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From the Cattedra di Cardiologia, Università di Brescia, Brescia, Italy; and the Division of Cardiology, Northwestern University Medical School, Chicago, Illinois, USA.

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Prevention and Management of Chronic Heart Failure in Patients at Risk

Livio Dei Cas, MD, Marco Metra, MD, Savina Nodari, MD, Alessandra Dei Cas, MD, and Mihai Gheorghiade, MD

The prevalence and incidence of chronic heart failure (HF) have now reached epidemic proportions. However, the issue of the prevention of HF has been raised only recently. New US guidelines have introduced a new classification system that includes 4 categories: patients at risk, patients with asymptomatic left ventricular dysfunction, patients with symptomatic HF, and those with refractory HF. Because coronary artery disease is the major cause of HF, its risk factors are also those of HF. Hypertension favors the development of HF through accelerated atherosclerosis and increased left ventricular wall stress and hypertrophy. Left ventricular hypertrophy is also a powerful risk factor for HF, independent of blood pressure. Angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and diuretics are the antihypertensive agents that have been associated with favorable effects in patients with overt HF. Therefore, they may be preferred in the prevention of this syndrome. Diabetes is the most frequent noncardiac comorbidity of HF and is independently associated with an increased risk. Normalization of glycemic and glycosylated hemoglobin levels is a desirable goal of treatment. However, no direct evidence exists in the prevention of HF. A greater control of the other risk factors (eg, hypertension, hyperlipidemia) is, on the other hand, particularly important. β-Blockers and ACE inhibitors have both been shown to have favorable effects across all spectrums of severity of HF. The ACE inhibitor ramipril has also been shown to prevent the development of HF in patients at risk without left ventricular dysfunction. The role of antithrombotic agents, warfarin, and statins is clear in the prevention of the coronary artery disease. However, it has not been adequately assessed in patients with HF and awaits the results of ongoing trials.

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diomyopathy is the second most frequent cause of HF, followed by valve disease, alcoholic cardiomypathy, cor pulmonale, and hypertrophic and restrictive cardiomyopathy. Because hypertension and coronary artery disease and, above all, their combination are the main causes of most cases of HF, it is clear that primary prevention of HF actually corresponds to the prevention of coronary artery disease and its risk factors.

HYPERTENSION

Hypertension is a major risk factor for HF. In the 20-year follow-up study of the 5,143 subjects included in the original Framingham Heart Study and the Framingham Offspring Study,10 hypertension antedated the development of HF in 91% of the subjects. After adjustment for age and other risk factors, the hazard for developing HF was about 2-fold in men and 3-fold in women with hypertension compared with those without hypertension: hypertension accounted for only 39% of cases of HF in men compared with 59% in women. Similarly, in the National Health and Nutrition Examination Survey Epidemiologic Study (NHANES), hypertension alone was associated with a 1.40 relative risk (RR) of HF (95% confidence interval [CI], 1.24 to 1.59; p <0.001) at multivariate analysis with a population-attributable risk of 10.1%. Antecedent hypertension increases the risk of HF also in patients who have developed a myocardial infarction. In a study involving 1,093 consecutive patients with acute myocardial infarction, those with antecedent hypertension had greater neurohumoral activation, left ventricular dilatation, and incidence of symptomatic HF and HF hospitalizations.11 Most studies primarily evaluated diastolic blood pressure; however, more recent data from the Systolic Hypertension in the Elderly Program (SHEP) have shown the importance of the pulse pressure in elderly patients with isolated systolic hypertension. In this study, a 10-mm Hg increment in the pulse pressure in elderly patients with isolated systolic hypertension. In this study, a 10-mm Hg increment in the pulse pressure was associated with a 14% increase in the HF risk (95% CI, 0.05 to 0.24), and this risk remained significant at multivariate analysis, after adjustment for the other covariates and mean blood pressure values.12

The 2 main mechanisms through which hypertension causes HF are (1) accelerated atherosclerosis and (2) elevated left ventricular wall stress, with secondary neurohumoral activation and left ventricular hypertrophy. In addition to coronary atherosclerosis, hypertension may predispose one to myocardial ischemia also through an increase in coronary resistance secondary to endothelial dysfunction, decreased coronary reserve, augmented interstitial and perivascular collagen, and abnormalities in the responsiveness of the coronary vessels to vasoactive substances. Left ventricular mass is linearly related to the level of blood pressure. However, it is influenced by other factors, such as age, sex, race, body weight and height, salt and alcohol intake, and neuroendocrine factors (eg, the renin–angiotensin–aldosterone system and sympathetic nervous system, insulin, growth hormone activation). Left ventricular hypertrophy is a well-known risk factor for death, major cardiovascular events,14 and HF;15 both in the normotensive subjects and, to a greater extent, in hypertensive patients. In addition, an increased left ventricular mass is an independent predictor of a worse outcome at later stages of the disease, as shown by its independent prognostic value in patients with asymptomatic and symptomatic left ventricular systolic dysfunction studied in the Study of Left Ventricular Dysfunction (SOLVD) trials.16 The relation between left ventricular mass and the incidence of major cardiovascular events is linear without any threshold value, and it persists after adjustment for other risk factors and blood pressure.

The increase in left ventricular stress and hypertension may cause major cardiovascular events through multiple mechanisms, including (1) myocardial ischemia caused by a disproportionate increase in the myofibrillar component, perivascular fibrosis, and a reduction in the coronary vasodilatory capacity; (2) reduced left ventricular compliance; and (3) potentially malignant tachyarrhythmias. Other mechanisms that may contribute to the development of left ventricular dysfunction are myocardial fibrosis and fiber disarray, an acceleration of myocyte death with the mechanisms of ischemic necrosis and apoptosis, and the expression of a fetal gene program with a reduced efficiency of myocardial contraction. Reduction of blood pressure and left ventricular hypertrophy is therefore a desired goal of therapy for HF prevention. However, the relation between the regression of left ventricular hypertrophy and prognosis has not yet been thoroughly assessed. A trial showing the utility of left ventricular hypertrophy regression was the Heart Outcomes Prevention Evaluation (HOPE) trial, which showed an association among the regression of the electrocardiographic markers of left ventricular hypertrophy and a lower risk of major cardiovascular events and the prevention of HF.17

Treatment of both systolic and diastolic hypertension is associated with a reduction in the incidence of HF. In a systematic review and meta-analysis of 18 controlled studies published in 1997 that included a total of 48,220 patients, β-blocker therapy was associated with an RR of HF of 0.58 (95% CI, 0.40 to 0.84), and high-dose and low-dose diuretic therapies were associated with risk reductions of 0.17 (95% CI, 0.07 to 0.41) and 0.58 (95% CI, 0.44 to 0.76), respectively, compared with placebo. The reduction of the pulse pressure is also associated with a reduced incidence of HF. Treatment of hypertension has already demonstrated its benefit in the primary prevention of HF. In fact, the recent finding of a reduction in the incidence of HF in women has been related to the better treatment of hypertension.20 Blood pressure should be reduced according to the specific patient’s risk profile, with the general goal of a blood pressure measurement <140/85 mm Hg in all patients and <130/80 mm Hg in patients with diabetes.21,22 Among the different antihypertensive agents, those that are useful for the treatment of both hyper-
tension and HF (e.g., diuretics, β-blockers, and angiotensin-converting enzyme [ACE] inhibitors) should be preferred. Diuretics and β-blockers have been widely shown to be effective in the prevention of HF in the first trials of antihypertensive therapy. More controversial is the effectiveness of the α-agonists. The doxazosin arm of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was prematurely discontinued because doxazosin administration was associated with an increased risk of major cardiovascular disease and, in particular, of HF, compared with chlorthalidone treatment (RR, 2.04; 95% CI, 1.79 to 2.32; *p* < 0.001). Other data favor the use of ACE inhibitors, rather than calcium antagonists, for the prevention of HF. The frequency of development of HF was significantly lower in the ACE inhibitor group than in the calcium antagonist group in the Swedish Trial in Old Patients with Hypertension 2 (STOP Hypertension–2) study (RR, 0.78; 95% CI, 0.63 to 0.97). This trend was confirmed in a subsequent meta-analysis showing an increased RR of HF with calcium antagonists compared with both ACE inhibitors (RR, 1.24; 95% CI, 1.00 to 1.55) and diuretics, and β-blockers (RR, 1.22; 95% CI, 1.03 to 1.46). However, the use of calcium antagonists has been associated with a reduced incidence of stroke, and no significant difference in the prevention of HF was observed in another meta-analysis.

**DIABETES**

Similar to HF, the number of patients with diabetes mellitus is progressively increasing. Diabetes is a large comorbidity of patients with HF. In major clinical trials, it was observed in 20% to 30% of patients with higher values (35%) when blood glucose was measured at baseline and the recent diagnostic criteria were applied. Similar percentages (35% among patients treated by cardiologists, 38% among those treated by generalists) have been observed when less selected HF populations, not included in clinical trials, were studied.

Diabetes markedly increases the likelihood of HF in patients without cardiac disease. The Framingham study was the first study that showed an increased risk of HF in patients with diabetes, with an incidence of HF that showed a 4-fold and 8-fold increase in men and women with diabetes, respectively, compared with those without diabetes. In the NHANES study, diabetes was independently associated with an increased risk of HF (RR, 1.85; 95% CI, 1.51 to 2.28; *p* < 0.01). The association between glycosylated hemoglobin (HbA1c) levels and the incidence of HF was studied in a large, population-based sample of adult patients (29,958 men and 22,900 women) with diabetes with no known history of HF observed for a median duration of 2.2 years. After adjustment for other risk factors, concomitant therapy, and type and duration of diabetes, a significant independent association was found between HbA1c levels and incidence of HF. Each 1% increase in its level was associated with an 8% increase in the risk of HF hospitalization or death. An HbA1c level ≥10, relative to HbA1c < 7, was associated with 1.56-fold (95% CI, 1.26 to 1.93) greater risk of HF.

Diabetes is not only a risk factor for HF in patients without structural heart disease, but it is also associated with a worse outcome once a cardiac disease (e.g., a myocardial infarction or HF itself) has developed. A report from the SOLVD trial was the first to identify diabetes as an independent risk factor of increased mortality and morbidity in both symptomatic and asymptomatic patients with HF. A further analysis of this database showed that diabetes was associated with an increased risk of mortality only in patients with HF of ischemic origin (RR, 1.37; 95% CI, 1.21 to 1.55; *p* < 0.0001) but not in those with nonischemic cardiomyopathy. In addition, the increased mortality of patients with ischemic cardiomyopathy, compared with those with nonischemic cardiomyopathy, was limited to those with concomitant diabetes. Diabetes mellitus is also associated with an increased risk of HF and death in patients with an acute myocardial ischemic event.

Many mechanisms may explain both the increased incidence of HF in patients with diabetes without any initial cardiac disease and the worse outcome of patients with diabetes in whom a cardiac disease has developed. Population-based studies have demonstrated an increased left ventricular mass and wall thickness with subclinical impairment in left ventricular systolic function, shown by a lower left ventricular fractional shortening, midwall shortening and stress-corrected midwall shortening, and increased arterial stiffness in patients with diabetes, compared with those without diabetes. Diabetes likely acts on the intrinsic properties of the myocardium with an effect that is independent and additive to the more common and widespread coronary artery disease and to the associated abnormalities of autonomic function, with increased sympathetic and decreased vagal stimulation. Accordingly, histology studies have shown that diabetes is associated with myocyte hypertrophy, perivascular fibrosis, and an increase in matrix collagen, cellular triglycerides, and cell membrane lipids, consistent with nonenzymatic glycation of vascular and membrane proteins, increased cellular fatty acid uptake, and hyperglycemia-induced oxidative stress. Abnormalities of left ventricular diastolic function with a reduced left ventricular compliance occur early in the course of diabetes, even before hypertension, vasculopathy, and even fasting hyperglycemia have developed, thus suggesting that they are secondary to diabetes. Metabolic abnormalities may also explain the unfavorable synergy observed between diabetes and coronary artery disease in patients with HF. The impaired glucose uptake caused by diabetes may, in fact, be particularly deleterious in patients with concomitant coronary artery disease, which is, in turn, generally associated with a shift in myocardial metabolism from free fatty acids to glucose and glycolysis.
It is therefore clear how the treatment of diabetes should reduce both the incidence of new cases of HF and the morbidity and mortality of patients in whom HF has already developed. Glycemic and HbA1c serum levels should be controlled and reduced to normal levels, even with the possibility of untoward effects of intensive insulin treatment. Tighter blood pressure control with reduction of blood pressure to \(<130/80\) mm Hg has been shown to be associated with a reduced risk of HF in the United Kingdom Prospective Diabetes Study (UKPDS). In addition, ACE inhibitors can prevent the development of major cardiovascular events and HF in patients with diabetes, even when they do not have concomitant hypertension.

**CORONARY ARTERY DISEASE**

**Epidemiology and mechanisms:** Coronary artery disease is the single most common cause of HF. It was present in almost 70% of patients included in major multicenter HF trials, and similarly, it was associated with an RR of 8.11 (95% CI, 6.95 to 9.46; \(p <0.001\)), with a population-attributable risk of 61.6% in an epidemiologic study. These percentages, although high, likely underestimate the real prevalence of coronary artery disease. In fact, patients with a recent myocardial infarction or unstable angina have been excluded from most of the trials, and coronary angiography or stress myocardial imaging were not systematically used either in multicenter trials or in epidemiologic studies. In a general population–based study on incident cases of HF, coronary artery disease was identified as the principal cause in 29% of patients, on the basis of only the clinical criteria, versus 52% of patients when either coronary angiography or stress perfusion imaging was systematically used.

Coronary artery disease is important, not only as a risk factor and a precursor of HF, but also as a variable associated with a worse outcome in patients in whom HF has developed. Many studies have shown that patients with ischemic cardiomyopathy have a worse prognosis compared with those with nonischemic cardiomyopathy. In addition, new ischemic events may further worsen the outcome of patients with HF. In the SOLVD trials, the occurrence of a new myocardial infarction and of unstable angina has more than doubled the 1-year risk of HF hospitalizations (from 8.6% to 20.5% and from 8.4% to 15.3%, respectively). These results are likely to be even more significant when patients with a recent ischemic event are also included, as occurs in clinical practice.

In addition to new ischemic events with new scar formation, there are many other mechanisms through which coronary artery disease may cause the progression of left ventricular dysfunction and HF: (1) left ventricular dysfunction may be secondary to severe and widespread coronary artery disease causing episodes of reversible ischemia (myocardial stunning) or a sustained severe reduction of blood flow (myocardial hibernation); (2) the noninfarcted myocardium may undergo the process of left ventricular remodeling with left ventricular dilatation, spherical conformation, and reduced contractility; and (3) coronary artery disease may be attended by endothelial dysfunction with reduced release of nitric oxide and prostacyclin and an increased release of toxic factors for the myocardium, such as angiotensin II and endothelin. Endothelial dysfunction may also favor new acute ischemic events, because it may cause vasoconstriction, smooth muscle cell proliferation and migration, lipid deposition in the vessel wall, and finally, plaque rupture and thrombosis. There is, therefore, a tight link between the progression of left ventricular dysfunction and the induction of new ischemic events in patients with coronary artery disease. However, this link has been pointed out only recently.

**\(\beta\)-Blockers and ACE inhibitors—efficacy from prevention to therapy:** The 2 classes of drugs that have been associated with the most favorable effects on the prognosis of patients with HF, \(\beta\)-blockers and ACE inhibitors, are both characterized by their action both as neurohumoral antagonists and as powerful anti-ischemic agents. The long-term administration of \(\beta\)-blockers has been associated with a highly significant improvement in symptoms, left ventricular function, morbidity, and mortality in patients with HF studied in large multicenter controlled trials. These agents may cause a highly significant improvement in the left ventricular function, with reversal of the remodeling process. Their beneficial effects on left ventricular function are likely of the greatest degree that has been obtained in clinical practice to date, and they represent a main mechanism of their favorable effects on the prognosis. However, although the increase in the left ventricular ejection fraction after \(\beta\)-blockade is greater in patients with idiopathic cardiomyopathy, their beneficial effects on prognosis are present also, if not primarily, in patients with ischemic cardiomyopathy. It is therefore likely that the prevention of the ischemic events is a main mechanism of their favorable action. Long-term \(\beta\)-blocker administration has been associated with (1) a decrease in myocardial oxygen consumption, (2) a shift in myocardial metabolism toward the more favorable glucose, rather than free fatty acid uptake, (3) a reduction in lipid accumulation in coronary plaques, (4) an enhancement of endogenous thrombolysis, and (5) a reduced incidence of plaque rupture and coronary thrombosis. In addition to the protection from the \(\beta\)-adrenergic receptor–mediated toxic effects of the catecholamines on the myocardium, these anti-ischemic mechanisms of \(\beta\)-blockade may reduce the incidence of new ischemic events and prevent the development of left ventricular dysfunction and symptomatic HF in patients at risk.

Similar beneficial effects have been described with ACE inhibitors. In addition, these agents have been associated with favorable effects on left ventricular remodeling. Their action seems, however, milder than that of \(\beta\)-blockers. In contrast, and relatively unexpectedly, ACE inhibitors have been shown to be powerful anti-ischemic agents. The administration of
the ACE inhibitors may (1) reduce myocardial oxygen consumption through a decrease in afterload, preload, and left ventricular myocardial mass; (2) improve myocardial oxygen supply through a reduction in perivascular and interstitial fibrosis and an improvement in endothelial-dependent vasodilation; (3) inhibit the migration and proliferation of the smooth muscle and inflammatory cells, with a slowing of the atherosclerosis progression; and (4) favor endogenous thrombolysis through its mild antiplatelet action and the enhancement of the plasminogen activator inhibitor activity. The long-term administration of ACE inhibitors has been associated with a reduction in the incidence of ischemic events (reinfarction, unstable angina, revascularization procedures) in the SOLVD\textsuperscript{57} and Survival and Ventricular Enlargement (SAVE) trials\textsuperscript{48} performed in patients with symptomatic or asymptomatic left ventricular dysfunction. The best evidence of the anti-ischemic effects of the ACE inhibitors has been obtained in the HOPE trial, performed in patients at risk of vascular events (previous cerebral, coronary, or peripheral arterial vascular event) or with diabetes plus 1 other risk factor and with the exclusion of patients with left ventricular dysfunction or HF.\textsuperscript{42} During a mean follow-up period of 5 years, treatment with ramipril versus placebo was associated with a significant reduction in cardiovascular death (6.1% vs 8.1%; RR, 0.74; p < 0.001), myocardial infarction (9.9% vs 12.3%; RR, 0.80; p < 0.001), revascularization procedures (16% vs 18.3%; RR, 0.85; p = 0.002), and HF (9% vs 11.5%; RR, 0.77; p < 0.001). The HOPE trial is therefore one of the first trials that directly addressed the issue of the prevention of cardiovascular events, including the primary prevention of HF. This trial shows the tight link between recurrences of vascular ischemic events and the development of symptomatic HF, and it shows how the administration of an ACE inhibitor may prevent both these untoward unwanted events.

**Antiplatelet agents and coronary revascularization—**

**the efficacy with prevention and the uncertainty with treatment:** In addition to the administration of \( \beta \)-blockers and ACE inhibitors, other drugs and procedures are beneficial for the treatment of coronary artery disease and thus may prevent the development of HF. However, the effects of these drugs and procedures have been assessed mainly in patients without HF and, in some cases, with evidence of only a mild left ventricular dysfunction. Therefore, although we know these procedures are beneficial when used before the development of left ventricular dysfunction (primary prevention), data obtained in patients with HF are more controversial; 2 examples are those of antiplatelet agents and of coronary revascularization. Aspirin is universally accepted as first-line treatment of coronary artery disease. However, in addition to some inconsistencies in the data of multicenter trials,\textsuperscript{57} the results in the 2 large, long-term aspirin trials, including those of patients with HF, have not shown significant beneficial effect on mortality in this subgroup.\textsuperscript{59,60} Aspirin has many potentially unfavorable effects in patients with HF. It may reduce prostacyclin production, increase the vasoconstrictor response to endothelin, and favor the development of renal failure during the initiation of ACE inhibitor therapy.\textsuperscript{57} In addition, the beneficial effects of ACE inhibitors and \( \beta \)-blockers seem to be reduced, although rather weakly, by the concomitant aspirin therapy.\textsuperscript{53,61} Thus, whereas the favorable effects of aspirin in the prevention of new ischemic events and, therefore, in the primary prevention of HF are indisputable, its usefulness in patients with both asymptomatic and symptomatic left ventricular dysfunction are less clear. A large (4,500 patients) randomized, controlled trial comparing warfarin, aspirin, and clopidogrel in patients with HF is currently ongoing.\textsuperscript{62}

Similarly, whereas the benefits of the revascularization procedures in the prevention of new coronary events with secondary left ventricular dysfunction are well established, their efficacy in patients with symptomatic HF and advanced left ventricular dysfunction are less clear.\textsuperscript{57} Patients with HF were excluded from the first major coronary revascularization trials, and the data available are from small and selected study groups, are retrospective, and are not controlled. The vast majority of the studies indicate the usefulness of an assessment of myocardial viability in the prediction of the improvement in left ventricular function and symptoms after coronary revascularization. However, no data are available on the effects on mortality, and the effects of revascularization in patients with low amounts of viable myocardium at the imaging tests are not clear.\textsuperscript{63} Currently, 2 major trials are going to address these issues. A trial comparing a strategy of proceeding or not proceeding to coronary intervention leading to revascularization among patients with HF and meaningful amounts of myocardium, ischemic or stunned or hibernated, has been recently started in the United Kingdom (the Heart Failure Revascularization Trial).\textsuperscript{57} This trial is projected to include approximately 800 patients. A larger trial will be performed in the United States to compare both the role of an assessment of myocardial viability and the effects of revascularization (Surgical Treatment for Ischemic Heart Failure [STICH]).\textsuperscript{63} Unlike the previous study, all patients will undergo coronary angiography in this last trial. The duration of this trial is projected to be \( \geq 6 \) years.

**Statins: a promise for the future?** Patients with symptomatic HF have been excluded from the previous trials of lipid-lowering therapy. Thus, our knowledge of the role of hyperlipidemia and the effects of statin treatment are still insufficient. Serum cholesterol is widely recognized as a major risk factor for coronary artery disease and hence HF. However, patients with symptomatic HF tend to have low cholesterol levels and, in contrast with the results in patients without HF, low cholesterol, low-density lipoprotein, and triglyceride levels have been associated with a worse outcome in patients with HF.\textsuperscript{64–66} The relatively low incidence of new ischemic events in pa-
tients with advanced HF makes the role of lipid-lowering therapy even more uncertain.

Statins have many effects potentially useful for the prevention of HF: (1) they reduce the incidence of new ischemic events through an increase in plaque stability and an improvement of endothelial function; (2) they may inhibit the synthesis of proinflammatory agents, such as the cytokines and chemokines, which have been implicated in the pathogenesis of HF; and (3) they may improve autonomic function, with an increased parasympathetic drive; downregulate the angiotensin II type 1 receptors; cause neoangiogenesis; and cause an improvement in transmembrane calcium influx. However, statins also have potentially deleterious effects. In patients with advanced HF, congestion of the splanchnic circulation favors the absorption of gut endotoxins, such as lipopolysaccharides, which may then cause the activation of proinflammatory cytokines, such as tumor necrosis factor-α. Lipoproteins have, from this point of view, a favorable effect because they may bind to lipopolysaccharides and neutralize their effects. Second, ubiquinone, a coenzyme in mitochondrial oxidative phosphorylation and an antioxidant (potentially useful in patients with HF), is synthesized by the 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is the same enzyme that is inhibited by the statin administration. Accordingly, a decrease in ubiquinone plasma and, possibly, tissue levels have been described after statin therapy.

Although no study has been aimed primarily at the assessment of the role of statins in HF, favorable results have been obtained in retrospective analyses of data from some major trials. The Scandinavian Simvastatin Survival Study (4S) assessed the effects on the outcome of the administration of simvastatin in patients with a previous history of coronary artery disease and no signs or symptoms of HF. Approximately 2% of the 4,444 included patients developed HF during the 4 years of follow-up, and this event was associated with a >4-fold increase in mortality compared with the other patients. Simvastatin administration was associated with 20% reduction in the incidence of HF compared with placebo; in patients who had developed HF, there was a 19% reduction in the mortality rate compared with placebo. Among the major statin trials, the left ventricular ejection fraction was measured only in the Cholesterol and Reduction of Events (CARE) study. In this trial, pravastatin therapy was equally effective in reducing coronary events independent of the left ventricular ejection fraction (>0.40 or <0.40). However, patients with a left ventricular ejection fraction <0.25 were excluded from this trial. Favorable results have also been obtained in reanalyses of other trials. In the Evaluation of Losartan in the Elderly (ELITE) II trial, 11% of patients receiving a statin had a lower mortality compared with the others (10.6% vs 17.6%, p <0.003). Similar results were obtained in a reanalysis of the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL). Thus, despite the controversial physiopathologic issues, retrospective analyses of clinical trials seem to indicate that statins may have favorable effects in the prevention of HF and in HF after it has developed. This last issue, however, needs to be formally tested in a randomized trial.

Other factors: Many other agents have deleterious effects and may favor the development of HF. They include smoking, excessive alcohol consumption, abuse of cocaine or other illicit drugs, mediastinum radiation therapy, and chemotherapeutic agents, such as anthracyclines or trastuzumab. Avoidance of all these factors helps to prevent the occurrence of chronic HF. On the other hand, patients exposed to these substances are at risk of developing HF. Obesity, traditionally regarded as a coronary risk factor, has been recently shown to be independently related to the risk of HF.

CONCLUSIONS

Chronic HF is a progressive disease. Hence, a major goal of treatment is not only to improve the course of HF when it is already symptomatic, but, even more importantly, to prevent its development in patients at risk. Because coronary artery disease is the major cause of HF, risk factors of coronary artery disease are also those of HF. Hypertension, diabetes, and left ventricular hypertrophy, however, are also deleterious through other mechanisms. Other therapies, like statin therapy, may, on the other hand, be beneficial in other mechanisms in addition to the reduction in coronary events. Thus, the prevention of HF is an extremely broad and difficult task. Any significant achievement in the prevention of HF will be a major step forward in the management of cardiovascular diseases and in the improvement of human well-being.

1. Packer M, Cohn JN, on behalf of the Steering Committee and Membership of the Advisory Council to Improve Outcomes Nationwide in Heart Failure. Consensus recommendations for the management of chronic heart failure. II. Management of heart failure: approaches to the prevention of heart failure. Am J Cardiol 1999;83(suppl):8A–38A.


62. The WASH study (Warfarin/Aspirin Study in Heart failure) rationale, design and end-points: the WASH study Steering Committee and Investigators. *Eur J Heart Fail* 1999;1:95–99.


