF have been observed

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Table 3.1. Goals for the Management of Risk Factors for the Development of Heart Failure

Risk Factor	Population	Treatment Goal	Strength of Evidence
Hypertension	No diabetes or renal disease	<140/90 mmHg	A
	Diabetes	<130/80 mmHg	A
	Renal insufficiency and >1g/day of proteinuria	127/75	A
	Renal insufficiency and ≤1 g/day of proteinuria	130/85	A
	Everyone with hypertension	Limit sodium to ≤1500 mg/day	A
Diabetes	See American Diabetes Association (ADA) Guideline		
Hyperlipidemia	See National Cholesterol Education Program (NCEP) Guideline		
Physical Inactivity	Everyone	Sustained aerobic activity 20-30 minutes, 3-5 times weekly	B
Obesity	BMI >30	Weight reduction to achieve BMI <30	C
Excessive alcohol intake	Men	Limit alcohol intake to 1-2 drink equivalents per day	C
	Women	1 drink equivalent per day	
	Those with propensity to abuse alcohol or with alcoholic cardiomyopathy	Abstention	
Smoking	Everyone	Cessation	A
Vitamin/mineral deficiency	Everyone	Diet high in K^+/calcium	B
Poor diet	Everyone	4 or more servings of fruit and vegetables per day; One or more servings of breakfast cereal per week	B

in both men and women consuming diets consistent with DASH.[55] See Table 3.2 for sodium equivalents.

Hyperlipidemia. In a large randomized study of a statin versus placebo in patients with MI and elevated low-density lipoprotein, treatment with a statin was associated with a highly significant reduction in all-cause mortality and recurrent MI.[8,37] A 20% reduction in the incidence of HF was noted in patients treated with statin therapy. Recurrent MI during this study was associated with a large relative increase in mortality and HF; thus, it is possible that the reduction in the risk of incident HF may have been related to the reduction in recurrent MI rather than to a direct effect of the statin.

Similarly, in the Heart Protection Study, randomization to simvastatin was associated with a 14% reduction in the risk of hospitalization or death due to HF.[56] Whether the reduction was due to a direct effect on HF or an indirect effect through a reduction in vascular events could not be determined from the analysis. In large randomized, controlled trials, statins have not been shown to improve clinical outcome among patients with existing New York Heart Association (NYHA) class II-IV HF.[57,58]

Although dyslipidemia is clearly associated with the development of coronary heart disease, its contribution to incident HF is less clear. Data from the Physicians' Health Study did not find an association between high total cholesterol or low HDL cholesterol and incident HF after adjustment for traditional cardiovascular risk factors.[59] There is no indication to use statins specifically for the treatment of HF, but statins are indicated to treat hyperlipidemia in HF patients.

Table 3.2. Sodium Equivalents

Salt	Sodium Chloride	Sodium
¼ teaspoon	1550 mg	600 mg
½ teaspoon	3100 mg	1200 mg
¾ teaspoon	4650 mg	1800 mg
1 teaspoon	6100 mg	2400 mg

Obesity. The American Heart Association and the European Society of Cardiology recommend an ideal body mass index (BMI) of 25−27 kg/m^2. BMI is calculated by dividing the patient's weight in kilograms by his or her height in meters squared. Obesity is defined as a BMI ≥30, overweight as a BMI ≥25. Waist-to-hip ratio may be a more powerful predictor than BMI of the risk of MI and subsequent HF.[60] Adults with BMI of 25 or 30 kg/m^2 who had a higher waist circumference had higher rates of HF incidence than those with lower waist circumference.[61] Obesity is associated with metabolic syndrome, increasingly accepted as a major risk factor for the development of cardiovascular disease. Excessive body fat results in increased metabolic demand, ventricular hypertrophy, and sleep-disordered breathing, all of which promote the development of HF. The relationship between obesity and the risk of HF is well established,[7] although some data suggest that other pathophysiologic processes associated with obesity such as inflammation may have a greater influence on the development of HF than obesity itself.[62] There is an increasing body of opinion that obesity is associated with a distinct form of cardiomyopathy. A retrospective analysis of echocardiograms for 13,382 subjects with BMI data revealed no association between LV systolic function and BMI, suggesting that other mechanisms may play a role in the development of HF in obese

persons.[63] However, in a study of 2,042 adults in Olmsted County, Minnesota, LV diastolic dysfunction was strongly associated with waist-to-hip ratio, even after adjustment for standard cardiovascular risk factors.[64]

Weight reduction has been shown to improve most of the adverse effects of obesity. It is likely that weight reduction in obese individuals reduces the likelihood of subsequent HF, although no data exist to confirm this hypothesis.

Physical Inactivity. The benefits of exercise are well documented and include reduction of recurrent MI in survivors of MI, improved exercise capacity, improved affect and quality of life, and better control of hypertension. These results are achieved with a minimum of 20−30 minutes of sustained submaximal exercise 3−5 times per week (see Section 6).[65] In one population-based study of men, exercising 5 or more times per week reduced the lifetime risk of HF at age 40 years.[29]

Alcohol Intake. Alcoholic cardiomyopathy is associated with a substantial intake of alcohol (70 g or greater per day of chronic ingestion). Avoiding substantial ingestion of alcohol is clearly advisable, but the safe level of moderate ingestion has been difficult to define. Other factors such as drinking patterns, beverage type, and genetic variations affecting alcohol metabolism may also influence the relationship between alcohol and incident HF.[66] There are conflicting reports regarding the effects of alcohol ingestion upon left ventricular ejection fraction (LVEF) in those with and without HF. At present, 2 drinks per day for men and 1 drink per day for women is considered acceptable, even in individuals with other cardiovascular risk factors. One drink is equivalent to 12−14 g of alcohol, the amount in 1.5 ounces of 80 proof spirits, 12 ounces of beer, or 5 ounces of wine. Those with for a propensity to abuse alcohol should be counseled to abstain. Population-based studies have established an association between moderate alcohol intake (up to 2 drinks per day for men or 1 drink per day for women) and a reduction in incident HF.[29,67,68] One study also suggests that light to moderate alcohol consumption is not associated with an adverse prognosis in patients with LV systolic dysfunction.[68] While some data suggest that low risk drinking decreases the risk of HF in patients with antecedent coronary artery disease, it seems prudent to follow the national recommendations referred to above.

Smoking Cessation. There is a substantial body of data concerning the adverse effects of smoking in patients with vascular disease or reduced LVEF. Smoking cessation is associated with a 50% reduction in 5-year mortality in survivors of acute MI.[69] In the Studies of Left Ventricular Dysfunction (SOLVD) study of patients with either symptomatic or asymptomatic LV dysfunction, nonsmokers or former smokers showed improved mortality when compared with current smokers.[70,71] These and other observational data suggest smoking cessation dramatically reduces adverse outcomes in patients with established vascular disease and those with established ventricular remodeling or dysfunction.

Diabetes. Diabetes is a known predictor of HF in patients with and without established cardiovascular disease.[72−75] Women with diabetes are at particular risk. In the Heart and Estrogen/Progestin Replacement Study (HERS), postmenopausal women with diabetes had a 3.0% annual incidence of developing HF even in the absence of other risk factors.[72] Leung et al reported the adjusted rate of incident HF among patients with type-2 diabetes as 794 cases per 100,000 person years, compared with 275 per 100,000 person-years in the general population, even after adjustment for demographic differences.[76] In the diabetic heart, myocyte free fatty acid uptake and oxidation is increased. This leads to free fatty acid induced insulin resistance and intracellular accumulation of triglyceride and free fatty acids, which may contribute to the development of cardiomyopathy. Downregulation of PPAR-α also appears to play an important role.[77] Additionally, many patients with diabetes have other comorbidities that are also associated with the development of HF, including ischemic heart disease, hypertension, and LV hypertrophy.[77] More research is needed to evaluate the effect of glycemic control on HF risk. In the United Kingdom Prospective Diabetes Study (UKPDS), the absolute risk of a HF event was significantly lower for patients randomized to tight glycemic control as compared to less tight control (RR 0.44, 99% CI 0.2−0.94, P=.0043).[78]

Recommendation

3.3 ACE inhibitors are recommended for prevention of HF in patients at high risk of this syndrome, including those with coronary artery disease, peripheral vascular disease, or stroke. Patients with diabetes and another major risk factor or patients with diabetes who smoke or have microalbuminuria are also at high risk and should receive ACE inhibitors. (Strength of Evidence = A)

Background

Findings from at least three randomized, controlled trials support the use of ACE inhibitors in patients at high risk for the development of HF. In one study of patients older than age 55 with documented vascular disease or multiple cardiac risk factors, including diabetes, treatment with an ACE inhibitor reduced the annual risk of developing HF by 23%.[20] A study of patients older than age 18 with documented coronary artery disease showed that treatment with an ACE inhibitor reduced total mortality by 14% over 4.2 years, even though patients were already receiving aggressive treatment for vascular disease.[44] In a third study, patients with previous stroke and mild hypertension treated with an ACE inhibitor-based antihypertensive regimen showed a 26% reduction in subsequent HF.[33]

Several trials studied the use of an ARB in patients at high risk for developing HF.[79,80] In one the composite cardiovascular event rate did not differ in patients with diabetes treated with an ARB, amlodipine, or placebo.[79] In another, patients at risk for or with cardiovascular disease, including HF, did better when treated with an ARB on top of conventional antihypertensive therapy as compared supplementary conventional treatment.[80] A recent trial comparing the use of an ACE inhibitor versus an ARB in a population with vascular disease or high-risk diabetes, but no HF, found that the ARB was non-inferior to the ACE inhibitor in preventing the primary end point of cardiovascular death, MI, stroke, or HF hospitalization.[81] Based on these results, it is reasonable to say that, at least in those high risk patients who do not tolerate an ACE inhibitor, an ARB should be used.

Recommendation

3.4 Beta blockers are recommended for patients with prior MI to reduce mortality, recurrent MI, and the development of HF. (Strength of Evidence = A)

Background

Beta blockers are known to reduce cardiac ischemia, reinfarction, and myocardial remodeling after acute MI. Studies in patients with recent MI (most published in the prethrombolytic era) have shown that beta blockers are associated with a large reduction in HF and recurrent all-cause hospitalizations, HF hospitalizations, and recurrent MI.[46,82–90] More recent data confirm this finding, showing risk reduction for the development of HF in the 25% to 45% range 1 year after MI.[91] Data from the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) Echo Substudy demonstrated a significant decrease in LV end systolic volume and a significant increase in LVEF at 6 months post-MI for patients randomized to carvedilol as compared to placebo.[92] Patients most at risk for HF and death after MI - women and patients with advanced age, diabetes, renal disease, or previous revascularization - appear to derive the most benefit, but unfortunately are less likely to receive beta blockade post MI.[93,94] Even among patients with asymptomatic LV dysfunction without a recent MI, beta blocker therapy has been shown to decrease LV end systolic and end diastolic volume and increase LVEF at 6 and 12 months as compared to placebo.[95]

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