Chronic Heart Failure in the United States
A Manifestation of Coronary Artery Disease

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Despite significant progress in the prevention and treatment of cardiovascular disease in the United States in the past two decades,[1] national statistics indicate that the incidence and prevalence of chronic heart failure have been increasing steadily in recent years,[2] especially in the elderly.[3] It is estimated that ≈4 to ≈5 million individuals living in the United States have chronic heart failure, with 400 000 new cases occurring each year.[4–6] Chronic heart failure results in almost 1 million hospitalizations each year[7] and is the most common hospital discharge diagnosis in patients above the age of 65 years.[8] The evaluation and care of patients with heart failure, not taking into account lost wages and productivity, cost our society in excess of $11 billion each year.[7–9]

In the past two decades, considerable attention has been placed on left ventricular (LV) dysfunction, loading conditions, and neuroendocrine activation as pathophysiological mechanisms for progression of heart failure,[10,11] and pharmacological therapy has been targeted against these mechanisms.[12–14] However, the fundamental shift in the etiology of heart failure often is underemphasized. The most common cause of chronic heart failure is no longer hypertension or valvular heart disease, as it was in past decades, but rather coronary artery disease (CAD).[15] In 13 multicenter heart failure treatment trials reported in the *New England Journal of Medicine* over the past 10 years,[16–28] involving >20 000 patients, CAD was the underlying etiology of heart failure in nearly 70% of the patients (Fig 1). This probably is an underestimation of the true prevalence of CAD among unselected heart failure patients because the possibility of CAD was not explored in a systematic manner in many trials and because in most trials, patients with a recent myocardial infarction, angina, or objective evidence of active ischemia were excluded. The importance of CAD is underscored by the observations that the prognosis of patients with heart failure and CAD is considerably worse than that of patients without coronary disease and is related to the angiographic severity of coronary disease.[29,30]

Heart Failure Treatment Trials

In the past two decades, numerous clinical trials have examined the effects of a variety of drugs on survival in patients with chronic systolic heart failure. Most of these trials, in terms of patient enrollment and data analysis, were performed as if heart failure were a homogeneous disease process, regardless of whether patients had underlying CAD. The main enrollment criterion in most clinical trials was, and continues to be, symptoms of congestion and/or evidence of LV systolic dysfunction. The diagnosis of CAD, the leading cause of heart failure in these studies, has often been based on subjective evidence such as history of angina pectoris and has not always required definitive criteria, such as objective evidence of previous myocardial infarction, significant obstructive CAD on coronary arteriography, or evidence of inducible myocardial ischemia. Thus, the true prevalence of CAD, and its contribution to LV dysfunction, may be higher than actually reported in many of the trials. It follows that the efficacy or lack of efficacy of the heart failure agents under investigation in these trials is difficult to determine in patients with CAD. In addition, the possibility of progression of CAD during the study period has not been assessed, nor has the possibility that mortality in many patients with heart failure may be related more to the progression of CAD than to the progression of LV dysfunction per se.

The only intervention that has proved unequivocally to be beneficial in improving symptoms and prolonging life in patients with LV dysfunction is treatment with ACE inhibitors.[17,19,20,22,31–33] It is possible that angiotensin II type I receptor antagonists have similar beneficial effects.[34] There has been a trend for improved survival in patients receiving hydralazine/isosorbide dinitrate combination without a clear benefit in preventing worsening heart failure.[16] Established therapies such as diuretics and/or digoxin that reduce the need for hospitalization do not appear to improve survival.[28,35] Some calcium channel–blocking agents have a neutral effect on mortality in patients with systolic dysfunction.[27,36] However, other calcium channel blockers actually increase the risk of dying or worsening heart failure,[37,38] as do other classes of drugs, such as phosphodiesterase inhibitors;[21] β-adrenergic agonists,[39] including ibopamine[40]; systemic vasodilators such as prostaglandins[41] and flosequinan[42]; antiarrhythmic agents[43,44]; and possibly newer inotropic agents, such as pimobendan[45] and vesnarinone (Letter to the Vesnarinone Evaluation of Survival Trial (VEST) Investigators and Study Coordinators, July 29, 1996). These findings were unexpected because many of these agents improve rest and exercise hemodynamics both acutely and chronically,[46,47] reduce short-term symptoms,[18,48,49] and even increase exercise tolerance.[18,48,50,51] The dissociation between improvement in hemodynamic profile and symptoms on the one hand and survival on the other suggests that controlling abnormal hemodynamic conditions does not in and of itself prevent the progression of heart failure or death. Moreover, β-adrenergic–blocking agents that initially worsen left ventricular function[52] may improve symptoms and/or survival[26] and

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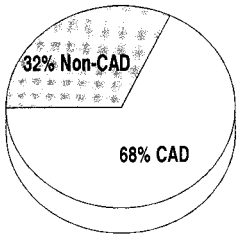

	year	n	CAD
VHEFT-1	1986	642	282
CONSENSUS	1987	253	146
Milrinone	1989	230	115
PROMISE	1991	1088	590
SOLVD-T	1991	2569	1828
VHEFT-2	1991	804	427
SOLVD-P	1992	4228	3518
RADIANCE	1993	178	107
Vesnarinone	1993	477	249
CHF-STAT	1995	674	481
Carvedilol	1996	1094	521
PRAISE	1996	1153	732
DIG	1997	6800	4793
Total		20190	13789

Figure 1. Prevalence of CAD in 13 randomized, multicenter heart failure trials reported in the *New England Journal of Medicine* since 1986.[16–28] Underlying CAD was present in 68% of patients.

decrease the need for cardiac transplantation.[53] These paradoxical responses have been attributed to the fact that many inotropic and vasodilating agents enhance cardiac performance at the expense of further neuroendocrine activation that ultimately contributes to progressive LV dysfunction, whereas ACE inhibitors and β-blockers exert their beneficial effects through a reduction in neuroendocrine activity.[11,13,14]

Although activation of neurohormonal systems accounts for the negative results with some drugs, this concept fails to explain the negative results of other drugs that do not appear to worsen the neurohormonal profile, such as vesnarinone[54] and ibopamine.[55] In addition, HMG-CoA reductase inhibitors, which have no hemodynamic effect, may prevent the development of heart failure and possibly improve survival in patients with LV dysfunction.[56,57]

It is conceivable that in many patients with heart failure and underlying CAD, the effects of medical therapy can be explained, at least in part, by the influence of these agents on the pathophysiology and progression of CAD. Lipid-lowering therapy may stabilize lipid-rich plaques, preventing plaque rupture that may result in myocardial infarction or sudden death[58]; such therapy may also improve endothelial function and reduce ischemia.[59,60] In addition, in patients with CAD and LV dysfunction, ACE inhibitors and β-blockers may have specific beneficial actions beyond those achieved in patients without CAD, related to their effects on the vasculature and ischemic myocardium. ACE inhibitors may improve endothelial dysfunction[61] and inhibit proliferation of vascular smooth muscle cells,[62] and β-adrenergic–blocking agents not only reduce myocardial ischemia but also may reduce the risk of plaque rupture.[63] On the other hand, chronic adrenergic stimulation directly with a positive inotropic agent or indirectly via a systemic vasodilator may be detrimental in ischemic and/or hibernating myocardium with limited flow reserve and may result in myocyte necrosis or ischemia if adequate perfusion is not first restored.[64–66] Chronic adrenergic stimulation may also enhance the risk of plaque rupture.[63,67,68]

Clinical Trials of Coronary Artery Disease and Heart Failure

Several of the more recent clinical trials of drug therapy for heart failure attempted to assess the effects of therapy in patients with CAD separately from the effects in primary cardiomyopathy, although most failed to use strict criteria to establish the presence and severity of CAD.[25–27] Drugs that may improve survival in primary cardiomyopathy, such as amiodarone[25] and amlodipine,[27] appear to have no survival benefit in patients with CAD. Only ACE inhibitors,[31,32,69,70] and possibly carvedilol,[26] have been shown to enhance survival in patients with CAD and LV dysfunction as effectively as in patients with primary cardiomyopathy.

CAD and Heart Failure

Heart failure in the setting of CAD is itself a heterogeneous condition, with several possible factors contributing to LV dysfunction and heart failure symptoms and with several factors that might influence the effect of drug therapy; these include, most importantly, the sequelae of acute myocardial infarction, with loss of functioning myocytes, development of myocardial fibrosis, and subsequent LV remodeling. The resulting chamber dilatation and neurohormonal activation lead to progressive dysfunction of the remaining viable myocardium. This is a well-recognized clinical process that can be ameliorated after acute myocardial infarction by the use of ACE inhibitor therapy[31–33,69,70] and possibly β-adrenergic–blocking agents[71] and myocardial revascularization.[72–74] In addition, the majority of patients surviving a myocardial infarction have significant atherosclerotic disease in coronary arteries other than the infarct-related artery. Thus, superimposed on the ventricle with irreversibly damaged myocardium, there often is a considerable degree of jeopardized myocardium served by stenotic coronary arteries either within the infarct zone or remote from the infarcted tissue. In addition to the possibility that ischemia and recurrent myocardial infarction may produce future deterioration of LV function, endothelial dysfunction in atherosclerotic coronary arteries may contribute importantly to progression of LV dysfunction.

Myocardial Ischemia, Stunning, and Hibernation

Episodes of reversible myocardial ischemia caused by a critical coronary artery stenosis, superimposed on a left ventricle with depressed systolic function under basal conditions, may produce transient worsening of ventricular function that will exacerbate exertional dyspnea and fatigue. In many patients, these heart failure symptoms induced by exercise represent an anginal equivalent that may occur in the absence of chest pain. In addition, episodes of transient but severe ischemia may cause prolonged systolic dysfunction that persists after the ischemic insult itself has resolved, a process termed exercise-induced "stunning,"[75–77] that is similar to the more severe and protracted myocardial stunning that results from coronary occlusion and reperfusion.[78,79] Thus, recurrent episodes of myocardial ischemia, producing repetitive myocardial stunning, may contribute to the overall magnitude of LV dysfunction and heart failure symptoms.

Another mechanism for systolic dysfunction, with additive effects on left ventricular performance, is myocardial "hibernation."[80–82] Hibernation develops as an adaptive response to a sustained reduction in myocardial blood flow, in which the level of tissue perfusion is sufficient to maintain cellular

viability but insufficient for normal contractile function. The reduction in contractility permits the myocardium to reduce its oxygen demands in the setting of reduced oxygen supply, and the metabolic activity of the myocytes is channeled into processes essential for cell viability, such as maintenance of transmembrane electrochemical gradients, rather than contraction. However, this protective mechanism may result in a considerable mass of myocardium that is rendered hypocontractile and contributes to overall LV dysfunction.[83,84] There also is recent evidence that 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 ultimately occur if blood flow is not increased.[85,86]

Thus, in addition to irreversibly damaged, fibrotic myocardium, it is likely that ischemia, stunning, and hibernation occur together in various degrees in many patients with LV dysfunction and contribute to the manifestations and progression of heart failure. These patients represent an important subset of heart failure patients in whom myocardial revascularization offers the potential for reduced symptoms and enhanced prognosis. Although the role of myocardial revascularization is uncertain in patients with LV dysfunction whose sole symptom is dyspnea or fatigue,[87–89] it is noteworthy that numerous nonrandomized series consistently demonstrate significant improvement in survival in patients treated with revascularization rather than medical therapy,[87–92] especially if angina or objective evidence of reversible ischemia is present.[87,88,91] Hence, noninvasive investigation of the presence and extent of myocardial ischemia is an important component of the diagnostic evaluation of all patients with heart failure and known CAD.[5,6] In addition, the clinical relevance of detecting patients with viable, hibernating myocardium has become apparent in recent years because many such patients have the potential for substantial improvement in regional and global LV function after myocardial revascularization.[80,93–95] The limited data to date, from small nonrandomized series, suggest that this improvement in ventricular function after revascularization translates into an improvement in heart failure symptoms and enhanced survival.[96–99]

Endothelial Dysfunction

Recent data suggest that the coronary endothelium plays an important role not only in the control of blood flow and vascular patency but also in the physiological modulation of myocardial structure and function.[100–104] Hence, endothelial dysfunction, an inherent component of the pathophysiology of atherosclerotic CAD,[105–109] may have a direct effect on ventricular function. The endothelial production and release of nitric oxide and prostacyclin, two potent vasodilating substances, are diminished in patients with CAD, and the production and release of endothelin and angiotensin II, potent vasoconstrictor substances, are increased.[110,111,111a] In addition to their well known vascular effects, endothelin and angiotensin II have been implicated in potentiating myocyte hypertrophy, interstitial fibrosis, and induction of a fetal pattern of gene expression of contractile proteins,[111] raising the distinct possibility that this pathway may contribute directly to the pathophysiology of heart failure.[100,104,110,112,113]

Disordered endothelial function in patients with CAD stimulates vasoconstriction, smooth muscle migration and proliferation, increased lipid deposition in the vessel wall, and possibly coronary thrombosis,[108,109,111,114] thereby promoting myocardial ischemia, which may further contribute directly or indirectly to progression of LV dysfunction. There also is evidence that release of endothelin is increased in failing myocardium[104] and that angiotensin II promotes the release of endothelin and the excessive degradation of nitric oxide.[111] These observations suggest an interplay between the failing myocardium and the coronary endothelium that potentiates the progression of both CAD and LV dysfunction.

The recent Trial on Reversing Endothelial Dysfunction (TREND) demonstrated that the ACE inhibitor quinapril improved endothelial function in patients with mild nonobstructive CAD who were normotensive and without severe dyslipidemia.[61] The improvement in endothelial function in the TREND study is of similar magnitude to that reported in studies of HMG-CoA reductase inhibitors in hypercholesterolemic patients.[115–118] Although patients in the TREND study did not have LV dysfunction, these observations identify a potential vascular mechanism of action by which ACE inhibitors may be beneficial in heart failure. This vascular hypothesis is supported by the Scandinavian Simvastatin Survival Study (4S) and Cholesterol and Recurrent Events (CARE) trials, in which simvastatin reduced development of heart failure[57] and pravastatin reduced reinfarction and mortality in patients with asymptomatic LV dysfunction.[56]

CAD and Left Ventricular Diastolic Dysfunction

It has become apparent during the past decade that the percentage of patients with heart failure and preserved LV systolic function is increasing and may account for 30% to 40% of patients admitted with a diagnosis of chronic heart failure.[119] This is an intriguing and challenging group of patients in whom diagnostic and therapeutic measures to date have been disappointing. As systolic function is preserved, it is assumed that the majority of these patients have heart failure signs and symptoms on the basis of abnormal LV diastolic function. Diastolic dysfunction of the left ventricle increases with age,[120] and an increase in the prevalence of diastolic rather than systolic dysfunction in patients above the age of 65 may have contributed to the increasing number of hospital admissions for heart failure in the past two decades.[121,122]

There are a number of factors that predispose to abnormalities in diastolic behavior of the left ventricle and lead to impaired forward output, elevated filling pressures, or both, despite normal systolic function.[123,124] Principal among these is myocardial ischemia. Transient, reversible episodes of ischemia can impair LV relaxation and elevate LV filling pressures to the point of causing pulmonary congestion.[125] CAD accounts for more than half of the patients in many series of heart failure and normal systolic function and for two thirds or more of patients in some series.[119]

The prognosis of patients with heart failure and preserved systolic function has been the subject of controversy. Although the prognosis of such patients is better than that of patients with chronic systolic dysfunction in some series,[126] in others

the overall mortality rates of patients with depressed systolic function and normal systolic function are similar.[119,127,128] The disparate estimates of prognosis among series of heart failure and normal systolic function may relate to differences in the prevalence and severity of CAD. In the Coronary Artery Surgery Study (CASS) Registry, the 6-year survival rate of patients with normal ejection fractions and heart failure symptoms was 92% in patients with no CAD, 83% in patients with one- or two-vessel CAD, and 68% in patients with three-vessel disease.[129]

One final implication of the high prevalence of CAD in patients with heart failure and normal systolic function is the need for reappraisal of whether systolic function is truly normal at the time when heart failure symptoms are present. In the majority of studies of this syndrome, the timing of the evaluation demonstrating normal systolic function relative to the episode of heart failure itself is not reported, and in others, the evaluation was performed days to weeks after the episode.[119] Transient ischemia causes regional systolic dysfunction that in many patients is severe and sufficiently extensive to cause transient but profound reduction in global LV function. These pathophysiological changes in regional and global systolic function are well established and form the basis for exercise echocardiography and exercise radionuclide ventriculography as diagnostic tests for CAD. It is probable that many patients with apparently normal systolic function and heart failure caused by CAD do not have isolated diastolic dysfunction but instead have systolic dysfunction at the time when myocardial ischemia precipitates their heart failure symptoms.

Progression of CAD and Progression of Heart Failure

It is well established that chronic LV dysfunction of any cause sets in progress a series of events leading to LV dilatation and remodeling with further deterioration of LV function and that this process is mediated in large part by activation of neurohormonal systems. In addition to the deleterious effects of vasoconstriction, tachycardia, and increased contractility, chronic neurohormonal activation affects myocyte growth, interstitial connective tissue, myocardial energy utilization, and receptor regulation, and chronic neurohormonal stimulation may have also direct toxic effects on the heart. These interrelated effects and their consequences have been discussed in depth by other investigators.[11,13,14,130–132] Reduction of these long-term harmful mechanisms with ACE inhibitors and β-blockers clearly contributes to the beneficial effects of these drugs on mortality and heart failure progression, and these beneficial effects are observed in patients with primary cardiomyopathies as well as those with CAD. However, in patients with CAD, there may be additional mechanisms of action by which these agents provide benefit.

In the SOLVD and SAVE trials, the ACE inhibitors enalapril and captopril not only reduced overall mortality in patients with CAD but also appeared to reduce the rate of nonfatal myocardial infarction and unstable angina.[31,69,133] The magnitude of reduction in myocardial infarction has ranged from 10% to 25%.[134] The 25% decrease in myocardial infarction with captopril in the SAVE study occurred despite the selection criteria that excluded patients with residual ischemia who were considered at greatest risk of reinfarction. The reduction in acute ischemic events would not be anticipated purely on the basis of hemodynamic or neurohormonal effects of ACE inhibitors. Moreover, the reduction in unstable angina and myocardial infarction with enalapril in the SOLVD trial was not apparent until $\geq$6 months after randomization.[69] This suggests that the beneficial effects of enalapril on ischemic events were unlikely to be due to an immediate effect related to a primary or secondary reduction in LV afterload. This delay in reduction of ischemic events resembles the pattern observed in trials with cholesterol-lowering agents.[57,135,136]

These recent trials suggest that the progression of LV dysfunction, worsening of heart failure, and death in many patients with CAD and LV dysfunction may be related to progression of CAD as well as to neurohormonal mechanisms that exacerbate muscle dysfunction. This progression does not require a discrete coronary event such as a myocardial infarction with diagnostic elevation of serum enzymes. Ischemia and/or hibernation may lead to myocyte apoptosis,[86,137–140a] which may result in progression of LV dysfunction without a clear ischemic event. As noted previously, endothelial dysfunction may also lead to progressive myocardial dysfunction. When observed in this light, it is apparent that progression of CAD, with further endothelial dysfunction, myocardial ischemia, and/or plaque instability, may contribute importantly to the progression of heart failure in large numbers of patients (Fig 2). Thus, measures that lower the risk of subsequent acute ischemic events, decrease ischemia, and/or improve endothelial function, coupled with ACE inhibitors, may be the most effective means to improve outcome in patients with heart failure and CAD. It follows that the major future breakthroughs in the management of heart failure may stem from the application of aggressive secondary prevention measures and from future research advances in vascular biology in addition to measures designed to reduce neurohormonal activation or prevent deterioration of LV function per se.

Implications for Secondary Prevention

Most physicians have developed strategies for the management of patients with known CAD and LV dysfunction. In addition

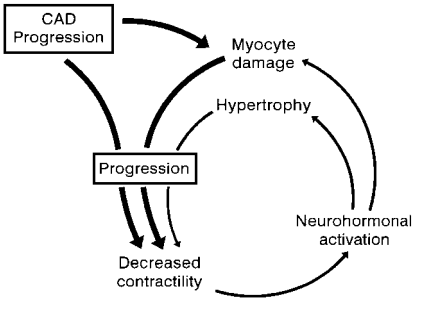

Figure 2. Contribution of coronary artery disease (CAD) to progression of left ventricular dysfunction. Decreased contractility stimulates activation of neurohormonal systems leading to chamber remodeling, hypertrophy and myocyte damage, which contribute importantly to progressive decreases in cardiac function. Coronary artery disease may set this process in motion, with myocardial infarction as the initiating event. In addition, progression of coronary artery disease, with further myocardial infarction, myocardial ischemia, and endothelial dysfunction, may accelerate this process, leading to progressive cardiac dysfunction and neurohormonal activation.

to determining the severity of ventricular dysfunction, it is standard practice to identify candidates for revascularization based on evidence of multivessel CAD and/or the extent and severity of myocardial ischemia; to treat with ACE inhibitors, β-blockers, and aspirin; and to pursue risk factor modification in an aggressive manner according to accepted guidelines.[141] However, when the clinical presentation is that of a patient with heart failure symptoms alone, underlying coronary disease often is not considered,[5] and the management strategy shifts to a treatment paradigm involving drug therapy with ACE inhibitors, digoxin, and diuretics; the diagnostic, therapeutic, and preventive options for ischemic heart disease are often neither considered nor used.

Recognition that CAD is the leading cause of heart failure in the United States is of critical importance if the mortality from this condition is to be reduced. Many patients may be candidates for myocardial revascularization to improve LV function, prevent further LV remodeling, and/or improve survival. The importance of recognizing CAD does not end with the consideration for revascularization, however, because this will be available for only a subset of patients. Alterations in medical therapy are applicable to all patients. It is likely that secondary prevention interventions designed to reduce progression of CAD,[141] such as aggressive lowering of serum cholesterol resulting in plaque stabilization and improved endothelial function, cessation of smoking, and therapy with aspirin or other antiplatelet agents, may have as an important an impact on survival in patients with CAD and heart failure as agents designed to prevent worsening of LV dysfunction or restore cardiovascular neurohormonal mechanisms. Although this specific hypothesis must be tested in future prospective clinical trials, there are already strong pieces of evidence that support this hypothesis. The recent CARE trial[56] of lipid lowering in patients with mild hypercholesterolemia after myocardial infarction excluded patients with overt heart failure symptoms or severe LV dysfunction. However, lowering of serum cholesterol with pravastatin decreased cardiac events in the subset of patients with reduced systolic function (ejection fraction, 25% to 40%).[56] Similarly, in the 4S trial, simvastatin decreased the rate of development of heart failure symptoms after myocardial infarction.[57] Finally, the use of antiplatelet agents and anticoagulants was associated with an improvement in survival in patients with symptomatic or asymptomatic LV dysfunction in the SOLVD study.[142] These emerging data suggest that secondary prevention measures, in addition to treatment with ACE inhibitors and β-blockers, may ultimately prove to be among the most effective interventions for treating heart failure. Until definitive data are available, it is critical that physicians caring for heart failure patients consider the diagnosis of CAD in patients of appropriate age and gender, especially if coronary risk factors are present, and to make diagnostic, therapeutic, and risk reduction decisions accordingly.

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KEY WORDS: coronary disease ■ endothelium ■ heart failure ■ ischemia

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