Navigating the Crossroads of Coronary Artery Disease and Heart Failure

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Chronic heart failure (HF) affects 5 million patients in the United States and is responsible for ≈1 million hospitalizations and 300 000 deaths annually.[1] The total annual costs associated with this disorder have been estimated to exceed $40 billion.[1,2] Chronic HF is the only category of cardiovascular diseases for which the prevalence, incidence, hospitalization rate, total burden of mortality, and costs have increased in the past 25 years.[1,2] Fueling this epidemic is the increasing number of elderly patients developing impaired left ventricular (LV) function as a manifestation of chronic coronary artery disease (CAD).[1,2] With the aging of the population and decline in mortality of other forms of cardiovascular diseases, it is likely that the incidence of HF and its impact on public health will continue to increase.[1–3]

CAD and HF: Epidemiology and Prognosis

In the past 3 decades, considerable attention has focused on LV dysfunction, loading conditions, neuroendocrine activation, and ventricular remodeling as the principal pathophysiological mechanisms underlying HF progression.[4] There has been a fundamental shift, however, in the origin of HF that often is underemphasized.[3–5] The Framingham Heart Study suggests that the most common cause of HF is no longer hypertension or valvular heart disease, as it was in previous decades, but rather CAD.[4]

This shift may be related to improved survival of patients after acute myocardial infarction (MI). Over the past 40 years in the United States, the odds of previous MI as a cause for HF increased by 26% per decade in men and 48% per decade in women. In contrast, there has been a 13% decrease per decade for hypertension as a cause of HF in men and a 25% decrease in women, as well as a decrease in valvular disease by 24% per decade in men and 17% in women.

In the 24 multicenter HF treatment trials reported in the *New England Journal of Medicine* over the past 20 years involving >43 000 patients, CAD was the underlying cause of HF in nearly 65% of patients (Table).[6–30] This percentage is probably an underestimate of the true prevalence of CAD among unselected HF patients, when one considers that origin was not explored in a systemic manner in many trials. Another reason for probable underestimation is that most of these trials excluded patients with a recent MI, angina, or objective evidence of active ischemia. However, as recently suggested in a population-based incidence cohort study from Olmsted County, although HF remains frequent after MI, its incidence is declining over time.[31]

In HF patients, the presence of CAD has been shown to be independently associated with a worsened long-term outcome in numerous studies.[32] In the Studies of Left Ventricular Dysfunction Treatment (SOLVD-T) trial, patients who developed MI had an ≈2-fold-higher rate of hospitalization for chronic HF and a 4-fold-higher mortality rate compared with patients who did not develop MI.[9] Similarly, in the Survival and Ventricular Enlargement (SAVE) trial, evidence of a previous MI before the enrollment identified patients with a significantly greater risk of cardiovascular death and/or LV enlargement.[33] Recent data from the Global Registry of Acute Coronary Events (GRACE) study demonstrated that patients with CAD who present with HF on admission are at increased risk of both in-hospital and long-term mortality.[34] The Duke database[35] showed that CAD significantly and independently increases mortality rates in HF patients. During a mean follow-up period of 4.4 years, patients with CAD had a much worse prognosis than patients with idiopathic cardiomyopathy after adjustment for baseline variables.[36] In a more recent study, Felker et al[37] assessed angiographic data in 1921 patients with HF and demonstrated that the extent of CAD provides additional important prognostic information in patients with HF caused by LV systolic dysfunction. Retrospective analyses of the SOLVD Prevention (SOLVD-P) and SOLVD-T trials indicated that the adverse prognosis of ischemic cardiomyopathy could be limited to HF patients with diabetes mellitus.[38,39] Recent 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 patients with CAD.[40]

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Prevalence of CAD in Multicenter HF Trials Published in the *New England Journal of Medicine* From 1986 to 2005

Trial	Year	All Patients	CAD Patients
V-HeFT I	1986	642	282
CONSENSUS	1987	253	146
Milrinone	1989	230	115
PROMISE	1991	1088	590
SOLVD-T	1991	2569	1828
V-HeFT II	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
VEST	1998	3833	2230
RALES	1999	1663	907
DIAMOND	1999	1518	1017
COPERNICUS	2001	2289	1534
BEST	2001	2708	1587
Val-HeFT	2001	5010	2866
MIRACLE	2002	453	244
COMPANION	2004	1520	842
A-HeFT	2004	1050	242
SCD-HeFT	2005	2521	1310
CARE-HF	2005	813	309
Total	19 y	43 568	26 877(62%)

V-HeFT indicates Vasodilator–Heart Failure Trial; Consensus, Cooperative North Scandinavian Enalapril Survival Study; Milrinone, Milrinone Trial; PROMISE, Prospective Randomized Milrinone Survival Evaluation; RADIANCE, Randomized Assessment of the effect of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme; Vesnarinone, Vesnarinone Trial; CHF-STAT, Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy; Carvedilol, Carvedilol Trial; DIG, Digitalis Investigation Group trial; VEST, Vesnarinone Trial; RALES, Randomized Aldactone (spironolactone) Evaluation Study for Congestive Heart Failure; DIAMOND, Distensibility Improvement With ALT-711 Remodeling in Diastolic Heart Failure; COPERNICUS, Carvedilol (Coreg) Prospective Randomized Cumulative Survival; BEST, Beta-Blocker Evaluation of Survival Trial; Val-HeFT, Valsartan Heart Failure Trial; MIRACLE, Multicenter InSync Randomized Clinical Evaluation (North America); COMPANION, Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure; A-HeFT, African-American Heart Failure Trial; and CARE-HF, Cardiac Resynchronization–Heart Failure study.

Among patients with HF or evidence of LV dysfunction after acute MI enrolled in the Optimal Trial in Myocardial Infarction With the Angiotensin II Antagonist Losartan (OPTIMAAL), recurrent MI found at autopsy was common and often had not been clinically detected.[41] These findings emphasize the importance of accurate differentiation between ischemic and nonischemic causes of HF and the potential role of revascularization in patients with ischemic cardiomyopathy.

Impact of CAD on the Pathophysiology of HF

Reduced Systolic Function

Traditionally, the progression of HF has been attributed to LV remodeling and thought to be unrelated to the causes of LV dysfunction (eg, hypertension, diabetes, CAD) (Figure 1A).[39,41,42] Accordingly, therapies have been directed at neurohormonal modulation and the prevention of LV remodeling. However, the available data suggest that the factors (eg, hypertension, diabetes, CAD) that initiate LV dysfunction also contribute to its progression (Figure 1B).

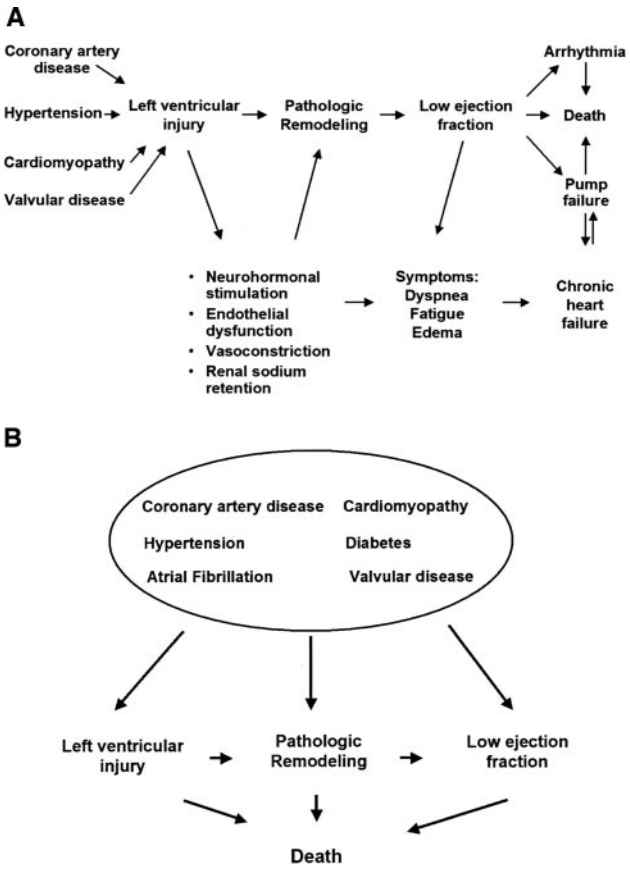

Figure 1. The progression of HF has been attributed mostly to LV remodeling and thought to be unrelated to the causes of LV dysfunction (A). Currently available data suggest that the factors that initiate LV dysfunction also contribute to its progression (B).

In particular, the presence and extent of CAD may accelerate the progression of HF, explaining the higher mortality among ischemic compared with nonischemic HF patients.[36,37] After acute MI, loss of functioning myocytes occurs, with ensuing myocardial fibrosis and LV dilatation. The resulting neurohormonal activation and LV remodeling lead to progressive deterioration of the remaining viable myocardium.[43] This well-recognized but incompletely understood process can be ameliorated by the use of angiotensin-converting enzyme (ACE) inhibitors,[44] β-blockers,[45] and aldosterone antagonists[46] in the post-MI period. Although revascularization with thrombolytic agents or percutaneous coronary intervention has been shown to significantly decrease mortality in post-MI patients, it is important to note that LV remodeling may occur despite sustained patency of the infarct-related artery.[47]

Ischemia can produce a rapid and massive increase in the concentration of endogenous catecholamines such as norepinephrine, epinephrine, endothelin, and dopamine in the myocardial interstitial fluid with a deleterious effect on cardiac

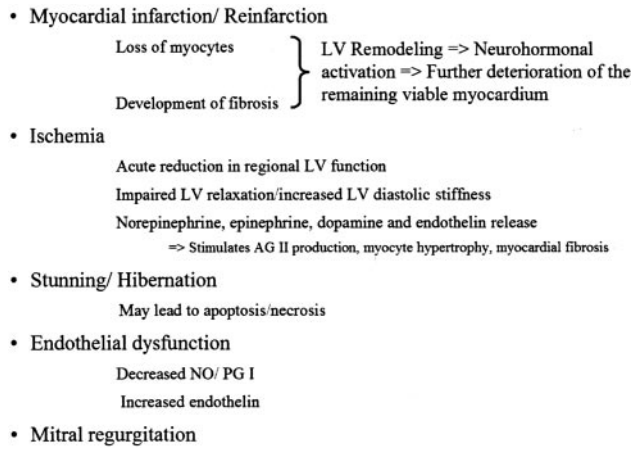

Figure 2. Role of CAD in the pathophysiology of HF with reduced systolic function.

myocytes,[48] culminating in myocardial apoptosis, fibrosis, and susceptibility to ventricular arrhythmias. Thus, ischemia may contribute to the progression of LV systolic dysfunction without an obvious clinical ischemic event.[49]

Chronic ischemia may result in hibernation/stunning with further decline in LV function.[50] In a meta-analysis of 24 studies, patients with evidence of viability who underwent revascularization had an 80% reduction in mortality compared with those who were treated medically.[51] In contrast, patients without viability had a similar mortality with the 2 therapeutic strategies.[51] Unfortunately, most studies examining treatment of hibernating myocardium have been biased by variability in the methods used to identify and define hibernation and by the influence that the results of these investigations have had on patient treatment strategies. So far, no prospective trials have evaluated the role of noninvasive testing in determining the most suitable candidates for revascularization in patients with severe LV systolic dysfunction.[52]

Another complication of CAD is ischemic mitral regurgitation (MR) caused by changes in ventricular structure and function.[53] Higher incidence and greater severity of ischemic MR are associated with the chronic phase of inferior rather than anterior MI because of more severe geometric changes in the mitral valve apparatus.[54] Notably, even mild MR is an independent predictor of long-term mortality after MI[53,55] (Figure 2). All these processes can be "punctuated" at any time by a sudden coronary occlusion leading to sudden death.

HF With Preserved Systolic Function

During the past 20 years, the percentage of patients with HF and preserved systolic function has been increasing and may account for 30% to 40% of patients admitted with a diagnosis of HF.[56] This is an intriguing, challenging group of patients in whom, until now, diagnostic and therapeutic measures have been disappointing. When systolic function is preserved, it is assumed that most of these patients have HF signs and symptoms on the basis of abnormal LV diastolic function.[57]

A variety of factors contribute to abnormalities in LV diastolic function and lead to elevated filling pressures, impaired forward output, or both, despite normal systolic function.[58] Myocardial ischemia, together with gender, age, and hypertension, is one of the leading factors. Pulmonary congestion can be caused by transient "reversible" episodes of ischemia, which impair LV relaxation and elevate LV filling pressures.[59] Vasan et al[56] showed that CAD accounts for one half to two thirds of patients with HF and normal systolic function; the prevalence of CAD in patients with HF and preserved systolic function varies from 14% to 100%.

There has been much controversy about the prognosis of HF patients with preserved systolic function. The prognosis for such patients has been reported to be better than for patients with chronic systolic dysfunction in some series,[60] whereas others reported a similar overall mortality rate for hospitalized patients with depressed systolic function compared with those with normal systolic function.[56] Tsutsui et al[61] showed that the prognosis of CAD patients with HF and preserved systolic function was similar to that of patients with systolic dysfunction. The disparity in prognosis among clinical studies of HF and normal systolic function may correlate to the differences in prevalence and severity of CAD.[62]

Ischemic Events in Patients With HF

Reinfarction

Most patients surviving an acute MI also have CAD present in other than the infarct-related artery[63] and are therefore at high risk of reinfarction. In clinical trials, the rate of infarction or reinfarction is relatively low using clinical criteria, with a fatal MI rate of 3%.[64] However, 56% of patients with HF and CAD who die suddenly have autopsy evidence of an acute ischemic event (eg, coronary clot, recent infarct); this percentage does not take into account the number of patients with plaque rupture.[65] It is possible that even a small MI in patients with severe LV dysfunction may present as sudden death rather than a nonfatal MI. Death may therefore be attributed to a lethal arrhythmia rather than MI, and this may account for the apparently low observed rate of MI in patients with HF and CAD.

Sudden Death

LV dysfunction is a major independent predictor of total cardiovascular mortality and sudden cardiac death in patients with both CAD and primary cardiomyopathy origins. In several clinical HF trials, sudden death ranged between 20% and 60%, depending on the severity of HF.[66] In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), 64% of patients with New York Heart Association class II HF had sudden and unexpected death compared with 59% of patients with class III and 33% of patients with class IV HF.[67] Several factors have been implicated in the high rate of sudden death in patients with HF with or without CAD. These include subendocardial ischemia, ventricular hypertrophy, stretching of myocytes, high sympathetic tone, abnormal baroreceptor responsiveness that lowers the threshold for a malignant arrhythmia, potassium and magnesium depletion, and coronary artery emboli from atrial or LV thrombi.[66] It is likely, however, that CAD contributes directly to sudden death.[66] Some patients with CAD and HF have dilated hearts, with large regions of myocardial scarring.[68] In addition, CAD, with its major consequences (ie, plaque rupture, thrombosis, and infarct),

constitutes the most common structural basis of sudden cardiac death.[69]

Holmes et al[70] compared the impact of medical therapy alone with that of coronary artery bypass grafting (CABG) on the incidence of sudden cardiac death among 13 476 patients enrolled in the Coronary Artery Surgery Study (CASS) registry who had significant CAD, operable vessels, and no significant valvular disease. Notably, in a high-risk patient subset with 3-vessel disease and history of HF, 91% of surgically revascularized patients had not suffered sudden death compared with 69% of medically treated patients.[70] Uretsky et al[65] reported the relative importance of an acute coronary event as a trigger for sudden death in patients with HF in the Assessment of Treatment With Lisinopril and Survival (ATLAS) trial, including 3164 patients with moderate to severe HF caused by systolic dysfunction. There were 1383 deaths (43.7%) during the follow-up period of 3 to 5 years. An autopsy was performed in only 188 patients, and the postmortem data were available in only 171 patients (12.4% of the total). Patients who died were older and had both more symptoms and a higher prevalence of CAD than the surviving patients. Acute coronary findings were observed in 54% of the patients with significant CAD who died suddenly.[65] The ATLAS study was the first to demonstrate that recent coronary events are frequently unrecognized in patients with moderate to advanced symptoms of HF who die suddenly, especially in patients with CAD. Other studies have documented a high percent of plaque rupture or coronary thrombosis in CAD patients without HF who died suddenly.[69]

A recent analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT) assessed the incidence and timing of sudden death in post-MI patients with LV systolic dysfunction. Of 14 609 patients, 1067 (7%) had an event a median of 180 days after MI: 903 died suddenly and 164 were resuscitated after cardiac arrest.[40] The event risk was highest (1.4%) in the first 30 days after MI and decreased to 0.14% per month after 2 years. The rate of sudden death according to LV ejection fraction (LVEF) showed that the increased early incidence was most apparent among patients with low LVEF.[40]

CAD and HF: Management

The most important evaluation for risk of adverse events, in addition to extent and severity of CAD and LV function, is the assessment of the presence and severity of MR, loading conditions, and myocardial ischemia, stunning, or hibernation. All of these parameters can be evaluated with a combination of invasive and noninvasive testing such as dobutamine echocardiography, nuclear myocardial perfusion imaging, positron-emission tomography, cardiac magnetic resonance, and cardiac catheterization.

Patients with LV dysfunction and CAD may be classified into 2 distinct groups for whom the workup and management may be very different: (1) patients presenting with chronic HF who have CAD and/or a remote history of MI and (2) patients presenting with an acute MI that results in LV dysfunction with or without signs of HF.

The management of these patients should be aimed at preventing progression of CAD, LV remodeling, sudden death, and reinfarction and should be tailored for the individual patient. There are 3 important management considerations in patients with CAD and HF: pharmacological treatment, electrophysiological devices, and revascularization strategies. Although there are a multitude of options for the management of these patients, a comprehensive strategy that includes surgery often is not used. Better care of the post-MI CAD patient with LV dysfunction and HF requires a management strategy that draws on all evidence-based therapies.

Pharmacological Treatment

In recent years, large-scale clinical trials have documented the benefits of pharmacological therapies in the post-MI period aimed at limiting LV remodeling, recurrent ischemia, and progressive CAD.

ACE Inhibitors

Treatment with ACE inhibitors is beneficial for all patients with moderate to severe HF and impaired LV systolic function but may have additional benefits on ischemic events in those patients with underlying CAD.[71,72]

Several studies have shown that ACE inhibition reduces the incidence of HF and mortality after an acute MI, possibly by preventing LV remodeling, reinfarction, and sudden death.[73] In the SAVE trial, which enrolled patients with LVEF $<$40% and no symptoms and signs of HF, captopril-treated patients had a significantly reduced incidence of mortality and experienced a 22% reduction in the risk of hospitalization for HF and 25% of recurrent MI.[33] The Acute Infarction Ramipril Efficacy (AIRE) trial differed from SAVE in that the patients had overt signs of HF after an acute MI and a measure of LVEF was not obtained in all patients.[74] Patients treated with ramipril had a 27% reduction in mortality. In addition, analysis of prespecified secondary outcomes revealed a risk reduction of 19% for the combined outcome of death, severe/resistant HF, MI, or stroke.[74] In the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) trial, a 34% reduction in mortality and incidence of severe HF was observed at 6 weeks, and a 29% reduction in mortality was observed after 1 year in the patients treated with zofenopril.[75] Finally, the Trandolapril Cardiac Evaluation (TRACE) study evaluated the effect of trandolapril on patients with an LVEF $\leq$35% after MI.[76] During the study period, 34.7% of patients in the trandolapril group died compared with 42.3% in the placebo group (P=0.001). The risk of progression to advanced HF was decreased by 29% with trandolapril, whereas the drug had no effect on the risk of recurrent MI.[76]

Therefore, these data suggest that the use of ACE inhibitors after an acute MI may reduce the incidence of mortality and prevent LV remodeling and reinfarction.

Angiotensin Receptor Blockers

The OPTIMAAL trial was designed to prove that losartan would be superior or not inferior to captopril in decreasing all-cause mortality in patients with MI complicated by LV systolic dysfunction.[77] After a median follow-up of 2.7 years, a trend toward lower all-cause mortality was observed in the captopril group as compared with losartan, and fewer captopril-treated patients experienced sudden death or a resuscitated cardiac arrest.[77] VALIANT was an even larger

study that simultaneously addressed whether valsartan can be considered superior to or as good as captopril in high-risk post-MI patients with clinical or radiological evidence of HF, an LVEF ≤40%, or both.[78] Although this randomized trial showed that valsartan was not more effective than captopril in reducing all-cause mortality, cardiovascular mortality, or new MI, it did provide solid evidence that in high-risk post MI patients who cannot tolerate ACE inhibitors, angiotensin receptor blockers are as beneficial as ACE inhibitors in decreasing the rate of mortality and recurrent infarction.[78]

More information on the value of angiotensin receptor blockers in HF has been obtained from the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trials, which compared candesartan and placebo in symptomatic HF patients with or without preserved LV systolic function.[79] In a prespecified analysis of the combined CHARM-Alternative and CHARM-Added trials[80] of patients with an LVEF ≤40%, candesartan reduced all-cause mortality, cardiovascular death, and HF hospitalizations.

β-Adrenergic–Blocking Agents

Randomized clinical trials have shown conclusively the life-saving effects of β-blocker therapy in patients with mild to severe chronic HF.[81,82] In these trials, >60% of HF patients had CAD. Similar beneficial effects of β-blockers were noted in patients with ischemic or nonischemic origin.[81,82] In patients with stable CAD, treatment with β-blockers reduces the number and duration of ischemic episodes, mortality, or hospitalization.[83] In a meta-analysis of multiple trials of β-blockers and HF, the impact on total mortality was as much on sudden death as on MI.[84]

The Beta-Blocker Heart Attack Trial (BHAT) excluded patients with HF at randomization.[85] However, a subset analysis revealed that propranolol reduced total mortality to a similar extent in patients with a history of HF before randomization compared with patients without a history of HF (27% versus 25%) but reduced the incidence of sudden death to a greater extent in those with a history of HF (47% compared with 13%).[85] The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial enrolled 1959 patients with a proven acute MI and on LVEF ≤40% with or without symptoms of HF.[86] Carvedilol reduced all-cause mortality by 23% and reinfarction by 40%, a benefit achieved in patients already receiving ACE inhibitors, antiplatelet agents, and statins.[86]

The Australia-New Zealand Heart Failure study enrolled patients with ischemic cardiomyopathy and an LVEF ≤40%.[87] After 6 months of carvedilol treatment, LVEF increased by 5.2% in the carvedilol group compared with placebo ($P<0.0001$). The addition of carvedilol to standard therapy reduced the combined risk of all-cause mortality and all hospitalizations by 26%.[87]

In a prespecified subgroup analysis of MERIT-HF, patients with HF, an LVEF ≤40%, and a history of an acute MI (n=1926) were randomized to metoprolol succinate controlled release/extended release versus placebo. After treatment for 1 year, metoprolol succinate reduced total mortality by 40% and cardiac death/nonfatal acute MI by 45%.[88]

Aldosterone Antagonists

The effects of aldosterone antagonists in patients after MI complicated by HF with reduced LVEF have been tested in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS).[89] The trial randomized patients hospitalized with MI, after a mean of 7 days, to eplerenone or placebo in addition to standard medical therapy. Eplerenone (mean dose, 43 mg daily) produced significant reductions in all-cause mortality (by 15%) and in the combined end point of cardiovascular death or hospitalization for cardiovascular causes (by 13%).[89]

Recently, it has been demonstrated that eplerenone, in addition to conventional therapy, significantly reduces all-cause mortality and the risk of sudden cardiac death at 30 days in patients with an LVEF ≤40% and signs of HF.[90]

Lipid-Lowering Agents

Statins are of proven benefit in CAD patients.[91–93] Because many patients with HF have CAD, it is logical to expect that HF patients may also benefit from statins.

Of the 3 large statin secondary prevention studies,[91–93] only the Cholesterol and Reduction of Events (CARE)[92] study documented LVEF and prospectively randomized patients with LVEF <40%. Although patients with HF and patients with an LVEF <25% could not be randomized, the study randomized 706 patients with an LVEF between 25% and 40%. Pravastatin was equally effective in reducing coronary events in these patients as in patients with an LVEF >40%.[92] A post hoc analysis of the Scandinavian Simvastatin Survival Study (4S) showed a significant 20% reduction in the development of subsequent HF in patients randomized to simvastatin without HF at the time of entry into the study.[91] In the group of patients who developed HF, mortality was reduced by 19% in the simvastatin group.[91] A retrospective analysis of the Evaluation of Losartan in the Elderly Trial II (ELITE II) also showed a significant 40% reduction in all-cause mortality in patients with HF and CAD who were using statins.[94]

Two large trials, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Heart Failure (GISSI-HF) and the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA), are prospectively testing the hypothesis that statins benefit HF patients.

Antiplatelet and Anticoagulant Agents

Although these agents are indicated in post-MI patients, few data have tested their role in HF patients with concomitant CAD.

In the combined SOLVD trials, patients taking antiplatelet agents (primarily aspirin) had an 18% lower risk of death and a 19% lower risk of death or hospital admission for HF.[95] Although antiplatelet therapy was associated with an 18% lower hazard of death in the entire study population, this reduction was due entirely to a 32% lower hazard in the placebo arm, whereas antiplatelet therapy had no impact on mortality risk in those randomized to enalapril.[95] However, a meta-analysis of 4 major trials enrolling >20 000 patients showed that ACE inhibitors reduced all-cause mortality in HF patients, regardless of aspirin use.[96] Thus, at present, the use of aspirin is recommended in patients with CAD and HF.

In a retrospective analysis of SOLVD trials, patients receiving anticoagulation experienced a 24% lower risk of death and an 18% lower risk of death or hospital admission for HF.[97] The recently completed Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) study evaluated the role of aspirin, clopidogrel, and warfarin in HF patients.[98] Although the study was underpowered, no differences in mortality were observed between the 3 regimens. However, patients with HF and CAD were not analyzed separately, and patients receiving aspirin appeared to have a higher rate of HF hospitalizations.

The Clopidogrel and Metoprolol in Myocardial Infarction Trial—Second Chinese Cardiac Study (COMMIT-CCS2) is the largest trial to investigate the effect of clopidogrel; 45 852 patients admitted to 1250 hospitals within 24 hours of suspected acute MI onset were allocated to clopidogrel or placebo in addition to aspirin.[99] Patients categorized in Killip class II and III were included. Therapy with clopidogrel produced a significant 9% reduction in death, reinfarction, or stroke, as well as a significant 7% reduction in death from any cause.[99]

Calcium Channel Blockers

Although all calcium antagonists have antiischemic 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.[100] The first-generation calcium antagonists such as diltiazem and nifedipine exacerbate HF and/or increase mortality in patients after MI with pulmonary congestion or an LVEF <40%.[101] Amlodipine has fewer negative inotropic effects and does not have the deleterious effects seen with earlier-generation drugs. The long-term effect of amlodipine on morbidity and mortality in patients with advanced HF was examined in the first Prospective Randomized Amlodipine Survival Evaluation (PRAISE I) trial.[17] The trial tested the hypothesis that amlodipine is particularly beneficial in patients with CAD and HF. Contrary to the expectation, amlodipine had no effect in CAD patients on the frequency of worsening HF associated with hospitalizations or the rate of MI.[17]

Thus, given the available data, there is no basis for using first-generation calcium channel blockers in patients with CAD, HF, and LVEF <40%. Because it does not appear to have such harmful effects, amlodipine could be used in these patients to manage angina if β-blockers or nitrates are not tolerated or if angina is persistent despite therapy with β-blockers and nitrates.

Electrophysiological Devices

Implantable Cardioverter-Defibrillators

Nonsustained ventricular tachycardia in patients with previous MI and LV dysfunction is associated with a 30% 2-year mortality rate. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) I demonstrated the survival benefits of a prophylactic therapy with an implantable cardioverter-defibrillator (ICD) compared with conventional medical therapy in patients with prior MI, an LVEF ≤35%, and inducible, nonsuppressible ventricular tachyarrhythmia during electrophysiological study (EPS).[102] MADIT II tested the effect of an ICD on survival of post-MI patients with systolic dysfunction without performing an EPS. The study randomized 1232 patients with a prior MI and LVEF ≤30% to receive an ICD or conventional medical therapy.[103] During an average follow-up of 20 months, the mortality rates were significantly lower in the ICD group, regardless of age, sex, LVEF, New York Heart Association class, and QRS interval.[103] The utility of early ICD implantation in patients with recent MI was investigated in the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT).[104] Patients with LVEF ≤35% and decreased heart rate variability were enrolled between 6 and 40 days after MI. There was no improvement in overall mortality by early ICD implantation because the large reduction in arrhythmic death was offset by an increase in nonarrhythmic events.[104] Consistently, other studies[40,105] highlighted the importance of the timing device implantation after an MI and suggested that arrhythmic deaths probably are due to progressive remodeling and ventricular instability.

From these studies, considerable evidence indicates that prophylactic implantation of an ICD in patients with a prior MI and advanced LV dysfunction improves survival. Thus, ICD therapy is recommended in such patients who are beyond the acute phase of MI.[2]

Empirical antiarrhythmic therapy has not reduced mortality among patients with CAD and asymptomatic ventricular arrhythmias. Previous studies have suggested that antiarrhythmic therapy guided by EPS might reduce the risk of sudden death. The Multicenter Unsustained Tachycardia Trial (MUSTT), a randomized controlled trial, tested the hypothesis that EPS-guided antiarrhythmic therapy reduces the risk of sudden death among patients with CAD, LVEF ≤40%, and asymptomatic, nonsustained ventricular tachycardia.[106] Patients with sustained ventricular tachyarrhythmias induced by programmed stimulation were randomized to receive either antiarrhythmic therapy, including drugs and ICD, or no antiarrhythmic therapy. After 5 years, the primary end point of cardiac arrest or death from arrhythmia was 25% among those receiving EPS-guided therapy and 32% among the patients assigned to no antiarrhythmic therapy, representing a reduction in risk of 27%.[106] This trial suggested that neither the frequency nor rate of nonsustained ventricular tachycardia had any impact on prognosis, inducing subsequent studies to enroll simply patients with LV dysfunction. In the recent Sudden Cardiac Death–Heart Failure Trial (SCD-HeFT), HF patients with a median LVEF of 25% were randomized to conventional therapy for HF plus placebo, conventional therapy plus amiodarone, or conventional therapy plus a conservatively programmed ICD.[29] Amiodarone had no favorable effect on survival, whereas single-lead, shock-only ICD therapy reduced overall mortality by 23%, resulting in an absolute reduction of 7.2 percentage points at 5 years. The benefit of ICD implantation on mortality was similar in patients with ischemic and nonischemic HF.[29]

Although the implantation of an ICD has been shown to be beneficial in post-MI patients with LV dysfunction, the impact on the incidence of new HF needs to be determined.

Cardiac Resynchronization Therapy

Electric conduction defects in HF are associated with a decrease in contractile performance, development or prolongation of MR, and wasted cardiac work as a result of development of mechanical asynchrony.[107] These electrical alterations translate into abnormal myocardial metabolism and redirection of regional coronary perfusion[108] that could be deleterious in patients with underling CAD. Thus, restoring electrical synchrony could potentially be a major goal in the treatment of HF patients with CAD.

To date, >4000 HF patients with LV systolic dysfunction and ventricular dyssynchrony have been evaluated in randomized controlled trials of optimal medical therapy alone versus optimal medical therapy plus cardiac resynchronization therapy with or without an ICD.[26,27,30] These devices have reduced the risk of death and hospitalization with similar efficacy among patients with or without CAD. Therefore, cardiac resynchronization therapy should be considered in addition to an ICD in suitable patients with HF, reduced LVEF, and evidence of LV dyssynchrony. However, the effects of cardiac resynchronization therapy in patients with reduced LV systolic function after a recent MI are unknown. Ongoing studies and newer methods for identifying indexes of dyssynchrony that indicate responsiveness to therapy beyond simple QRS prolongation may help guide therapy choice in the future.

Surgical Approaches to CAD and HF

Surgical treatments for HF caused by CAD include revascularization, mitral valve repair, and surgical ventricular restoration (SVR).

Surgical Revascularization

More than 3 decades after the introduction of CABG, uncertainty still exists about the role and benefits of revascularization in patients with CAD and HF. The evidence for the impact of CABG in CAD patients with HF is limited almost entirely to observational cohorts. Large clinical trials of CABG versus medical therapy typically excluded patients with significant LV dysfunction.[109] Only CASS enrolled patients with impaired LV function (LVEF, 35% to 50%),[110] although the degree of dysfunction was only in the mild to moderate range. In this trial, CABG improved survival over medical therapy in a small subset of patients with 3-vessel disease at 7 years of follow-up.[110] In the large CASS registry of ≈20 000 patients,[111] there were only 231 patients with LV dysfunction (LVEF <50%) who had CABG, in whom survival at 5 years was 32%, and 420 in the medically treated group, who had a 5-year survival of 46%. CABG was associated with improved survival only in the subset of patients with an LVEF <26%. The registry patients receiving CABG had more angina and ischemia in the setting of less LV dysfunction and fewer symptoms of HF compared with the medical group.[111] Notably, a retrospective analysis of this registry suggested that the benefit of CABG was partially confined to patients who had angina as the predominant symptom as opposed to patients with symptoms caused primarily by HF.[112]

Interpreting the results from observational, retrospective comparisons and case series is challenging because of potential biases in selecting a specific therapy for a given group of patients.[109] In these retrospective case reviews,[109,113] usually representing the experience of a single center, the CABG patients usually had more severe angina, coronary anatomy favorable for grafting, and fewer HF symptoms, and there was little statistical correction for baseline differences between CABG and medical cohorts.[50] Moreover, patients in the CASS trial and registry, along with virtually all retrospective cohorts, received medical therapy for either CAD or HF that preceded recent clinical trials and is not up to the standards of current guidelines and recommendations. These data also preceded trials demonstrating the benefits of ICDs and cardiac resynchronization therapy. Finally, there was limited use of internal mammary grafts in patients undergoing CABG in these reports.

Surgical Treatment of MR

MR is a common feature of HF arising from ischemic LV systolic dysfunction.[55,114] Patients with HF who have MR have more severe LV dysfunction compared with patients without associated MR,[55,114] and the available data indicate that MR also confers a greater mortality risk.[115] Recent data indicate that therapies that induce beneficial reverse remodeling and improve LV function, including β-blockers[116] and cardiac resynchronization therapy,[117] also improve MR. It is unclear whether MR is merely a marker for more advanced LV dysfunction or whether MR contributes to further LV dysfunction or remodeling.[55,114] It is also uncertain whether MR itself should be a target for therapy. To date, no prospective trial has addressed the impact of therapies intended to reduce or eliminate MR on symptoms, LV function, quality of life, and clinical end points.

Surgical treatment for ischemic MR usually combines mitral valvuloplasty or replacement with CABG because outcome is improved compared with CABG alone.[118] In such patients, mortality is generally better after surgical repair than after replacement of mitral valve.[119] With either technique, the surgical risk for ischemic mitral valve dysfunction is greater than that for nonischemic mitral valve disease.[120] Data developed at a few surgical referral centers have now demonstrated that mitral valve repair using a reduction annuloplasty procedure can be accomplished at low perioperative risk, even in patients with severe LV systolic dysfunction, and may result in substantial reverse remodeling, improved hemodynamics, and a reduction in symptoms.[121,122] A recent retrospective analysis of 682 consecutive patients with significant MR and LV systolic dysfunction (60% with ischemic origin), however, has not demonstrated a convincing survival benefit of this approach over the long term compared with medical therapy.[123] These surgical series have been carried out in the absence of comparative data in matched patients undergoing medical treatment, and no prospective randomized trials have addressed the possible benefit of surgical valve repair in patients with ischemic or nonischemic HF.

Surgical Ventricular Restoration

Recognition of the importance of LV remodeling and the negative impact of akinetic or dyskinetic myocardium on LV

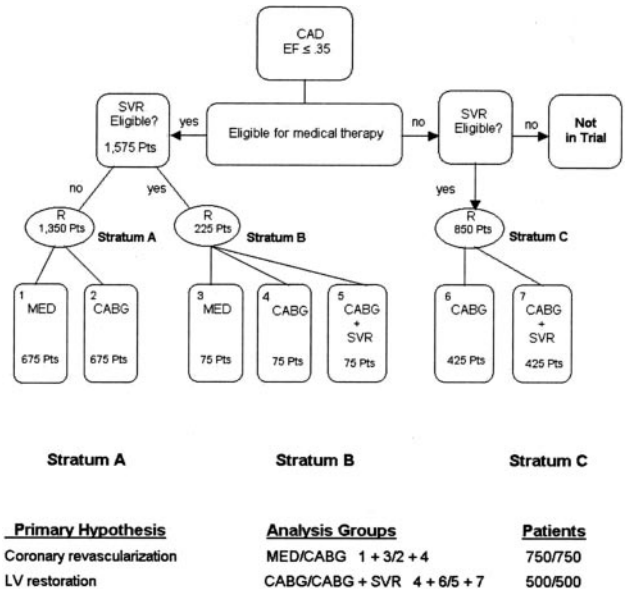

Figure 3. Study protocol of the STICH trial.

size and performance has led to surgical intervention specifically targeting those factors. The objective of restoring a more normal size and shape to the left ventricle is the same as that of aneurysmectomy operations but differs in that it is applied to akinetic myocardium as opposed to only dyskinetic, fibrotic myocardial segments. Additionally, the SVR procedure incorporates technical refinements to result in a more normal size and shape of the LV cavity than was the common result of early LV aneurysm operations.[124] Although SVR is physiologically appealing because it relieves extensive LV dilatation and may help to improve LV wall stress, it must be evaluated prospectively in an unbiased, large sample in which proper estimates can be made of an additive benefit or unnecessary harm. Therefore, a prospective randomized trial is needed now to validate the safety and efficacy of the SVR procedure, in addition to CABG and optimal medical therapy for HF and CAD, before it is accepted as a validated therapeutic option.

The Surgical Treatment for Ischemic Heart Failure Trial

The Surgical Treatment for Ischemic Heart Failure (STICH) trial is a multicenter, international, randomized, National Heart, Lung, and Blood Institute–funded trial designed to address many of the key concepts and issues discussed above. It is based on 2 specific primary hypotheses in patients with LV dysfunction who have CAD amenable to surgical revascularization: (1) CABG with optimal medical therapy improves long-term survival compared with medical therapy alone, and (2) in patients with anterior LV dysfunction, CABG, and SVR to achieve more normal LV size and geometry improves survival free of subsequent hospitalization compared to CABG alone (Figure 3). The eligibility criteria include New York Heart Association HF class II to IV, LVEF ≤35%, coronary anatomy suitable for revascularization, and willingness to consent to the entire study protocol, including SVR, if eligible.

The primary end point for the first hypothesis (CABG versus medical therapy) is all-cause mortality at 3 years. The primary end point for the second hypothesis (SVR plus CABG versus CABG) is death and HF hospitalization. Additional end points include morbidity, quality of life, cost and resource use, myocardial viability, and LV function.

The STICH trial also will address several specific mechanistic questions that promise to contribute new knowledge that will help the physician understand observed therapeutic outcomes. The key questions focus on the role of a management strategy that uses physiological myocardial viability testing to define subgroups of patients who will or will not have a survival advantage from myocardial revascularization. This includes the impact of underperfused but viable myocardium assessed by nuclear myocardial perfusion imaging on cardiac function evaluated by cardiac magnetic resonance and echocardiography 3 months after treatment. Answers to these questions promise to greatly refine the initial evaluation strategy of patients with HF.

Conclusions

CAD represents the most common underlying disease in HF patients in industrialized countries. Recent clinical trials have conclusively shown the life-saving effects of pharmacological and device therapy in HF patients with CAD.

Along the broad spectrum of severity of ischemic HF, specific clinical information such as severe angina or left main coronary artery stenosis may clearly indicate the need for surgical therapy. However, most patients with HF and CAD continue to fall into a gray zone without clear evidence of the need for surgical therapy over optimal modern medical therapy. For these patients, evidence supporting choice between therapies was never strong and has only been confused by recent studies showing improved outcomes with both therapies. No randomized trial has ever directly compared the long-term benefits of surgical and medical treatment of patients with ischemic HF. The general medical community often overestimates surgical risks and manages the high-risk patients medically without investigating the presence and extent of CAD. Furthermore, myocardial viability studies are widely used in a clinical setting to identify HF patients who would or would not benefit from myocardial revascularization. Although this is appealing intuitively, it lacks solid evidence from prospective randomized trials. Conceptually, it could be argued that the advances in treatment of both CAD and HF, the increasing HF population, the lack of data from randomized trials on the benefits and risks of surgical revascularization over aggressive medical alone, and the uncertainties about the role of noninvasive testing of ischemia and viability all create a reasonable base for equipoise and the strong rationale for rigorous investigation of anticipated benefit between modern medical and surgical therapy, as well as the benefit of advanced diagnostic testing, applied to a broad population of such patients. The STICH trial represents this critical step in the evaluation of our current diagnostic and therapeutic practices.

Disclosures

None.

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