Prevention of Heart Failure: Effective Strategies to Combat the Growing Epidemic

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In light of the increasing prevalence, morbidity, and mortality of heart failure, effective preventative strategies are urgently needed. Risk factors for heart failure include coronary artery disease and other atherosclerotic vascular diseases, hypertension, diabetes, renal insufficiency, obesity, and family history of cardiomyopathy. Essential strategies for prevention of heart failure are modification of risk factors for heart failure development; comprehensive hypertension, atherosclerosis, and diabetes treatment; and detection and treatment of asymptomatic left ventricular dysfunction. The B-type natriuretic peptide assay may aid in identifying asymptomatic left ventricular dysfunction in patients with risk factors for heart failure. In patients with hypertension, atherosclerosis, and/or diabetes, angiotensin-converting enzyme inhibitor, ß-blocker, aspirin, and statin therapy can prevent progression to symptomatic heart failure. Avoidance of calcium channel-blockers as first-line antihypertensive therapy can also reduce the risk of heart failure. There remain substantial opportunities to improve implementation of therapies proven to prevent heart failure in the large number of patients at risk.
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Key words: Heart failure • Ischemic heart disease • Hypertension • Diabetes • Asymptomatic left ventricular dysfunction

Heart failure (HF), with over 500,000 new cases per year and a current U.S. prevalence nearing 5 million,[1] is an important public health issue. This condition results in 15 million office visits and 6.5 million days of hospitalization each year. In contrast to the declining incidence and mortality of coronary artery disease (CAD) and stroke, hospital discharges and deaths from HF have increased more than 100% over the past 2 decades. Mortality with this condition remains high, with 5-year mortality rates being close to 50%.[1] In view of this considerable prevalence, morbidity, and mortality, there is an urgent need for implementation of strategies to detect high-risk patients

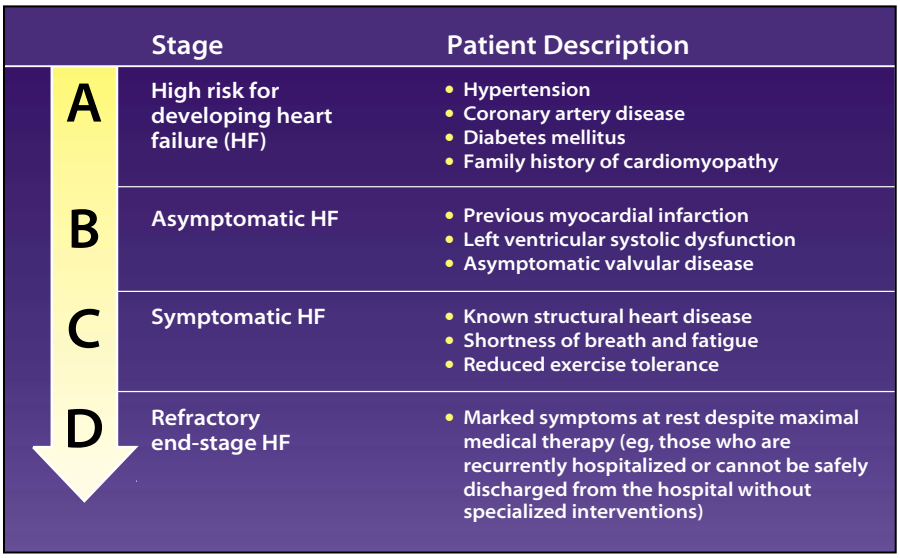

Figure 1. *The ACC/AHA staging system for heart failure.*

and to prevent HF onset to combat this growing epidemic. This article will highlight effective clinical interventions aimed at preventing the development of HF in high-risk patients.

New Staging System for Heart Failure

In developing the 2001 American College of Cardiology/American Heart Association Guidelines for the Evaluation and Management of Heart Failure in the Adult, the writing committee developed a new approach to the classification of HF.[2] The resulting staging system, identifying four stages of HF, emphasizes both the evolution and progression of the disease. Stage A identifies the patient who is at high risk for developing HF but has no structural disorder of the heart; Stage B refers to a patient with a structural disorder of the heart but who has never developed symptoms of HF; Stage C denotes the patient with past or current symptoms of HF associated with underlying structural heart disease; and Stage D designates the patient with end-stage disease who requires specialized treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation, or hospice care (Figure 1). This classification recognizes that there are established risk factors and structural prerequisites for the development of HF and that therapeutic interventions performed even before the appearance of left ventricular dysfunction or symptoms can reduce the incidence as well as the morbidity and mortality of HF.

Risk Factors for Development of Heart Failure

Stage A Heart Failure: Patients at High Risk

The leading risk factor for development of HF in the United States is ischemic heart disease, accounting for approximately 60% of new HF cases.[3] Hypertension also plays a major role in the incidence of HF.[4] Patients with diabetes are also at substantially increased risk for HF, even with adequate blood sugar control.[4] Other risk factors for HF include dyslipidemia, smoking, obesity, and valvular heart disease.[3,4] Recent epidemiologic studies have identified new risk factors, including renal insufficiency, microalbuminuria, metabolic syndrome, depression, and low physical activity level[3,5-7] (Table 1). Patients with a family history of cardiomyopathy are also at significant risk.[2] These patients who are at high risk for developing HF but have no structural disorder of the heart would be classified as Stage A HF patients. At exceptionally high risk of future symptomatic HF are patients with asymptomatic left ventricular dysfunction (ALVD), now classified as Stage B HF.[2] Efforts to curb the rising incidence of HF should focus on detection and treatment of risk factors.

Stage B Heart Failure: Asymptomatic Left Ventricular Dysfunction

Usually defined by an ejection fraction less than 40%, ALVD is common, with prevalence ranging between 1%–5% of the general population. Patients with ALVD often develop symptomatic HF, and 4-year mortality rates have been reported as high as 25%.[4,8] Ischemic heart disease is the number one risk factor for ALVD, and additional risk factors include age, history of long-standing hyperten-

Table 1
Risk Factors for the Development of Heart Failure

Atherosclerotic vascular disease
Hypertension
Diabetes
Metabolic syndrome
Renal insufficiency
Obesity
Dyslipidemia
Smoking
Physical inactivity
Genetic (family history of cardiomyopathy)

sion, left bundle branch block, diabetes, and family history of cardiomyopathy. Neurohumoral activation plays a key role in the progression from risk factors to ALVD to symptomatic HF and death, as illustrated in Figure 2.

In light of the effectiveness of current medical interventions to decrease the risk of progression to clinical HF and to decrease associated mortality, detection of ALVD is an important component of HF prevention. Detection of ALVD via echocardiography screening for populations at risk, although accurate, may be prohibited by high cost. An alternative strategy for detection of ALVD is the use of the serum assay for B-type natriuretic peptide (BNP), a protein released by the ventricles in response to increased ventricular pressure or increased myocardial stretch. The BNP blood test has high sensitivity and specificity for detection of left ventricular dysfunction in the general clinic population with risk factors for HF[8,9] and may be a rapid, accurate, and cost-effective screening tool for patients with Stage B HF.

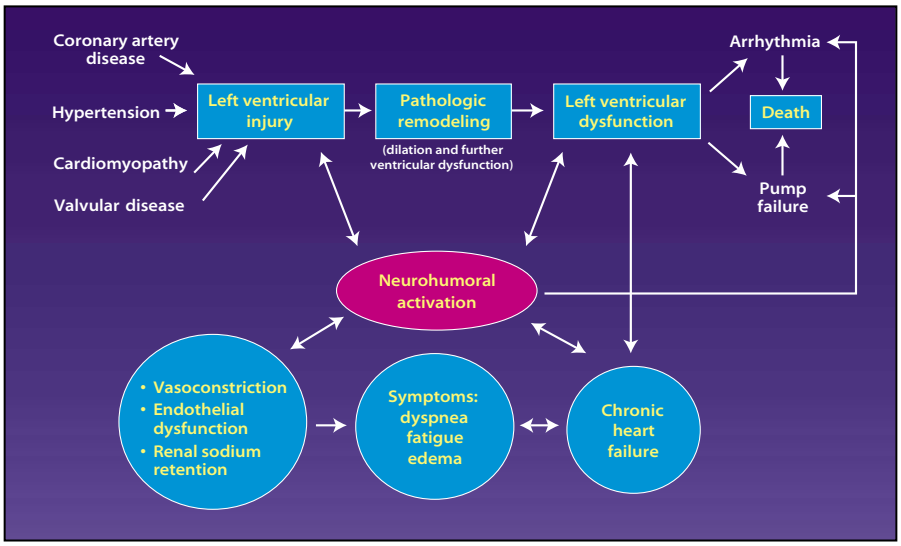

Figure 2. *The progression of heart failure from risk factors to left ventricular dysfunction to symptomatic heart failure and death.*

Recent epidemiologic studies have identified new risk factors.

Preventive Measures for Patients at Risk

Stage B Heart Failure: Asymptomatic Left Ventricular Dysfunction

As established by the Studies of Left Ventricular Dysfunction (SOLVD) Prevention Trial, angiotensin-converting enzyme (ACE) inhibitor therapy is indicated in all patients with ALVD.[10] β-blocker therapy in addition to ACE inhibitor therapy for ALVD may provide further protection from progression to HF, and this strategy has recently been promoted.[2,11] Observational data support β-blocker therapy in addition to ACE inhibitor therapy in patients with ALVD. In a recent subanalysis of SOLVD, HF hospitalization and mortality were found to be decreased in patients receiving a combination of ACE inhibitor and β-blocker, independent of etiology of left ventricular dysfunction.[12] Analysis of the Survival and Ventricular Enlargement (SAVE) study demonstrated similar cardioprotective effects of β-blockers in a cohort of post-MI patients with decreased ejection fraction; β-blocker use was associated with decreased incidence of symptomatic HF as well as decreased cardiovascular mortality (Table 2).[13]

Risk factors for the development of HF in patients with ALVD[4,8,14-16] are similar to those in patients without left ventricular dysfunction. Thus, in addition to ACE inhibitor and β-blocker therapy, management of ALVD also requires rigorous implementation of the general preventative strategies to be described in the upcoming sections.

Stage A Heart Failure: Coronary Artery and Other Atherosclerotic Vascular Disease

The leading etiology of HF in Western countries is ischemic heart disease. Approximately 7 million Americans have a history of myocardial infarction (MI), and the 6-year risk of disabling HF after acute MI is 22% for women and 46% for men.[1] Patients with peripheral vascular disease and cerebral vascular disease have also been recognized to be at similar high risk for HF and cardiovascular events. It is imperative that CAD and other atherosclerotic vascular disease management includes interventions to reduce HF incidence (Table 2).

The Heart Outcomes Prevention Evaluation (HOPE) study demonstrates ACE inhibitor therapy to be an effective means of curbing progression from established atherosclerotic vascular disease to HF.[17] This randomized, double-blind, placebo-controlled trial studied 9297 patients with vascular disease or diabetes plus an

Table 2
Medical Therapies to Reduce Risk of Heart Failure

	Clinical Trial	Number of patients	Patient Inclusion Criteria	Heart Failure Incidence	Relative Risk Reduction
Randomized, Placebo-Controlled Trials					
Angiotensin-converting enzyme inhibitor	HOPE[17] (ramipril, 2.5 mg or 10 mg)	9297	Vascular disease (coronary artery disease, peripheral vascular disease, or stroke) or diabetes plus cardiac risk factor; creatinine < 2.4	Ramipril vs placebo, 9% vs 11%	↓ 23%
Antiplatelet (adenosine diphosphate inhibitor)	CURE[19] (clopidogrel 300 mg load, then 75 mg)	12,562	Acute coronary syndrome: non-ST elevation EKG changes or elevated cardiac enzymes	Clopidogrel vs placebo, 3.7% vs 4.4%	↓ 18%
Angiotensin-receptor antagonist	RENAAL[36] (losartan, 50–100 mg)	1513	Type II diabetes, nephropathy	Losartan vs placebo, 11.9% vs 16.7%	↓ 32%
Angiotensin-receptor antagonist	IDNT[37] (irbesartan, 300 mg)	1715	Hypertension, type II diabetes, nephropathy	Irbesartan vs placebo, n/a	↓ 23%
Statin	4S[23] (simvastatin 20–40 mg)	4444	History of myocardial infarction or angina, cholesterol 213–309 mg/dL, triglycerides < 221 mg/dL	Simvastatin vs placebo, 8.3% vs 10.3%	↓ 19%
Randomized, Active-Controlled Trial					
β-blocker or angiotensin-converting enzyme inhibitor with tight BP control	UKPDS[32] (captopril or atenolol, goal BP < 150/85)	1148	Type II diabetes, hypertension	Captopril or atenolol (BP drugs < 150/85) vs other (BP < 180/105) 3.6% vs 8.1%	↓ 56%
Retrospective Studies					
β-blocker	SOLVD[12] (subanalysis of prevention trial)	4223	Asymptomatic left ventricular dysfunction, ejection fraction < 35%	Enalapril plus β-blocker vs enalapril plus no β-blocker, N/A	↓ 36%
β-blocker	SAVE[13] (subanalysis)	2231	Ejection fraction < 40%, no overt heart failure, post–myocardial infarction patients	β-blocker vs no β-blocker, 16.5% vs 22.6%	↓ 32%
Meta-Analysis					
Aspirin	Antithrombotic Trialists[18]	135,000	High-risk patients	Aspirin vs placebo	↓ 41%

BP, blood pressure.

additional cardiac risk factor. The ACE inhibitor ramipril afforded a significantly decreased risk (23%) of new-onset HF as well as a decreased rate of MI and all-cause mortality (Figure 3). The benefits of ACE inhibitor therapy were additive to preexisting therapies such as aspirin, β-blockers, and lipid-lowering therapy. The HOPE trial expands the indication for ACE inhibitor therapy to all patients with documented CAD, presumed CAD based on presence of other atherosclerotic vascular disease, or diabetes.

Antiplatelet therapy with aspirin in patients with established vascular disease or similar risk has been demonstrated to reduce the risk of cardiovascular events and HF.[18] The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial demonstrated that clopidogrel in combination with aspirin reduces the risk of major cardiovascular events in patients with acute coronary syndromes.[19] This randomized, double-blind, placebo-controlled trial of 12,652 patients with acute coronary syndromes demonstrated a significant reduction in HF incidence (18%) with combined antiplatelet therapy.

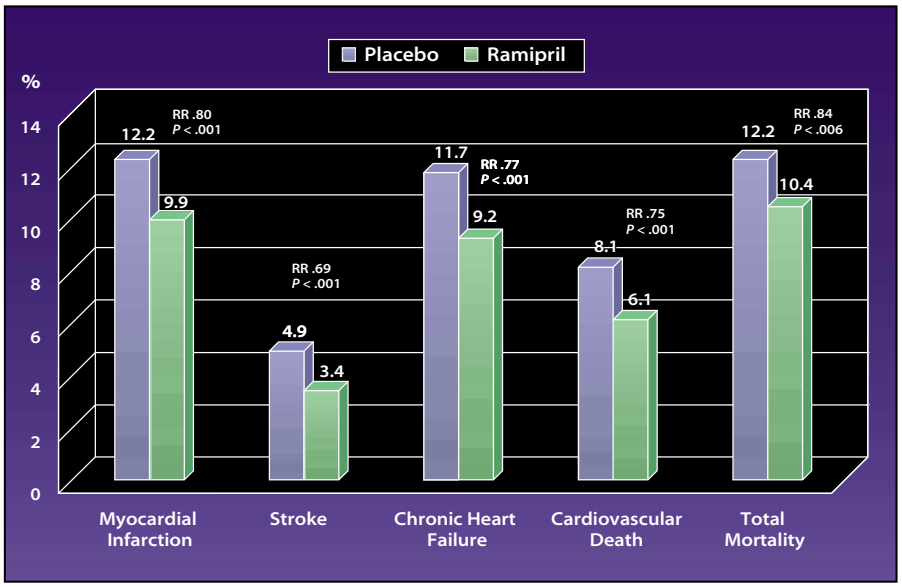

Figure 3. *The Heart Outcomes Prevention Evaluation (HOPE) trial randomized 9297 patients with vascular disease or diabetes plus an additional cardiac risk factor to the angiotensin-converting enzyme (ACE) inhibitor ramipril versus placebo. The ACE inhibitor afforded a significantly decreased risk (23%) of new-onset heart failure as well as a decreased rate of myocardial infarction and all-cause mortality.*

Furthermore, the integral role of β-blockers in the treatment of ischemic heart disease is reinforced by the recent Carvedilol Postinfarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial, which found a significant reduction in all-cause mortality when the nonselective β-blocker and α1-blocker, carvedilol, was added to the treatment regimen of post-MI patients with left ventricular dysfunction already treated with ACE inhibitors.[20] Thus the combination of ACE inhibitors and β-blockers is beneficial in all post-MI patients regardless of symptom status and even if the patient has been completely revascularized.

Dyslipidemia, an important risk factor for CAD, is likewise implicated in the development of HF. While elevated total cholesterol is not a strong predictor of HF development,[3,21] increased total-to-HDL-cholesterol ratio is associated with HF risk.[22] Furthermore, hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitor treatment in CAD patients was demonstrated to reduce HF incidence in an analysis of the Scandinavian Simvastatin Survival Study (4S) trial.[23] The Heart Protection Study demonstrated a significant reduction in cardiovascular events and all-cause mortality with statin treatment (simvastatin 40 mg/d) in patients with established atherosclerotic vascular and/or diabetes, regardless of baseline low-density lipoprotein (LDL)-cholesterol.[24] Specifically, patients with LDL below 100 mg/dL at baseline not only benefited from statin treatment but had similar risk reduction to patients with higher baseline LDL. This landmark study establishes statin treatment as being an essential part of treatment in any patient with clinically evident atherosclerosis or diabetes in the absence of contraindications.

Interestingly, more recent experimental evidence suggests that HMG CoA reductase inhibitors play a cardioprotective role independent of their lipid-lowering capacity via mechanisms such as inhibition of myocardial hypertrophy and fibrosis and decreased ventricular remodeling.[25,26] This line of evidence is being investigated in a prospective clinical trial. If confirmed in clinical trials, statins may soon be used as a treatment to prevent HF in patients with ALVD and to reduce morbidity and mortality in patients with established HF, regardless of etiology and baseline LDL levels.

HF incidence will be lowered only if evidence-based treatments are effectively initiated in patients at risk. Hospital-based treatment programs aiming to increase treatment rates and long-term patient compliance have been successful, demonstrating improved long-term cardiovascular outcomes and a marked reduction of mortality.[27] The American Heart Association has recently launched the Get With The Guidelines Program to encourage in-hospital initiation of lipid-lowering medications and other secondary-prevention measures proven to save lives in patients hospitalized with coronary heart disease.

Hospital-based treatment programs aiming to increase treatment rates and long-term patient compliance have been successful.

Stage A Heart Failure: Hypertension

Hypertension, often in conjunction with CAD, is a common factor predisposing to HF. Risk of HF increases along a continuum of blood pressure (BP).[4] Control of hypertension is essential for protection from cardiovascular disease, yet antihyperten-

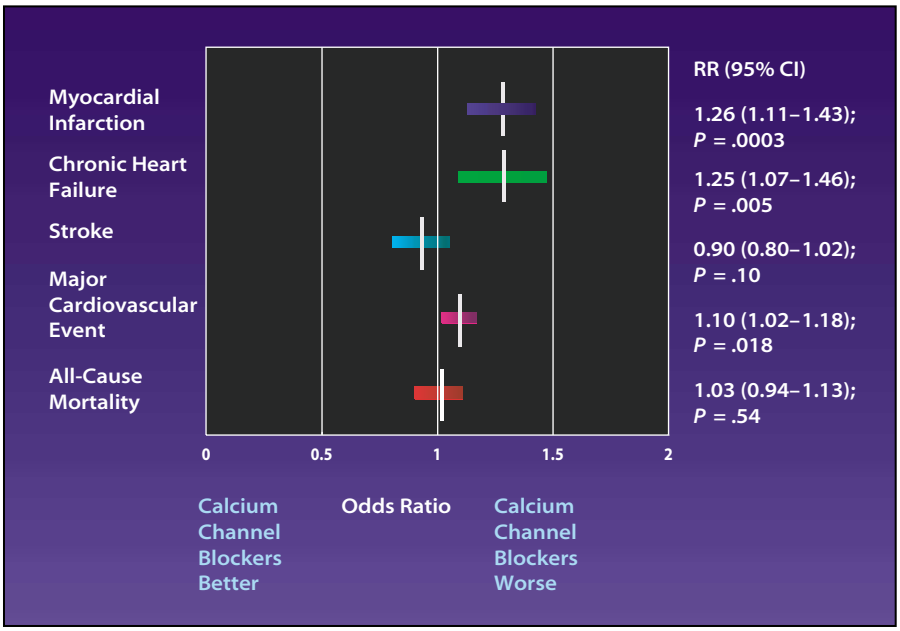

Figure 4. *Meta-analysis of nine trials with 27,743 patients randomized to intermediate or long-acting calcium channel blocker versus antihypertensive therapy with diuretic, ß-blocker, or angiotensin-converting enzyme inhibitor. There were 700 heart failure events, 1000 myocardial infarctions, 1100 cerebral vascular accidents, and 2300 deaths included in this analysis. The use of calcium channel blockers was associated with a 25% increased risk of heart failure (95% CI 1.07–1.46;* P = .005*).*

sive medications are not all equal in this respect.

The doxazosin arm of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was discontinued earlier than planned due to an increased rate of adverse events, which included a doubling of HF incidence with the peripheral α-blocking agent doxazosin compared to the diuretic chlorthalidone.[28] The question of cardioprotection afforded by calcium channel antagonist therapy for hypertension was also addressed recently. A large-scale, prospective, randomized trial, Intervention as a Goal in Hypertension Treatment (INSIGHT), reported a doubling of nonfatal HF risk in patients receiving a long-acting form of nifedipine compared to those receiving a diuretic.[29] A meta-analysis of randomized controlled trials evaluating intermediate-acting and long-acting calcium channel antagonists was published in December 2000.[30] Although overall BP reduction and all-cause mortality were similar for calcium channel antagonists compared to other antihypertensive therapies (β-blockers, diuretics, and ACE inhibitors) a significantly higher risk of HF (25%; $P < .005$) as well as MI was seen with calcium channel blockers, whether long-acting formulations, dihydropyridines, or nondihydropyridines (Figure 4).

In light of recently published clinical trial evidence, first-line antihypertensive therapy should consist of diuretics, ACE inhibitors, and β-blockers, drugs with superior efficacy in reducing the risk of MI and HF.

Stage A Heart Failure: Diabetes

Diabetes, with an approximate prevalence of 17 million Americans,[1] is highly associated with risk factors for HF such as CAD and hypertension. Diabetes is also an independent risk factor for development of HF, with incrementally increased risk seen at higher hemoglobin A_{1c} levels.[3,31]

Evidence from the UK Prospective Diabetes Study Group (UKPDS) is of critical importance in forming preventive strategies for diabetic patients. UKPDS highlights BP control with ACE inhibitors and/or β-blockers as an integral part of cardioprotective, preventative therapy in diabetics (Table 2). The UKPDS clinical trial comparing tight BP control (< 150/85 mm Hg) to less tight BP control (< 180/105 mm Hg) in 1148 diabetic, hypertensive patients demonstrated that a 10 mm Hg decrease in systolic BP was associated with a 56% decreased risk of incident HF.[32] ACE inhibitor and β-blocker therapy were equally efficacious in reducing risk of HF and other diabetes-related complications.[33] Despite the cardiac and vascular protective effects of β-blockers in patients with diabetes, this class of medication is frequently not utilized due to concerns regarding negative effects on lipids, insulin sensitivity, and glycemic control. The nonselective β-blocker and α-blocker carvedilol has been shown to have favorable effects on lipids, insulin sensitivity, and glycemic control[34] (Figure 5) Patients with diabetes can thus derive all of the beneficial effects of β-blocker therapy without the adverse metabolic consequences through the use of carvedilol.

In contrast to the benefits of ACE inhibitors and β-blockers, a UKPDS trial evaluating glycemic control reported that tight blood glucose control (blood glucose < 108 mg/dL) with insulin or oral sulfonylureas compared to conventional treatment (blood glucose < 270 mg/dL) did not affect HF incidence, although microvascular disease decreased.[35] Patients with the metabolic syndrome are at increased risk for cardiovascular

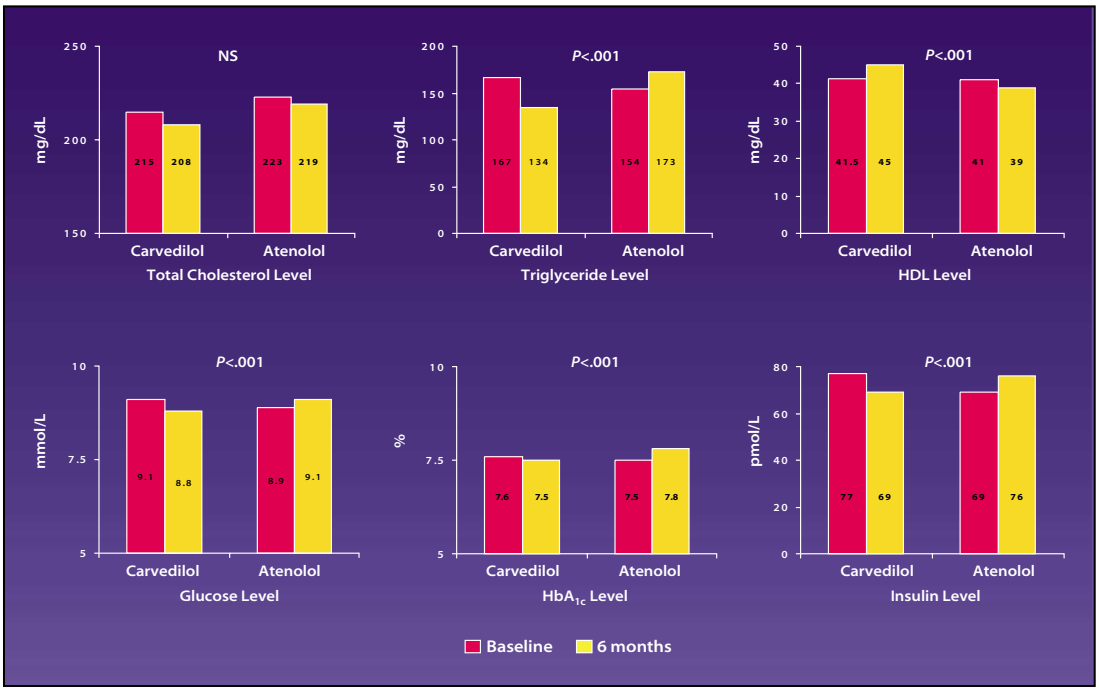

Figure 5. *This study[34] randomized 45 patients with non-insulin-dependent diabetes mellitus and hypertension to carvedilol or atenolol. Fasting plasma glucose and insulin levels decreased with carvedilol and increased with atenolol. There was also a decrease in triglyceride levels, increase in high-density lipoprotein (HDL) cholesterol levels, and decrease in lipid peroxidation with carvedilol relative to atenolol. By improving glucose and lipid metabolism and reducing lipid peroxidation, carvedilol may offer advantages in patients with diabetes and hypertension.*

events, HF, and transition to full diabetes. ACE inhibitors, statins, dietary modification, and exercise have been shown to lower the risk of new-onset diabetes.

Stage A Heart Failure: Renal Insufficiency

The kidneys, involved in sodium homeostasis, play an important role in the pathophysiology of HF. Activation of the renin-angiotensin-aldosterone system and sympathetic nervous system has been shown to play a pathophysiologic role in the initiation and progression of both renal disease and cardiovascular disease. Thus it is not surprising that renal insufficiency and microalbuminuria were recently established as independent risk factors for new-onset HF.[5,6,14]

ACE inhibitor therapy reduces HF risk, in addition to delaying progression to renal failure, in patients with renal insufficiency (Table 2). In HOPE, ACE inhibitor therapy afforded enhanced HF protection to a subset of patients with renal insufficiency (creatinine 1.4–2.3 mg/dL), compared to those without renal insufficiency.[5] Decreased risk of HF with angiotensin-receptor antagonist (ARB) treatment is evidenced by two recently published, randomized, placebo-controlled trials studying patients with diabetes and nephropathy.[36,37] There was, however, no reduction in cardiovascular or all-cause mortality with the use of ARB therapy in diabetics with proteinuria. Based on recent randomized controlled trials, it is clear that ACE inhibitor therapy (or as an alternative in patients who do not tolerate ACE inhibitors, ARB therapy) should be considered in all patients with renal insufficiency. The common practice of withholding ACE inhibitor therapy in renal insufficiency is unwarranted.

Sympathetic nervous system activation occurs with chronic kidney disease and likely plays a role in the increased risk of cardiovascular events in patients with HF. Some lines of evidence also support a role in progression of renal insufficiency. Carvedilol has been demonstrated significantly to reduce proteinuria in patients with hypertension and/or diabetes to a greater extend than β1-selective β-blockers.[38]

Health-Related Behaviors and Heart Failure Risk

Although chronic, excessive alcohol abuse may cause a dilated cardiomyopathy, recent evidence points towards moderate alcohol intake as protective against development of HF, both in the general population and those with ALVD.[15,39] A prospective cohort study in the elderly reported that up to four drinks per day were associated with a lowered risk of incident HF, even after adjustment for history of MI or angina.[39]

Recent studies have substantiated that current smokers have significantly higher risk for the development of HF compared to prior smokers and nonsmokers.[2,15] Counseling on

smoking cessation must take high priority in patients at risk for HF.

Possibilities for the Future

With rapidly advancing basic and clinical research in the HF arena, wide-ranging possibilities for the future of HF prevention are emerging. Improved survival with aldosterone antagonism in advanced HF may in part stem from its inhibition of cardiac fibrosis,[40] an effect that makes aldosterone antagonist therapy an attractive candidate for prevention of HF. Other pharmacotherapies have potential for HF prevention via inhibition of the myocardial hypertrophy and remodeling, including calcineurin and matrix metalloproteinase inhibitors.[41,42] As mentioned, statins may have a major therapeutic benefit in preventing HF.[25,26]

More invasive strategies currently under investigation for treatment of established HF, if successful, carry the potential to prevent progression from ALVD to overt HF. Improved left ventricular ejection fractions have been preliminarily reported with the Acorn cardiac support device, autologous skeletal myoblast transplantation, and stem cell transplantation.[43,44] Biventricular pacing, which improves symptoms in patients with advanced HF and interventricular conduction delay, also reverses myocardial remodeling[45] and thus may have potential for HF prevention in patients certain patients with ALVD. With further advances and testing, gene therapy may have a role in preventing and reversing heart failure.

Conclusions

Recently published clinical studies have identified highly effective therapies for prevention of HF. ACE inhibitor and β-blocker therapy is strongly indicated in all patients with ALVD, hypertension, CAD, peripheral vascular disease, cerebral vascular disease, and diabetes. Antiplatelet therapy and statins are indicated in all patients with atherosclerosis or diabetes, in the absence of contraindications. Preferred antihypertensive medications are ACE inhibitors, β-blockers, and diuretics. Blood pressure control is especially important in the diabetic population. Renal insufficiency is an indication for ACE inhibitor therapy and perhaps β-blocker therapy, which offers both cardioprotection and renal protection. Aldosterone-receptor blockade will likely have a major role in prevention of HF. Smoking cessation is also an essential part of HF prevention. In light of the rising incidence of and mortality from HF, more aggressive screening and detection of ALVD and wider application of evidence-based preventative strategies are clearly necessary. ■

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Main Points

- Hospital discharges and deaths from heart failure (HF) have increased more than 100% over the past 2 decades, and 5-year mortality rates are close to 50%.
- Recent epidemiologic studies have identified new risk factors, including renal insufficiency, microalbuminuria, metabolic syndrome, depression, and low physical activity level; patients with a family history of cardiomyopathy are also at significant risk.
- Detection of asymptomatic left ventricular dysfunction (ALVD) via echocardiography screening for populations at risk, although accurate, may be prohibited by high cost; an alternative strategy is the use of the serum assay for B-type natriuretic peptide (BNP), which has high sensitivity and specificity and may be a rapid, accurate, and cost-effective screening tool.
- Angiotensin-converting enzyme (ACE) inhibitor therapy is indicated in all patients with ALVD; the combination of ACE inhibitors and β-blockers is beneficial in all post–myocardial infarction (MI) patients regardless of symptom status and even if the patient has been completely revascularized.
- Clopidogrel in combination with aspirin reduces the risk of major cardiovascular events in patients with acute coronary syndromes.
- A significantly higher risk of HF as well as MI has been seen with calcium channel blockers, whether long-acting formulations, dihydropyridines, or nondihydropyridines.
- First-line antihypertensive therapy should consist of diuretics, ACE inhibitors, and β-blockers.

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