

Section 13: Evaluation and Therapy for Heart Failure in the Setting of Ischemic Heart Disease

Overview

In the United States (US) it is estimated that 16,800,000 people have a history of coronary heart disease, including myocardial infarction (MI), angina pectoris, or both.¹ The most common cause of chronic heart failure (HF) is no longer hypertension or valvular heart disease; it is coronary artery disease (CAD).² The changing pattern in the risk factors for HF is evidenced in the Framingham Heart Study, which documents a decrease in valvular disease and left ventricular (LV) hypertrophy and an increase in MI from 1950 to 1998.³ As survival from MI continues to improve, it is expected that the number of patients with CAD and HF will also increase.

In 25 multicenter HF treatment trials reported in the *New England Journal of Medicine* over the past 20 years, involving more than 45,000 patients, CAD was present in nearly 65%.^{4–29} This figure probably underestimates the true prevalence of CAD among unselected HF patients, because the presence of CAD was not explored systematically in many trials.

Prognostic Significance of Underlying CAD Etiology in Patients with HF

Several studies have shown that CAD is associated with an increase in mortality rates in patients with HF.^{30–36} One study assessing angiographic data in patients with HF demonstrated that the extent of CAD in patients with HF and reduced left ventricular ejection fraction (LVEF) provides important prognostic information.³⁷ Data also suggest that the mechanism of sudden death may differ between ischemic and nonischemic HF patients, with acute coronary events representing the major cause of sudden death in HF patients with CAD.³⁸ In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, CAD was associated with higher in-hospital and post-discharge mortality compared to patients without CAD.³³ In the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trial, patients who experienced an acute coronary syndrome (ACS) during follow-up had a significantly increased risk of death as compared to those who did not experience an ACS.³⁹ These findings further emphasize the importance of accurate differentiation between ischemic and nonischemic causes of HF.

Managing HF in patients with CAD or a history of CAD may be significantly different than managing HF due to primary cardiomyopathy. Antiplatelet agents, smoking

cessation, and lipid-lowering therapy are particularly important interventions in patients with HF due to CAD.⁴⁰ Trials of milrinone,⁴¹ amiodarone,¹⁸ amlodipine,¹⁵ and digoxin suggest that patients with HF in the setting of CAD may have a less favorable outcome than patients with HF from primary cardiomyopathy. Revascularization in highly selected patients with reduced LVEF and significant CAD, particularly those with anginal symptoms, may be associated with improved survival and may be considered in addition to risk modification.^{33,42–49} No prospective randomized trials of coronary artery bypass surgery have been completed in patients with clinical HF, although the ongoing Surgical Treatment for Ischemic Heart Failure (STICH) and the Heart Failure Revascularization Trial (HEART) studies should clarify the role of revascularization in this population.^{50,51}

Pathophysiology of HF in the Setting of CAD. HF in the setting of CAD is a heterogeneous condition with several factors contributing to LV systolic dysfunction and HF symptoms. After an MI, there is loss of functioning myocytes, development of myocardial fibrosis, and subsequent LV remodeling, resulting in chamber dilatation and neurohormonal activation—all leading to progressive dysfunction of the remaining viable myocardium.⁴⁹ This well-recognized process may be ameliorated after an acute MI by myocardial revascularization^{47,49,52–55} and by medical therapy with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists (ARBs),^{56,57} beta blockers,⁵⁸ and aldosterone antagonists.⁵⁹

The majority of patients surviving a MI have significant atherosclerotic disease in coronary arteries other than the infarct-related vessel.⁶⁰ Under basal conditions, episodes of reversible myocardial ischemia caused by a severe coronary artery stenosis superimposed on the left ventricle with depressed LVEF may produce transient worsening of LV function. In many patients, HF symptoms, such as dyspnea or fatigue induced by exercise, may represent an anginal equivalent.

Episodes of transient myocardial ischemia may cause prolonged systolic dysfunction that persists after the ischemic insult itself has resolved. This process, called stunning, is similar to the more severe and protracted myocardial stunning that results from coronary occlusion and reperfusion.⁶¹

Another important mechanism for systolic dysfunction with additive effects on LV performance is myocardial hibernation,⁶² a process in which myocardial contraction is reduced in response to chronic reduction in myocardial blood supply.^{63,64} More than 50% of patients with HF and CAD have evidence of viable but dysfunctional (hibernating) myocardium.^{65,66} Hibernation may develop as an adaptive response to sustained reduction of myocardial blood flow. Thus, the level of tissue perfusion is sufficient to maintain cellular viability but insufficient for normal contractile function.⁶⁷ Recent evidence supports the long-held concept that hibernation represents a precarious balance between perfusion and tissue viability that cannot be

maintained indefinitely, and that myocardial necrosis will occur eventually if blood flow is not increased.⁶²

In addition to ischemia, hibernating myocardium should be considered in all patients with CAD and chronic LV systolic dysfunction of any degree.⁶⁸ Hibernating myocardium can be identified using low-dose dobutamine stress echocardiography to assess contractile reserve, single photon emission tomography with thallium-201 or technetium-99m perfusion tracers to assess membrane integrity, and positron emission tomography (PET) to assess residual metabolic activity.^{69,70} Magnetic resonance imaging (MRI) has also been used to identify potentially viable but dysfunctional myocardium.⁷¹

Identification of hibernating myocardium is important, as the restoration of blood flow by revascularization or with agents that improve endothelial function and blood flow (eg, statins) may improve contractility in hibernating areas.^{72–75} However, it should be noted that current testing modalities are limited in their ability to identify areas that will recover with revascularization.

Evaluation for CAD

Recommendations

- 13.1 Ongoing assessment for risk factors for CAD is recommended in all patients with chronic HF regardless of LVEF. (Strength of Evidence = A)**
- 13.2 It is recommended that the diagnostic approach for CAD be individualized based on patient preference and comorbidities, eligibility, symptoms suggestive of angina and willingness to undergo revascularization. (Strength of Evidence = C)**
- 13.3 It is recommended that patients with HF and symptoms suggestive of angina undergo cardiac catheterization with coronary angiography to assess for potential revascularization. (Strength of Evidence = B)**
- 13.4 It is recommended that, at the initial diagnosis of HF and any time symptoms worsen without obvious cause, patients with HF, no angina, and known CAD should undergo risk assessment that may include noninvasive stress imaging and/or coronary angiography to assess severity of coronary disease and the presence of ischemia. (Strength of Evidence = C)**
- 13.5 It is recommended that patients with HF, no angina, and unknown CAD status who are at high risk for CAD should undergo noninvasive stress imaging and/or coronary angiography to assess severity of coronary disease and the presence of ischemia. (Strength of Evidence = C)**
- 13.6 In patients with HF, no angina, and unknown CAD status who are at low risk for CAD noninvasive evaluation should be considered and coronary**

angiography may be considered. (Strength of Evidence = C)

13.7 Any of the following imaging tests should be considered to identify inducible ischemia or viable myocardium:

- Exercise or pharmacologic stress myocardial perfusion imaging
- Exercise or pharmacologic stress echocardiography
- Cardiac magnetic resonance imaging (MRI)
- Positron emission tomography scanning (PET) (Strength of Evidence = B)

Background

Evaluation for CAD in Patients with HF. Multiple studies have evaluated the impact of nuclear viability imaging on intermediate to long-term survival in patients with CAD and LV systolic dysfunction.^{76–89} However, none of these studies met the criteria published by the Evidence-Based Medicine Group on therapeutic interventions and prognosis.^{90,91} In these studies treatment allocation to revascularization or medical therapy was often made by physicians who requested and, in some cases, interpreted the viability tests. Viability was never blindly evaluated without impacting subsequent treatment allocation. A randomized clinical trial is necessary to properly evaluate the utility of viability imaging to determine treatment allocation between revascularization and medical therapy and subsequent prognosis.

Recommendation

13.8 It is recommended that the following risk factors be managed according to the indicated guidelines:

- Lipids (see National Cholesterol Education Program Adult Treatment Panel III) (<http://www.nhlbi.nih.gov/guidelines/cholesterol>)^{92,93}
- Smoking (see Section 3)
- Physical activity (see Section 6)
- Weight (see Section 3)
- Blood pressure (see Section 14 and JNC VII Guidelines) (<http://www.nhlbi.nih.gov/guidelines/hypertension>)⁹⁴

Background

For more information on lipid management, smoking cessation, weight management, and physical activity see Sections 3 and 6 in this guideline.

Therapy for Patients With HF and CAD

Recommendation

- 13.9 Antiplatelet therapy is recommended to reduce vascular events in patients with HF and CAD unless contraindicated. (aspirin, Strength of Evidence = A; clopidogrel, Strength of Evidence = B)**

Background

Aspirin. In patients with stable CAD, unstable angina or acute MI, treatment with aspirin 81–325 mg daily provides a 25% to 30% reduction in all-cause mortality, MI, and stroke.⁹⁵ In a retrospective review of the Studies of Left Ventricular Dysfunction (SOLVD) trial, antiplatelet use (mostly aspirin) was associated with 28% reduction in all-cause mortality and HF death or hospitalizations.⁹⁶ Despite conflicting data about aspirin reducing the benefits of ACE inhibitors,^{96,97} all patients with CAD and HF should receive 75–325 mg aspirin daily in absence of contraindications. Recent studies suggest that higher doses may be associated with increases in drug interactions and bleeding, so 75 to 81 mg is recommended. (See Section 7, Recommendations 7.33–7.38.)

In the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial, patients with symptomatic heart failure, LV dysfunction, and no atrial fibrillation, were randomized to aspirin 162 mg/day, clopidogrel 75 mg/day, or open-label warfarin to achieve an international normalized ratio (INR) of 2.5 to 3.⁹⁸ The primary endpoint of the study was the composite of all-cause mortality, non-fatal MI, and non-fatal stroke. The majority of patients had an ischemic etiology of heart failure, although the study population was not limited to patients with CAD. There were no statistically significant differences in the primary endpoint for warfarin versus aspirin, for clopidogrel versus aspirin, or for warfarin versus clopidogrel.⁹⁸

Clopidogrel. In patients admitted for unstable angina/non ST-elevation MI (STEMI), treatment with clopidogrel in addition to aspirin was associated with an 18% reduction in the incidence of HF.⁹⁹ All patients admitted with ACS and non-ST elevation treated medically without stenting should be given clopidogrel 300 mg, followed by 75 mg daily for at least 1 month and ideally for up to 1 year in addition to aspirin.¹⁰⁰ Patients with STEMI should be treated with clopidogrel or prasugrel, according to the 2009 STEMI/percutaneous coronary intervention (PCI) Focused Update Recommendations.¹⁰¹

Warfarin. Although warfarin is an acceptable alternative to antiplatelet agents when necessary for CAD, its effectiveness may be due to the large number of HF patients with atrial fibrillation. It was not superior to aspirin in the WATCH trial.¹⁰⁰ See Section 7 for more information.

Recommendation

13.10 ACE inhibitors are recommended in all patients with either reduced or preserved LVEF after an MI. (Strength of Evidence = A)

Background

In a study of patients with stable CAD and few other risk factors, treatment with the ACE inhibitor perindopril was

associated with a 20% reduction in cardiovascular mortality, new MI, or sudden death.¹⁰² HF hospitalizations were reduced by 39%. In a population at high risk for CAD, but without overt HF, treatment with ramipril was associated with a 22% reduction in cardiovascular mortality, new MI, or stroke.¹⁰³ The incidence of HF was reduced by 23% and HF hospitalizations by 12%. ACE inhibitors should be routine therapy in patients at high-risk for CAD and in patients with established CAD.

Four major trials proved the favorable effects of prophylactic ACE inhibition in reducing HF, HF hospitalizations and mortality after an acute MI.^{104–107} In patients with a recent MI, with or without symptoms of HF, ACE inhibitors should be started early (within 24 hours) and continued indefinitely.¹⁰⁸

The first trial to show a survival benefit for ACE inhibitors in patients with chronic HF, of whom the majority had underlying CAD, was the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial. This trial was conducted in New York Heart Association (NYHA) class IV patients who were randomized to receive enalapril or placebo.²⁰ At the end of the study (20 months), patients treated with enalapril had a significant 27% reduction in total mortality, the primary end point. It appeared that enalapril had no effect on sudden death, but decreased mortality from progressive HF by 50%. After CONSENSUS, the SOLVD Treatment trial examined the effect of enalapril in patients with mild to moderate HF.¹⁰⁹ Enalapril decreased all-cause mortality by 16%, mortality caused by progressive HF by 22%, and the combined point of death or hospitalizations for worsening HF by 26% compared with placebo. In the SOLVD Prevention trial of patients with asymptomatic LV dysfunction, enalapril reduced the total number of deaths and cases of HF by 29%.²² Taken together, these studies provide for the recommendation that ACE inhibitors should be administered to all patients with asymptomatic LV systolic dysfunction or with signs and symptoms of HF.

Recommendations

13.11 Beta blockers are recommended for the management of all patients with reduced LVEF or post-MI (Strength of Evidence = B)

13.12 It is recommended that ACE-inhibitor and beta blocker therapy be initiated early (<48 hours) during hospitalization in hemodynamically stable post-MI patients with reduced LVEF or HF (Strength of Evidence = A)

Background

In patients with stable CAD, treatment with beta blockers is associated with a reduction in the number and duration of ischemic episodes, mortality or hospitalization.¹¹⁰ Retrospective analyses of two large beta blocker trials demonstrated reduced mortality with beta blockers, especially in

high-risk subsets.^{111,112} In the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial of 1959 patients with a proven acute MI and LVEF $\leq 40\%$, with or without symptoms of HF, carvedilol reduced the number of deaths by 23%, a benefit attained on top of treatment with ACE inhibitors, antiplatelet agents, and statins.⁵⁸ There was no difference between carvedilol and placebo in the number of patients meeting the primary endpoint of all-cause mortality or hospital admissions. In all patients with a history of MI, regardless of LVEF, beta blockers should be used acutely and continued indefinitely. In studies of patients with chronic HF, more than 65% of whom had underlying CAD, use of bisoprolol, carvedilol, or metoprolol succinate was associated with a uniform 34% reduction in all-cause mortality and 20% to 25% reduction in hospitalizations.^{16,113,114} In the Australia-New Zealand study of patients with ischemic cardiomyopathy and LVEF $< 45\%$, carvedilol reduced the risk of all-cause mortality or any hospitalization by 26%.¹¹⁵ Based on the results from available studies, beta blockers should be routinely prescribed to all patients with asymptomatic LV dysfunction and stable HF caused by LV systolic dysfunction.

Recommendation

13.13 Nitrate preparations should be considered in patients with HF when additional medication is needed for relief of anginal symptoms. (Strength of Evidence = B)

Background

In patients with stable CAD, nitrates improve exercise tolerance and time to onset of angina.¹¹⁶ An overview of small studies of nitrates in acute MI from the pre-thrombolytic era suggested a 35% reduction in mortality rates,¹¹⁷ although 2 trials formally tested this hypothesis in patients with suspected acute MI and failed to confirm this magnitude of benefit.^{118,119} There was no difference in survival in the 14% of patients with HF at baseline in the Fourth International Study of Infarct Survival (ISIS-4) trial, nor was there a difference in the new cases of HF in Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico (GISSI-3) study. Nitrates did not decrease the rate of re-infarction, but they decreased the rate of post-infarct angina in GISSI-3, in which nitrates in combination with lisinopril also decreased all-cause mortality by 17%. The difference was mainly attributable to the lower numbers of deaths and cases with LVEF $\leq 35\%$. Nitrates are well tolerated in acute MI and appear safe to use early in acute MI for symptomatic relief of angina or for reduced LVEF. Patients with CAD, HF, and anginal symptoms should be considered for therapy with nitrates in addition to beta blockers.

Recommendation

13.14 Calcium channel blockers may be considered in patients with HF who have angina despite the

optimal use of beta blockers and nitrates. Amlodipine and felodipine are the preferred calcium channel blockers in patients with angina and decreased systolic function. Based on available data, first generation calcium channel blockers (i.e. diltiazem, verapamil) should be avoided in patients with CAD, HF, and LVEF < 40 , unless necessary for heart rate control or other indications. (Strength of Evidence = C)

Background

Although all calcium antagonists have anti-ischemic properties, a meta-analysis of 16 trials that used immediate-release and short-acting nifedipine in patients with MI and unstable angina reported a dose-related excess mortality.¹²⁰ First-generation calcium antagonists, such as diltiazem and nifedipine, were found to exacerbate HF or increase mortality in patients after MI with pulmonary congestion or an LVEF $< 40\%$.¹²¹ An alternative consideration regarding the worsening of heart failure in early calcium channel blocker trials is reflex neurohormonal activation. It is possible that the earlier-generation calcium channel blockers would not have proved deleterious if they had been investigated on a background of ACE inhibitors and beta blockers. Amlodipine does not have clinically significant negative inotropic effects, and it has not been associated with the deleterious effects seen with earlier drugs in this class. Although one trial of amlodipine in patients with advanced HF produced a 9% reduction in the combined risk of fatal and nonfatal events and decreased the risk of all-cause mortality by 16%, these reductions were not statistically significant overall or for patients with ischemic heart disease.¹⁵ Amlodipine had no effect on the frequency of worsening HF associated with hospitalizations or the rate of MI, but the amlodipine group had a higher incidence of pulmonary and leg edema, as well as renal failure.¹⁵ Based on available data, first-generation calcium channel blockers should not be used in patients with CAD, HF and LVEF $< 40\%$. Amlodipine or felodipine could be used in these patients to manage angina or hypertension if beta blockers or nitrates are not tolerated.^{122,123}

Recommendations

13.15 It is recommended that coronary revascularization be performed in patients with HF and suitable coronary anatomy for relief of refractory angina or ACS. (Strength of Evidence = B)

13.16 Coronary revascularization with coronary artery bypass surgery or percutaneous coronary interventions (PCI) as appropriate should be considered in patients with HF and suitable coronary anatomy who have demonstrable evidence of myocardial viability in areas of significant obstructive coronary disease or the presence of inducible ischemia. (Strength of Evidence = C)

Background

Despite advances in medical therapy, patients with severe CAD and symptomatic reduced LVEF have poor outcomes when treated medically.^{14,16,17,20,30–36,58,59,102–109,113,114,124,125} Although revascularization for patients with CAD and HF seems the logical approach because restoration of blood flow may improve LV function and possibly survival,^{73,74} there are no randomized controlled trials comparing revascularization with medical therapy to improve outcomes in patients with HF, demonstrated myocardial viability, and an LVEF <35%. Revascularization of viable myocardial segments could provide benefit by improving contractility or by preventing additional myocardial remodeling.^{126,127} Myocardial viability has been assessed by PET, single-photon emission computed tomography (SPECT), dobutamine echocardiography, and MRI. Registry and cohort studies provide some data for this group of patients. These data suggest that exercise capacity and HF symptoms improve after revascularization and the improvement is related to the amount of abnormal but viable myocardium.^{126,128,129} Improvement in LVEF also is directly related to the amount of viable myocardium.^{128,130} Finally, in non-randomized, observational studies, revascularization has been associated with improved survival compared to medical therapy in patients with myocardial viability and an LVEF <35%.^{69,128}

The results of medical therapy for both HF and CAD have improved markedly. It is impossible to estimate whether revascularization in well-treated HF patients will improve survival or clinical course. As a result, prospective randomized trials of revascularization in addition to optimal medical therapy compared to optimal medical therapy alone in patients with CAD, depressed LV systolic function, and symptoms of HF are necessary. At present, two such studies are underway.^{50,51} In the interim, when PCI or surgical intervention is considered, the decision should be made in the context of the patient's functional status, prognosis, and surgical risk. See Section 10, recommendation 10.1 for further information.

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