The Management of the Diabetic Patient With Prior Cardiovascular Events

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Patients with diabetes are at high risk for cardiovascular (CV) events and heart failure. Approximately 2–3 million diabetics in the U.S. have had a history of prior CV events. The prevalence of diabetes in patients with heart failure ranges from 24% reported in clinical trials to 47% among hospitalized patients, and an estimated 1–2 million persons in the U.S. have diabetes and heart failure. Diabetes substantially increases the risk of mortality after acute coronary syndromes and also increases the risk of hospitalizations and mortality in patients with heart failure. It is now recognized that activation of multiple neurohormonal systems is central in the pathophysiology of diabetes, CV events, and heart failure. Pharmacologic intervention in these systems (eg, angiotensin-converting enzyme (ACE) inhibition, aldosterone-receptor antagonism, and ß-blockade) has been shown to decrease morbidity and mortality in diabetics with prior CV events and/or heart failure. Despite this awareness, ACE inhibitors, aldosterone antagonists, and ß-blockers are underutilized, and deaths and hospitalizations caused by CV events and heart failure in diabetic patients have steadily increased. Concerns about an increased incidence of hypoglycemia, worsening dyslipidemia, and decreased insulin sensitivity resulting from the use of ß-blockers may be preventing physicians from prescribing these agents for diabetic patients. ß-blockade in conjunction with ACE inhibition should be standard therapy for all diabetic patients. Optimal glycemic control therapy for patients with heart failure has not been well-defined, and there is an urgent need for randomized clinical trials to determine optimal treatment.
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Key words: Diabetes • Cardiovascular events • Heart failure • Neurohormonal activation • Angiotensin-converting enzyme inhibition • ß-Blockade

Diabetes is a significant independent risk factor for cardiovascular (CV) events and heart failure. Neurohormonal activation plays a fundamental pathophysiologic role in insulin resistance, the development of diabetes, CV events, and the progression of heart failure. There are a substantial number

of patients with diabetes who have had a prior history of CV events and/or who have heart failure. Several clinical trials have shown that specific pharmacologic interventions (ie, angiotensin-converting enzyme [ACE] inhibition, aldosterone antagonists, and ß-blockade) reduce mortality and morbidity in diabetics with prior CV events and/or heart failure. This article examines the roles of these interventions in the optimal management of the diabetic patient with prior CV events or heart failure.

Diabetes and Cardiovascular Events

Diabetes is an independent risk factor for CV events, and its presence along with other risk factors more than doubles the risk for fatal coronary heart disease.[1] Stamler and colleagues[1] assessed predictors of CV mortality in 347,978 men, aged 35 to 57, who were screened as part of the Multiple Risk Factor Intervention Trial (MRFIT). Over 12 years of follow-up there were 603 (11.7%) cardiovascular deaths among 5163 men with diabetes versus 8965 (2.6%) deaths among 342,815 men without diagnosed diabetes. The absolute risk of CV disease-related death was much higher for men with diabetes at every age stratum, ethnic background, and level of risk factor. Mortality rates increased in men with diabetes more than expected on the basis of simply adding the effects of diabetes to other risk factors. The CV risk for a diabetic individual with only one additional risk factor exceeded that for a nondiabetic patient with three risk factors. Diabetes is now considered to be a coronary heart disease risk equivalent because patients with diabetes without a history of myocardial infarction (MI) have demonstrated survival rates similar to those of nondiabetic individuals who have suffered a prior myocardial infarction.[2] Approximately three quarters of deaths in diabetics result from CV disease.[3]

The risk of morbidity and mortality after a CV event is also higher in diabetics. Patients with diabetes who suffered a prior MI had a markedly increased risk of mortality over an 7-year follow-up period in the East-West study in Finland.[2] The 7-year incidence of recurrent MI was 45.0% for patients with diabetes and a prior MI versus 18.8% for patients with a history of MI, but without diabetes.[2] Patients with diabetes who sustain an acute coronary syndrome also have a substantially increased risk of developing new-onset heart failure. In the U.S., out of 8 million persons who have had a prior history of CV events, 15%–25% have diabetes.[3] Thus, there are approximately 2–3 million diabetics in the U.S. with a history of prior CV events.[3]

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Diabetes and Heart Failure

Diabetes is a well-recognized independent risk factor for the development of heart failure. The Framingham Study revealed a 2.4 fold increase in symptomatic heart failure in diabetic men and a 5.0 fold increase in diabetic women, independent of coexisting hypertension or ischemic heart disease.[4] Several mechanisms have been postulated to explain the correlation between diabetes and heart failure. Hypertension, hyperlipidemia, premature atherosclerosis, and left ventricular hypertrophy occur with increased frequency in diabetics and may directly contribute to the development of heart failure.[4-6] Both heart failure and diabetes are believed to share pathophysiologic processes such as neurohumoral activation, endothelial dysfunction, and oxidative stress.[4,5] Diabetes accelerates the development of atherosclerosis, MI, and the resulting ischemic heart failure.[7] Experimental and clinical studies support the existence of a specific diabetic cardiomyopathy, independent of atherosclerosis, related to microangiopathy, metabolic factors, and/or myocardial fibrosis, which may also contribute to the increased incidence of heart failure in diabetics.[7] The extent of metabolic impairment has been shown to be related to the risk of developing heart failure.

In the United Kingdom Prospective Diabetes Study (UKPDS), poor glycemic control was associated with an increased risk of heart failure in patients with type II diabetes.[8] Another study demonstrated that, after adjustment for age and sex, each 1% increase in baseline glycosylated hemoglobin levels correlated with a 12% increased risk of developing heart failure.[9] Thus, diabetes may contribute to heart failure both by promotion of atherosclerosis and coronary artery disease as well as by an independent, diabetes-induced cardiomyopathy.

More recently, heart failure itself has been shown to be associated with the development of insulin resistance and new-onset diabetes. Patients with coronary artery disease and moderate to severe heart failure were found to have a 1.7-fold (95% CI, 1.1-2.6) increase in the rate of development of diabetes compared to coronary artery disease patients

Table 1
Prevalence of Diabetes in Patients with Heart Failure Enrolled in Clinical Trials

Clinical Trial	Patients with diabetes, %
SOLVD	25.8
MERIT-HF	24.5
ELITE-II	24.0
Val-HeFT	25.4
COPERNICUS	25.7
OPTIME-CHF (hospitalized)	44.2
VMAC (hospitalized)	47.0

SOLVD, Studies of Left Ventricular Dysfunction; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; ELITE-II, Evaluation of Losartan in the Elderly; Val-HeFT, Valsartan Heart Failure Trial; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; OPTIME-CHF, Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure; VMAC, Vasodilation in the Management of Acute Congestive Heart Failure.

without heart failure, over 8 years of follow-up.[10] Diabetes predisposes patients to the development of heart failure, and heart failure predisposes patients to the development of diabetes.

The prevalence of diabetes in the adult U.S. population is 4%–6%.[3] The reported percentages of patients with heart failure who have concomitant diabetes is substantially higher, ranging from 15% to 25% among subjects enrolled in randomized clinical heart failure trials (Table 1).[11] The prevalence of diabetes is even higher in the registries of patients hospitalized with heart failure and ranges from 26% to 46%.[12] With an overall prevalence of 5 million persons with heart failure, an estimated 1–2 million patients in the U.S. have heart failure and diabetes.[3]

Diabetes has been demonstrated to increase the risk of mortality in patients with heart failure. An analysis of the prevention and treatment arms of the Studies Of Left Ventricular Dysfunction (SOLVD) identified diabetes as a modest independent predictor of increased mortality in both symptomatic and asymptomatic heart-failure patients.[11] A subsequent analysis of the same database revealed that the increased risk from diabetes was confined to patients with an etiology of ischemic heart failure (relative risk [RR], 1.37; 95% CI, 1.21-1.55; $P < .0001$).[13] In contrast, diabetes conferred no increase in risk to heart-failure patients with a nonischemic etiology (RR, 0.98; 95% CI, 0.76-1.32; $P = .98$).[13] In the Rotterdam Study, among a community cohort of patients found to have heart failure, diabetes was an independent predictor of mortality, along with renal insufficiency and atrial fibrillation.[14] In an analysis of a national cohort of 170,239 elderly patients, who were newly hospitalized with heart failure in 1986 and were followed over the next 6 years, diabetes was an independent predictor of mortality.[15]

Pathophysiologic Role of Neurohormonal Activation

There is substantial evidence that the activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) plays an important pathophysiologic role in diabetes, CV events, and heart failure. Factors that have been shown to contribute to cardiac and vascular injury and the subsequent activation of these neurohormonal systems include hypertension, hyperlipidemia, metabolic syndrome, diabetes, atherosclerosis, acute MI, and heart failure (Figure 1).[5,16]

Injury to the heart and blood vessels as a result of hypertension, insulin resistance, diabetes mellitus, atherosclerosis, and MI activates the RAAS, resulting in prolonged expression of angiotensin II. Angiotensin II acts both as a circulating hormone and as a locally-acting paracrine/autocrine/intracrine factor. Angiotensin II has a multiplicity of adverse effects on the heart, blood vessels, and kidneys.[17] Increased levels of angiotensin II produce elevated resistance to the pumping function of the myocardium, vasospasm, left ventricular remodeling, arrhythmias, alterations in the coagulation-fibrinolysis equilibrium, increased oxidative stress, and pro-inflammatory actions.[17] Angiotensin II also has mitogenic and trophic actions on vascular smooth muscle cells that lead to vascular hypertrophy.[17] The multiple effects of angiotensin II in the kidney have also been well described. Angiotensin II plays a central role in the maintenance of the glomerular filtration rate and sodium balance, increases the resistance of efferent arterioles, enhances tubular reabsorption of sodium in proximal tubules, stimulates the release of aldosterone from the adrenal cortex, increases cell growth, and promotes inflammatory responses.[18] Aldosterone induces cardiac and vascular fibrosis, left ventricular remodeling, vascular inflammation, impaired vascular

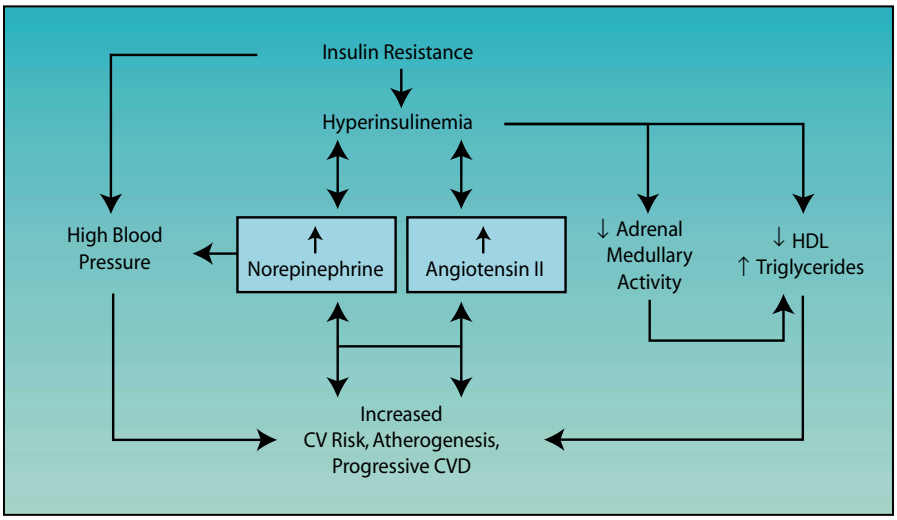

Figure 1. *Role of neurohormonal activation in the risk and progression of cardiovascular disease. Adapted with permission from Reaven et al.[5] CVD, cardiovascular disease; HDL, high density lipoprotein.*

compliance, sympathetic activation, baroreceptor dysfunction, and sodium retention.

Activation of the sympathetic nervous system has been demonstrated in diabetes, CV events, and heart failure.[17,19] Excessive activation of the sympathetic nervous system produces a variety of deleterious CV effects (Figure 2). Injury to the heart results in activation of the sympathetic nervous system. This activation produces a variety of negative effects in the heart, vasculature, and kidneys. In the heart, sympathetic activation promotes ongoing cardiac injury, hypertrophy and adverse remodeling, and increases the risk for life-threatening arrhythmias.[19] Sympathetic nervous system activation also produces arterial and venous vasoconstriction, increasing cardiac preload and afterload.

Catecholamines are also proatherogenic, playing a role in the initiation and propagation of atherosclerosis. The renal effects of activation of the sympathetic nervous system include vasoconstriction, salt and water retention, and increased renin release, which elevates the activity of the RAAS. Sympathetic activation can also increase activation of platelets and precipitate a procoagulant state. All of these actions contribute to the progression of cardiovascular disease.[17,19]

Metabolic Abnormalities and Cardiovascular Risk in Patients with Diabetes

Hyperinsulinemia is associated with increased free fatty acid levels in patients with diabetes. Activation of the sympathetic nervous system in patients with diabetes results in increased myocardial utilization of free fatty acids.[5] This increased free fatty acid metabolism causes increased myocardial oxygen consumption, which can lead to myocardial ischemia, reduced cardiac function, and cardiac arrhythmias.[5,20] An elevated resting heart rate has been shown to be a risk factor for death from coronary heart disease. Festa and colleagues[21] found that the heart rate is significantly associated with fasting insulin, intact proinsulin, split proinsulin, insulin sensitivity, and insulin secretion, supporting the link between heart rate, hyperinsulinemia, and activation of the sympathetic nervous system.

Effects of Neurohumoral Antagonists on Cardiovascular Mortality in Diabetics

Given the multiple deleterious effects on the cardiovascular system of overactivation of the RAAS and sympathetic nervous system, it should not be surprising that blocking these systems with ACE inhibitors, aldosterone antagonists, and ß-blockers has significant beneficial effects on survival in patients with diabetes with prior CV events and/or heart failure (Table 2).

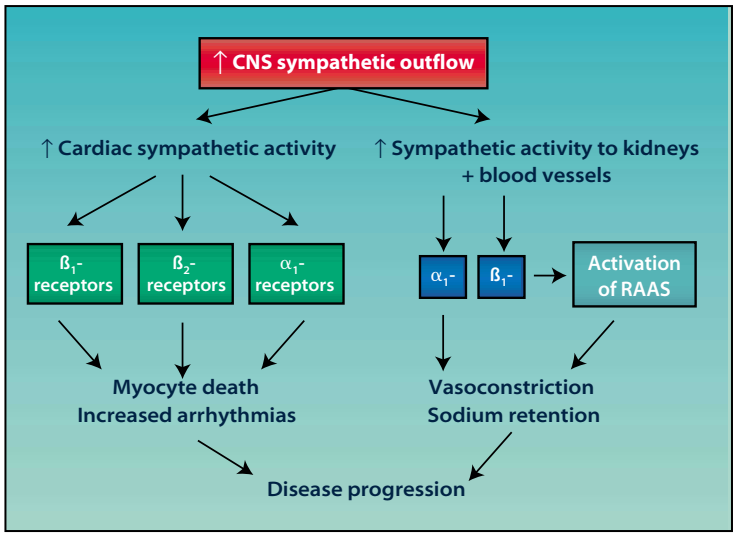

Figure 2. *The role of activation of the sympathetic nervous system in the progression of cardiovascular disease and heart failure. CNS, central nervous system; RAAS, renin-angiotensin aldosterone system.*

Table 2
Cardiovascular Benefits of Angiotensin-Converting Enzyme Inhibition and ß-Blockade

Angiotensin-Converting Enzyme Inhibition	ß-Blockade
• Anti-ischemic	• Reverses cardiac remodeling
– Stimulates endothelial nitric oxide production	• Prevents sudden death
– Reduces myocardial oxygen consumption	• Anti-ischemic
• Antiatherogenic	– Decreases heart rate and blood pressure
• Lowers systemic vascular resistance and mean blood pressure	– Prolongs diastole (filling coronary arteries)
• Reduces cardiac afterload and systolic wall stress	• Decreases myocardial wall stress, which reduces risk of cardiac rupture because of decrease in heart rate and blood pressure
• Attenuates remodeling in heart failure	• Antiatherogenic
	– Reduces sheer stress and endothelial dysfunction

Angiotensin-Converting Enzyme Inhibitor Therapy

The Heart Outcomes Prevention Evaluation (HOPE) study demonstrated the significant benefits of ACE inhibition in patients with documented coronary, cerebral, or peripheral vascular disease.[22] This study assessed the effects of treatment with the ACE inhibitor ramipril versus placebo in 9297 patients who had evidence of vascular disease or diabetes plus one additional CV risk factor and who did not have left ventricular dysfunction or heart failure.[22] Treatment with ramipril resulted in reduced rates of death from CV causes, MI, stroke, death from any cause, revascularization procedures, cardiac arrest, heart failure, and complications related to diabetes. In terms of heart failure, ramipril treatment reduced the risk of new-onset heart failure by 23%.[22]

A substudy of the HOPE trial, the MICRO-HOPE study, examined whether ramipril could lower the risks of CV disease and renal disease in patients with diabetes.[23] The analysis included 3577 patients with diabetes who had been included in the HOPE study. Ramipril reduced the risk of total mortality by 24%, MI by 22%, stroke by 33%, CV death by 37%, and revascularization by 17% in diabetics (Figure 3).[23] The HOPE and MICRO-HOPE studies provided compelling evidence that ACE inhibition could benefit patients with diabetes and prior CV events.

In patients with symptomatic heart failure, there is a wealth of data demonstrating the benefits of ACE inhibitor therapy. Garg and Yusuf[24] analyzed 32 randomized, controlled trials of ACE inhibitor therapy in patients with symptomatic congestive heart failure and found that ACE inhibitor treatment resulted in a 23% reduction in mortality. A more recent analysis of major clinical trials of ACE inhibitors further showed that diabetic patients with heart failure experience benefit from therapy with ACE inhibitors similar to that of their nondiabetic counterparts (Table 3).[25]

Figure 3. *Cardiovascular events in diabetic patients who received treatment with either ramipril or placebo in the Heart Outcomes Prevention Evaluation (HOPE) study. The graphs show the proportion of patients experiencing cardiovascular events and the reduction in relative risk (RR) for each of these events with ramipril therapy compared to placebo. Adapted with permission from the Heart Outcomes Prevention Evaluation (HOPE) Study Investigators.*[23]

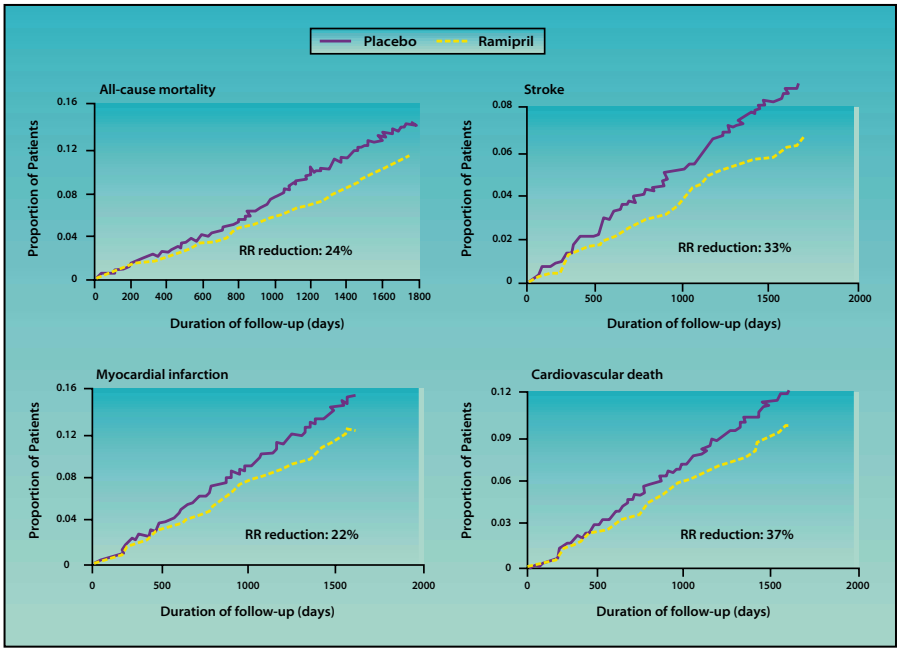

Table 3
Relative Risks of Using Angiotensin-Converting Enzyme Inhibitors in Diabetic and Nondiabetic Patients with Heart Failure: Data from a Meta-Analysis of Clinical Trials

		Analysis of Relative Risks				
Study	Total, N	Nondiabetic Patients, n	Diabetic Patients, n	Relative Risk, Nondiabetic (95% CI)	Relative Risk, Diabetic (95% CI)	Ratio of Relative Risks (95% CI)
CONSENSUS	253	197	56	0.64 (0.46-0.88)	1.06 (0.65-1.74)	1.67 (0.93-3.01)
SAVE	2231	1739	492	0.82 (0.68-0.99)	0.89 (0.68-1.16)	1.09 (0.79-1.50)
SMILE	1556	1253	303	0.79 (0.54-1.15)	0.44 (0.22-0.87)	0.56 (0.25-1.22)
SOLVD-Prevention	4228	3581	647	0.97 (0.83-1.15)	0.75 (0.55-1.02)	0.77 (0.54-1.09)
SOLVD-Treatment	2569	1906	663	0.84 (0.74-0.95)	1.01 (0.85-1.21)	1.21 (0.97-1.50)
TRACE	1749	1512	237	0.85 (0.74-0.97)	0.73 (0.57-0.94)	0.87 (0.65-1.15)
Random Effects Pooled Estimate	12,586	10188	2398	0.85 (0.78-0.92)	0.84 (0.70-1.00)	1.00 (0.80-1.25)

CI, confidence interval; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; SAVE, Survival and Ventricular Enlargement; SMILE, Survival of Myocardial Infarction Long-term Evaluation; SOLVD, Studies of Left Ventricular Dysfunction; TRACE, Trandolapril Cardiac Evaluation. Adapted with permission from Shekelle et al.[25]

Aldosterone Receptor Antagonist Therapy

ACE inhibitor therapy incompletely suppresses aldosterone production. Thus, aldosterone blockade in patients with prior CV events and/or heart failure theoretically might provide a benefit in addition to ACE inhibitor therapy. The Randomized Aldactone Evaluation Study (RALES) was designed to determine if the aldosterone antagonist spironolactone, when added to standard heart-failure therapy, would improve the prognosis in patients with severe heart failure.[26] The trial randomized 1663 patients who had a left ventricular ejection fraction (LVEF) ≤ 35% and New York Heart Association (NYHA) class IV heart failure in the prior 6 months.[26] All patients at the time of enrollment were being treated with an ACE inhibitor and a loop diuretic. After a mean follow-up period of 24 months, mortality in the spironolactone treatment arm was significantly less than that in the placebo arm, representing a relative reduction of 30%.[26] In addition, patients benefited from treatment without significant increases in the risk of serious hyperkalemia. In routine clinical practice, however, it is necessary to closely monitor patients for hyperkalemia after initiating therapy with a low dose of spironolactone to avoid this adverse effect.

A recent analysis of major clinical trials of ACE inhibitors showed that diabetic patients with heart failure experience benefit from therapy with ACE inhibitors similar to that of their nondiabetic counterparts.

The RALES trial did not report separate data for diabetic patients with heart failure. However, a more recent study of aldosterone blockade, the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), did look at diabetic patients as a specific subgroup.[27] This study enrolled patients post-MI with an LVEF ≤ 40% with a symptom of heart failure, or asymptomatic patients with diabetes. All-cause mortality was reduced by 15% in patients treated

with eplerenone. Patients with diabetes (n = 2122) also benefited from aldosterone blockade, and there was no significant heterogeneity with respect to the mortality benefit between diabetic and nondiabetic patients.[27] Thus, the use of aldosterone blockage lowered mortality beyond standard therapy in patients with mild-to-moderate as well as severe heart failure and in diabetics post-MI with left ventricular dysfunction. This survival benefit of aldosterone antagonists is additive to ACE inhibitor and ß-blocker therapy.

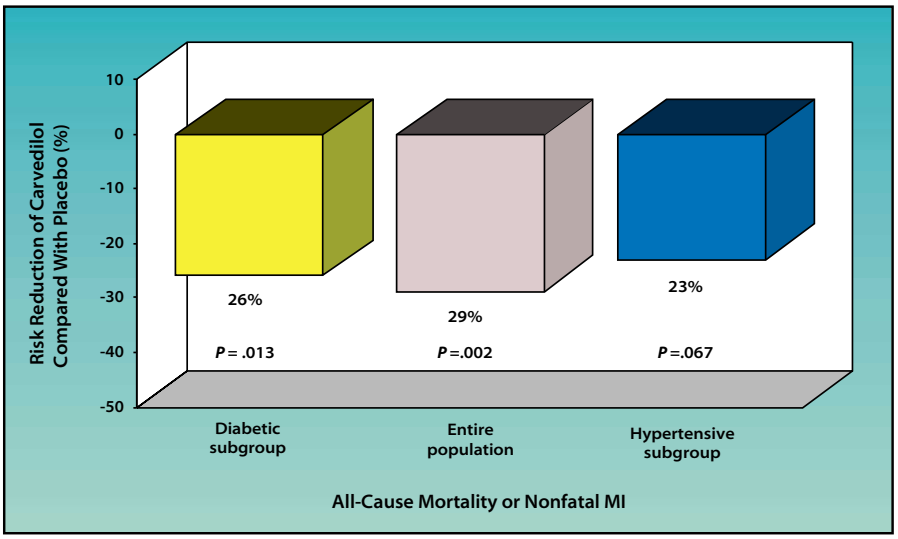

Figure 4. *Results of the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial. Carvedilol significantly reduced the risk of all-cause mortality or nonfatal myocardial infarction (MI) in post-MI patients with left ventricular dysfunction, with or without heart failure symptoms, as well as those with either diabetes or hypertension. Data from Dargie.*[30]

ß-Blocker Therapy

Because sympathetic activation plays a key role in the pathophysiology of diabetes, CV events, and heart failure, ß-blocker therapy would be expected to provide substantial benefit. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that ß-blockade can prevent heart failure in the diabetic patient.[28] Patients enrolled in the study received either a ß-blocker or an ACE inhibitor as their main treatment. The reduction in risk of heart failure in patients on tight control of blood pressure with either of these therapies was a remarkable 56%.[28]

ß-Blocker therapy provides substantial protection to patients after CV events. Freemantle and colleagues carried out a meta-analysis of outcomes from clinical trials in which post-MI patients were treated with a ß-blocker.[29] An analysis of results from 82 randomized short- or long-term trials that compared ß-blockers with control therapy and included a total of 54,234 patients indicated that long-term treatment with a ß-blocker significantly reduced the risk for mortality by 23% versus control therapy. An analysis of results from the long-term studies did show a trend for reduced effectiveness for ß-blockers with cardioselectivity and with intrinsic sympathomimetic activity.[29]

The effectiveness of one of the newer ß-blockers, carvedilol (a nonselective ß-blocker with α_1-blocking capabilities), in reducing morbidity and mortality in patients with left ventricular dysfunction after acute MI has been evaluated in the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial.[30] In this trial, 1959 patients with acute MI and left ventricular systolic dysfunction (ejection fraction ≤ 40%), with or without heart failure symptoms, were treated with carvedilol or placebo in addition to their usual therapy. Almost all patients in CAPRICORN were given ACE inhibitors, > 86% were on aspirin, and 45% received reperfusion therapy.[30] Study results showed that, compared with placebo, carvedilol significantly decreased the risks for all-cause mortality, cardiovascular mortality, nonfatal MI, and all-cause mortality plus nonfatal MI. An additional analysis of the results of CAPRICORN indicated that the benefits of carvedilol were not diminished in patients with either diabetes or hypertension. The reduction in risk for all-cause mortality or nonfatal MI for the entire population in this trial was 29% versus 26% for patients with diabetes and 23% for those with hypertension (Figure 4).[30]

The reduction in risk of heart failure in diabetic patients on tight control of blood pressure with either a ß-blocker or an ACE inhibitor as their main treatment was a remarkable 56%.

In addition to reducing post-MI mortality, ß-blocker therapy also significantly decreased mortality in patients with diabetes and coronary artery disease. Jonas and colleagues[31] assessed 3-year mortality in 2723 patients with type 2 diabetes who received (n = 911) or did not receive

(n = 1812) ß-blocker therapy in the Bezafibrate Infarction Prevention (BIP) study. Total mortality was reduced by 44% and cardiac mortality was reduced by 42% for the patients who received ß-blockers compared with those who did not. The 3-year survival curves showed significant differences in mortality with increasing divergence.[31]

Studies have shown that ß-blockade also reduces mortality in patients with established heart failure. ß-blockers have been evaluated in more than 10,000 heart-failure patients in more than 20 published clinical trials and have demonstrated a ≥ 34% reduction in the risk of mortality in mild, moderate, and severe heart failure (Table 4).[25,32-35]

Table 4
Effect of ß-Blockade on Overall Mortality in Heart-Failure Patients in Major Clinical Trials

Study	Drug	Heart-Failure Severity	Target Dosage, mg/day	Effect on Mortality
U.S. Carvedilol trial[33]	Carvedilol	Mild/moderate/ severe	6.25 to 25 bid	↓ 65% ($P < .001$)
CIBIS-II[35]	Bisoprolol	Moderate/ severe	10 qd	↓ 34% ($P < .0001$)
MERIT-HF[34]	Metoprolol succinate	Mild/ moderate	200 qd	↓ 34% ($P = .0062$)
COPERNICUS[32]	Carvedilol	Severe	25 bid	↓ 35% ($P = .0014$)

U.S. Carvedilol trial, U.S. Carvedilol Heart Failure Study Group; CIBIS-II, The Cardiac Insufficiency Bisoprolol Study II; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival. Data from Packer et al,[32] Packer et al,[33] MERIT-HF Study Group,[34] CIBIS-II Investigators and Committees.[35]

The safety and efficacy of ß-blockade in diabetic and nondiabetic patients with symptoms of severe heart failure were demonstrated in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study.[32] This study enrolled more than 2200 patients with heart-failure symptoms at rest or on minimal exertion (NYHA class IV) and an ejection fraction of < 25% to assess the effects of ß-blockade in patients with severe heart-failure symptoms.[32] The study was stopped early because carvedilol therapy in this population resulted in a dramatic reduction (35%) in all-cause mortality and a significant reduction (24%) in the combined risk of death or hospitalization.[32] Furthermore, the benefits of carvedilol were seen within the first 8 weeks across all patient subgroups, including the patients at highest risk.[32]

Some studies of ß-blockade in patients with heart failure have provided data for diabetic versus nondiabetic patients. Approximately 25% of the study subjects were diabetic patients in the Metoprolol CR/XL Randomised Intervention Trial in Heart Failure (MERIT-HF, which assessed the safety and efficacy of long-acting metoprolol), the U.S. Carvedilol Heart Failure Study Group trial, and the COPERNICUS trial (which assessed the safety and efficacy of carvedilol).[32-34] In the COPERNICUS and the U.S. Carvedilol trials, there was a significant reduction in all-cause mortality in patients with diabetes who received carvedilol therapy. In fact, in the COPERNICUS trial, the relative reduction in the risk of all-cause mortality was 35%. Whether the positive results observed with carvedilol can be generalized to other ß-blockers is not clear. In the MERIT-HF trial, there was a trend toward improvement in all-cause mortality in diabetic patients who received metoprolol therapy; however, this improvement was not statistically significant. Similarly, in the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), which examined the effects of bisoprolol in heart-failure patients, there was a trend toward improvement in the reduction of risk of mortality in diabetic patients treated with bisoprolol, but this improvement did not reach statistical significance.[35]

ß-Blockers have different pharmacological profiles that may impact clinical outcomes. Metoprolol, bisoprolol, and carvedilol reduced mortality in heart-failure patients, whereas bucindolol had no mortality benefit, and xamoterol increased mortality.[36,37] Metoprolol and bisoprolol have a high specificity for the $ß_1$-adrenergic receptor. Carvedilol blocks $ß_1$-, $ß_2$-, and α_1-adrenergic receptors. There is a shift in the ratio of receptors in the damaged heart versus the normal heart, with a greater proportion of $ß_2$- and α_1-receptors found in the damaged heart. Therefore, carvedilol may have an improved ability to antagonize the cardiotoxic effects of the adrenergic system in the failing heart. Several small studies have suggested that carvedilol is more effective than metoprolol in reversing ventricular remodeling, increasing left ventricular systolic function, and decreasing cardiac sympathetic drive.[38] Whether these differences would translate into differences in survival in patients with chronic heart failure is not known.

The Carvedilol Or Metoprolol European Trial (COMET) was designed to compare directly the effects of carvedilol and metoprolol on mortality and morbidity in patients with mild to severe chronic heart failure.[39] The study was performed in 15 European countries, involving 341 centers, and enrolled 3029 patients with NYHA class II to IV heart failure. Patients were randomized to carvedilol (target dose, 25 mg twice daily) or metoprolol tartrate (target dose, 50 mg twice daily). These doses were chosen because it was expected that they would produce a comparable degree of $ß_1$-adrenergic blockade in both groups. The mean LVEF was 26% at baseline; 99% of the patients were already taking diuretics, and 98% were receiving ACE inhibitors or angiotensin-receptor antagonists; 61% were also on digoxin, and 11% on spironolactone. The average daily dose of carvedilol received in the trial was 42 mg, and the average daily dose of metoprolol was 85 mg. There were similar reductions in resting heart rate and blood pressure compared to baseline over the duration of the trial, except for very mild differences in the first few months.[39]

The coprimary endpoint of the trial, all-cause mortality, showed a 17% relative reduction in risk with carvedilol relative to metoprolol. Mortality was reduced 39.5% with carvedilol and 33.9% with metoprolol (OR, 0.83; 95% CI, 0.74-0.93; $P < .0017$).[39] The annual mortality rate was reduced 10% in the carvedilol group and 8.3% in the metoprolol group. The survival advantage with carvedilol translated to a prolongation of median survival by an extra 1.4 years of life. There were similar reductions in the risk for sudden death and progressive heart-failure deaths with carvedilol. There was no significant heterogeneity in response in clinically relevant subgroups of patients, including men and women as well as those with and without coronary artery disease. Both diabetics and nondiabetics had a lower mortality risk with carvedilol.[39]

The favorable outcome with carvedilol could be attributed to the blockade of both $ß_1$- and $ß_2$-adrenergic receptors, the inhibition of α-adrenergic receptors, a greater anti-ischemic effect, the inhibition of apoptosis, or an antioxidant action. This trial convincingly demonstrated that carvedilol produces benefits in heart failure beyond those of $ß_1$-blockade alone. The calculated number of patient-years of treatment to save one life is 59.[39] Although the question has been raised whether the use of the metoprolol CR/XL preparation at higher doses might have produced different results, this remains speculative and would need to be demonstrated in a prospective, randomized mortality trial. As a result of the COMET study, carvedilol is clearly the preferred ß-blocker for the treatment of chronic heart failure.

Underutilization of ß-Blockers in Diabetic Patients

Even with the wealth of convincing data accumulated to date, evidence-based therapies for diabetic patients with prior CV events and/or heart failure continue to be underutilized. Concerns that may preclude physicians from prescribing ß-blockers for diabetic patients with prior CV events or heart failure include the resulting increased incidence of hypoglycemia, worsening dyslipidemia, and decreased insulin sensitivity. The risk of hypoglycemia with ß-blocker therapy is smaller, with greatest concern for those patients who are insulin dependent and those with a history of hypoglycemia. This concern, however, should perhaps be greater for insulin-dependent patients and those with a history of hypoglycemia.

Although evidence from several clinical trials justifies concerns about the effects of ß-blockade on glucose metabolism, lipids, and renal blood flow, it is important to note that not all ß-blockers, particularly vasodilating ß-blockers, were studied in these trials. ß-blockers have different pharmacologic properties based primarily on the types of adrenergic receptors they inhibit. Thus, newer, vasodilating ß-blockers, such as carvedilol, which have inhibitory effects on α_1-, $ß_1$-, and $ß_2$-receptors, may be blunting the negative metabolic effects in diabetic heart-failure patients. Studies pertaining to diabetic hypertensive patients show that many of the following benefits of carvedilol may be operative: 1) mediation of vasodilation, which can lead to improvements in both dyslipidemia and insulin resistance; 2) decreased plasma triglyceride concentrations; 3) improved renal blood flow and reduction of peripheral vascular resistance; 4) improvements in insulin sensitivity; and 5) reduction in microalbuminuria.[40-42]

These positive effects relating to the specific concerns cited above about diabetic patients with heart failure, coupled with the proven mortality and morbidity benefits of neurohormonal blockade in all patients with heart failure, support the use of carvedilol in conjunction with ACE inhibition as standard therapy for all diabetic patients with heart failure.

Improving Glycemic Control in the Patient with Diabetes

Control over blood glucose is central to the management of patients with diabetes, and it is reasonable to believe that it might also improve

cardiovascular outcomes for individuals with this disease. However, results from the United Kingdom Prospective Diabetes Study (UKPDS 33) failed to demonstrate benefit with the agents studied.[43] The UKPDS investigators compared the effects of intensive blood-glucose control with either sulfonylureas or insulin versus conventional treatment on the risk of microvascular and macrovascular complications in 3867 newly diagnosed patients with type 2 diabetes. Over 10 years of follow-up, intensive therapy reduced glycosylated hemoglobin (HbA_{1c}) to 7.0% versus 7.9% for the patients who received conventional therapy; the intensive therapy significantly decreased the risk for any diabetes-related end point, any diabetes-related death, and microvascular disease. However, reductions in risks for MI and all-cause mortality with intensive treatment versus conventional therapy did not reach statistical significance. Although it is likely that newer agents such as thiazolidinediones will favorably impact the risk of CV events, this will need to be demonstrated in clinical trials.[7]

Management of Diabetes in Heart-Failure Patients

There have been no randomized clinical trials of strategies to manage diabetes in patients with heart failure.

Sulfonylurea agents, which work by stimulating endogenous insulin production by closure of potassium adenosine triphosphate channels, potentially abolish ischemic preconditioning and leave the myocardium more susceptible to injury.

Each of the major classes of diabetic therapies has potentially deleterious effects in heart-failure patients.[7] The administration of exogenous insulin may contribute to heart-failure disease progression and increase the mortality risk. Insulin has been associated with increased sympathetic nervous system activation, increased vascular resistance, increased cardiac and vascular hypertrophy, and endothelial dysfunction.[5,7] Sulfonylurea agents, which work by stimulating endogenous insulin production by closure of potassium adenosine triphosphate (ATP) channels, potentially abolish ischemic preconditioning and leave the myocardium more susceptible to injury.[7] Moreover, by further increasing insulin levels these agents could worsen outcomes. This class of medications was found to be associated with an increased incidence of cardiovascular events in the University Group Diabetes Program (UGDP),[44] yet these results were not validated by the UKPDS 33 study.[43] Thiazolidinediones, acting as peroxisome proliferator-activated receptor γ-agonists, improve insulin sensitivity. These agents have effects, including decreased plasma insulin levels, improved endothelial function, decreased vascular inflammation, and decreased C-reactive protein levels,

TZDs have effects, including decreased plasma insulin levels, improved endothelial function, decreased vascular inflammation, and decreased C-reactive protein levels, that are potentially beneficial in patients with heart failure.

Main Points

- In the United Kingdom Prospective Diabetes Study (UKPDS), poor glycemic control was associated with an increased risk of heart failure in patients with type II diabetes.
- Neurohormonal activation plays a fundamental pathophysiologic role in insulin resistance, the development of diabetes, cardiovascular (CV) events, and the progression of heart failure.
- Several major clinical studies have shown that specific pharmacologic interventions such as angiotensin-converting enzyme inhibition, aldosterone antagonists, and ß-blockade reduce mortality and morbidity in diabetic patients with prior CV events and/or heart failure.
- These pharmacologic interventions are underutilized largely because of physicians' concerns about their potentially deleterious effects.
- Different ß-blockers have different metabolic effects; physicians should be aware of these differences when they select a therapy for diabetic patients with prior CV events or heart failure.

that are potentially beneficial in patients with heart failure.[45] The use of these agents, however, has been associated with fluid retention and increased risk of admission for heart failure. The biguanides, such as metformin, which work in part by decreasing glucose production by the liver, are also considered potentially unsafe in heart-failure patients. The renal dysfunction common in heart failure raises concerns regarding the risk of lactic acidosis.[46] Randomized clinical trials are urgently needed to determine the safety and effectiveness of each of the available diabetic therapies in heart-failure patients and to define the most optimal treatment strategy.

Conclusions

Diabetic patients are at an elevated risk for CV events and heart failure, and the risk of morbidity and mortality in diabetics with prior CV events and/or heart failure is high. Clinical trials have demonstrated that combined neurohormonal blockade with the use of ACE inhibitors, aldosterone antagonists, and ß-blockers is essential in the treatment of diabetic patients with prior CV events or heart failure. Combined neurohormonal blockade is especially important in patients with diabetes because they are at an increased risk for morbidity and mortality. ACE inhibitors and ß-blockers have been shown to be useful in diabetic patients across the CV disease continuum—before a CV event, for secondary prevention, and in heart failure. Different ß-blockers have different metabolic effects that may be important for physicians to be aware of when they select a therapy for diabetic patients with prior CV events or heart failure. The use of ACE inhibitors, aldosterone antagonists, and ß-blockers for the treatment of these diabetics patients represents a major therapeutic advance. Every effort should be made to apply these life-saving therapies in all diabetic patients with prior CV events and/or heart failure in the absence of contraindications or intolerance. Optimal glycemic control therapy for patients with heart failure has not been well defined, and there is an urgent need for randomized clinical trials to determine this optimal therapy. ■

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