Pharmacological Treatment and Prevention of Heart Failure in the Diabetic Patient

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Diabetes is a strong and independent risk factor for the development of heart failure, and once heart failure occurs, patients with diabetes have a much poorer prognosis than do those without diabetes. This difference has been explained by the existence of a distinct diabetic cardiomyopathy characterized by morphologic and structural changes to the myocardium and coronary vasculature. Despite diabetic cardiomyopathy, the pharmacologic treatment of heart failure in diabetic patients is similar to that in patients without diabetes, and in general, the clinical response of diabetic patients to drug therapies for heart failure is similar, if not superior, to that of nondiabetic patients. Subgroup analyses from large clinical studies have shown that angiotensin-converting enzyme inhibitors not only reduce mortality in diabetic patients with heart failure, but also reduce the incidence of heart failure in at-risk diabetic patients. ß-Blockers remain underused in the diabetic population despite overwhelming evidence of their efficacy in treating heart failure in patients with diabetes.

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Key words: Heart failure • Diabetes • ACE inhibitors • ß-blockers

Heart failure and its attendant morbidity and mortality are growing problems in the United States. In the most recent survey published by the American Heart Association,[1] it was estimated that about 2,300,000 men and 2,400,000 women are living with congestive heart failure (CHF). Each year 978,000 patients are hospitalized for treatment of CHF, another 550,000 new cases of CHF are diagnosed, and 285,000 patients with CHF die. The annual direct costs and indirect costs (lost productivity due to morbidity and mortality) associated with CHF are estimated to be $21 billion.

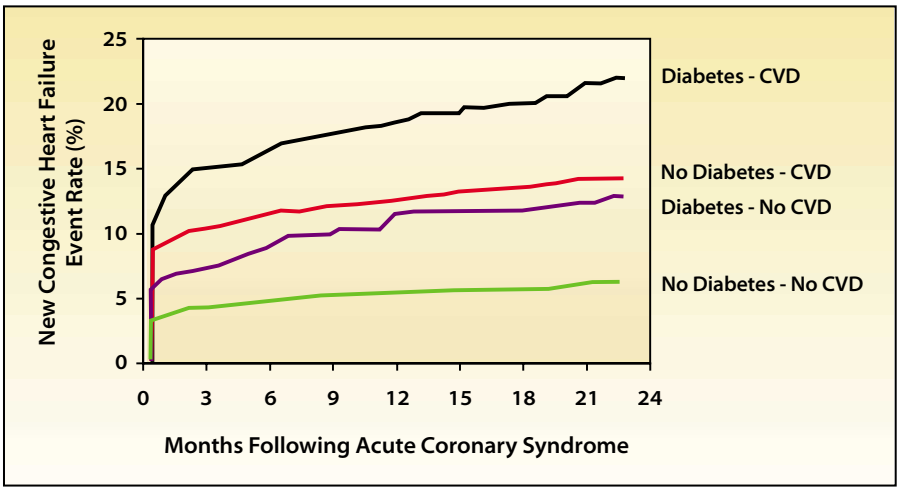

Figure 1. *Prevalence of heart failure in patients with type 2 diabetes following acute coronary syndrome. CVD indicates previous cardiovascular disease. Adapted with permission from Malmberg et al.*[4]

Although myocardial infarction and hypertension are the most common risk factors associated with CHF, diabetes mellitus is also a strong and independent risk factor.[2] Diabetes mellitus not only increases the risk of developing CHF, but also adversely affects the prognosis of those diabetic patients with CHF. An example of the impact of diabetes was reported by Shindler and colleagues,[3] who examined the Studies Of Left Ventricular Dysfunction (SOLVD) Trials and Registry and showed that diabetic patients with symptomatic heart failure or asymptomatic left ventricular dysfunction had an increased risk of all-cause mortality (risk ratio = 1.29; CI, 1.10-1.50) and hospitalization for CHF (risk ratio = 1.55; CI, 1.32-1.82) during the average 37 months of follow-up compared to non-diabetics.

Following an acute myocardial infarction, the presence of diabetes increases the risk of developing new CHF. Using the Organization to Assess Strategies for Ischemic Syndromes (OASIS) Registry, which provided long-term data on 8013 patients with unstable coronary syndromes in six countries, Malmberg and colleagues showed that diabetes increases the risk of developing new CHF following hospitalization for unstable angina or non–Q-wave myocardial infarction by 82% ($P < .001$). In diabetic patients with a history of previous coronary heart disease, the risk was considerably higher (Figure 1).[4]

Because of the increased morbidity and mortality of CHF in diabetic patients, treatment of both CHF and diabetes in these patients presents unique challenges. This review will focus on the current evidence-based medical treatment of CHF in diabetic patients and will also address the issues and controversies regarding the various strategies for controlling hyperglycemia in these patients. The primary prevention of CHF in diabetes will also be considered.

Factors Responsible for the Increased Incidence of Heart Failure in Diabetic Patients

The fundamental causes of heart failure are similar in diabetic and nondiabetic patients. The primary cause of chronic CHF is previous myocardial infarction and its resultant loss of contracting myocardium. Other influences include hypertension, left ventricular hypertrophy, and valvular heart disease.[2] While diabetes is also an important risk factor for CHF,[2] it is rarely associated with CHF independently of other risk factors, and in fact appears to act synergistically with them.

The structure and functioning of the diabetic heart are often abnormal, predisposing it to the development

Table 1
Comparison of Classes of Drugs Used to Treat Heart Failure in Diabetic Patients

Drug Class	Example(s)	Survival Benefit	Prevention Benefit	Comments
Inotropes	Digoxin	No[10]	No data available	Not useful in diastolic dysfunction
Diuretics	Hydrochlorothiazide and Furosemide	No data available	No data available	Required to treat edema and congestion
ACE inhibitors	Lisinopril Trandolapril Ramipril	Yes[14,15]	Yes[16]	Cough occurs in about 10%, rare angioedema
ARBs	Losartan	No data available	Yes[20,21]	Reserved for patients who cannot tolerate ACE inhibitors
Beta-blockers	Propranolol Metoprolol	Yes[30]	No data available	

ACE, angiotensin-converting enzyme; ARBs, angiotensin II–receptor blockers.

of heart failure. The existence of this distinct diabetic cardiomyopathy has been debated,[5] but most now agree that the increased susceptibility of the diabetic patient to the development of CHF is in part due to morphological changes to the myocardium that occur in diabetic patients.[6] Left ventricular mass is greater in diabetic patients than in glucose-tolerant patients, a difference accounted for by increased myocardial fibrosis.[7] Although cardiac output may not be affected, left ventricular function in diabetic hearts is depressed, as ascertained by echocardiographic determination of endocardial and midwall shortening. Increased fibrosis in the diabetic myocardium is likely responsible for this systolic dysfunction, and because fibrosis decreases left ventricular compliance, it contributes to slowing of myocardial relaxation and impaired diastolic filling, thus leading to diastolic dysfunction.[6]

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Pharmacological Treatment of Heart Failure in the Diabetic Patient

As is true in the nondiabetic patient, heart failure needs to be diagnosed early in the disease process so that treatment can be started to alleviate the symptoms and slow its progress. The goals of treatment of left ventricular dysfunction and heart failure in diabetic patients are the same as in nondiabetic patients: relieving congestion, slowing the progression of the disease, and prolonging survival.[8] In general, the clinical response of diabetic patients to drug therapies for heart failure is similar to, if not better than, that of nondiabetic patients.[8]

Drug Therapy

Inotropic Drugs. Inotropic agents, like digoxin, have been used to treat CHF for decades, but their use remains controversial.[9] Although these agents clearly increase myocardial contractility and raise cardiac output in the failing heart, they have little effect on long-term survival. In the Digitalis Investigation Group (DIG) Study, digoxin reduced the rate of hospitalization for worsening heart failure but had no effect on mortality.[10] Diabetic patients made up 28% of the DIG study population, and the results were similar in this subgroup.[8] Because other drugs have shown a survival benefit in the treatment of heart failure in diabetes, the continued use of these cardiac glycosides should be restricted to patients who are already receiving contemporary drug therapy.[9]

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Inotropic agents are not useful in treating heart failure due to isolated diastolic dysfunction.

Diuretics. Diuretics are commonly used in patients with heart failure to reduce volume and to avoid volume overload. Thiazide diuretics can impair glucose tolerance and the loop diuretics can lead to hypokalemia in the presence of renal insufficiency. However, the use of diuretics is mandatory when treating edema and pulmonary congestion of heart failure.

Angiotensin-Converting Enzyme Inhibitors. Angiotensin-converting enzyme (ACE) inhibitors have been clearly and convincingly shown to reduce the morbidity and mortality associated with left ventricular dysfunction. In the COoperative North Scandinavian Enalapril SUrvival Study (CONSENSUS),[11] captopril reduced mortality by 30% in patients with severe CHF, and in the SOLVD trials,[12,13] enalapril was associated with both a reduction in mortality and a slowing in the progression of left ventricular dysfunction. However, these studies were not large enough to rigorously address the question of whether ACE inhibitors could influence the morbidity and mortality associated with diabetes and heart failure. Several more recent studies have addressed this question[14,15] and have shown that ACE inhibitors are indeed effective in diabetic patients.

The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI–3) trial was a large study designed to determine if the ACE inhibitor lisinopril would reduce mortality when started within 24 hours of the onset of symptoms of an acute myocardial infarction.[14] The beneficial effect of ACE inhibition was confined to the diabetic population, in which lisinopril reduced 6-week mortality by nearly 30% compared with placebo. In the nondiabetic subset, lisinopril did not significantly affect 6-week mortality compared with placebo (5.6% vs 5.9%). In spite of its large effect on mortality in the diabetic subgroup, lisinopril had no effect on the incidence of heart failure or other signs

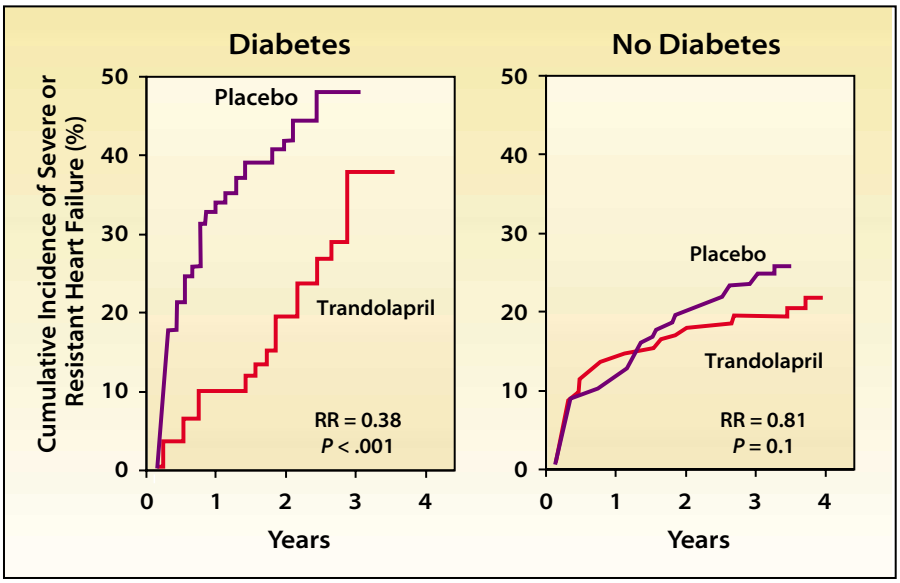

Figure 2. *Effect of angiotensin-converting enzyme inhibition with trandolapril on progression to severe or resistant heart failure in diabetic and nondiabetic patients with left ventricular dysfunction after acute myocardial infarction in the TRACE study. Adapted with permission from Gustafsson et al.*[15]

of left ventricular dysfunction.

In the TRandolapril Cardiac Evaluation (TRACE) study,[15] patients with an enzyme-confirmed acute myocardial infarction and left ventricular dysfunction (LVEF ≤ 35%) present 2 to 6 days after the myocardial infarction were randomized to receive either the ACE inhibitor trandolapril or matching placebo. All-cause mortality for patients treated with placebo was higher in the diabetic group (61%) than in the nondiabetic group (39%) during the average 26-month follow-up. In the diabetic patients treated with trandolapril, mortality was reduced to 45% (P = .01), and in the nondiabetic patients, mortality was reduced to 33% (P = .02). In the diabetic group, trandolapril reduced the rate of progression to severe heart failure by 62% (P < .001), a beneficial effect not seen in those without diabetes (Figure 2).

Of great interest to the diabetic population are the results of the Heart Outcomes Prevention Evaluation (HOPE) study, which suggest that ACE inhibitors may prevent heart failure in diabetic patients. The HOPE study[16] was designed to determine if the ACE inhibitor ramipril (10 mg/day) would prevent cardiovascular events in diabetic patients with a history of coronary artery disease or at least one additional risk factor (eg, hypertension, elevated low-density lipoprotein cholesterol). A total of 3577 diabetic patients with an average age of 65.4 years were enrolled in the study, and more than two thirds had a history of cardiovascular disease, but none had heart failure at baseline. During the 4.5-year study, not only did ramipril reduce the prespecified combined primary outcome (myocardial infarction, stroke, or cardiovascular death) by 25% (P = .0004) compared with placebo, it reduced the incidence of heart failure by 20% (P = .019) (Figure 3). However, the proportion of patients requiring hospitalization for heart failure was not affected by ramipril (4.5% in each treatment group). Overall, the protective effect of ramipril treatment was similar in both diabetic patients and in those without the disease.

The mechanism by which ACE inhibitors reduce morbidity and mortality in diabetic patients who are at high risk for heart failure is not fully understood. However, ACE inhibitors are known to positively influence many cardiovascular factors that are thought to put the postinfarction diabetic patient at higher risk. For example, ACE inhibitors improve fibrinolytic balance and reverse endothelial dysfunction in patients with atherosclerosis and are known to prevent ventricular remodeling and reduce ventricular mass in hypertensive patients. It is generally accepted that all patients with diabetes and with signs of left ventricular dysfunction or heart failure should be treated with an ACE inhibitor, and that the dose should be maximized based on the doses used in the clinical trials.[8]

ACE inhibitors are very well tolerated. The most common adverse event is a persistent dry cough, which occurs in about 10% of patients. A rare, but potentially life-threatening adverse effect is angioedema, which has been reported to occur with an incidence of less than 0.5%. Although ACE inhibition improves renal blood flow and stabilizes glomerular filtration rate in patients

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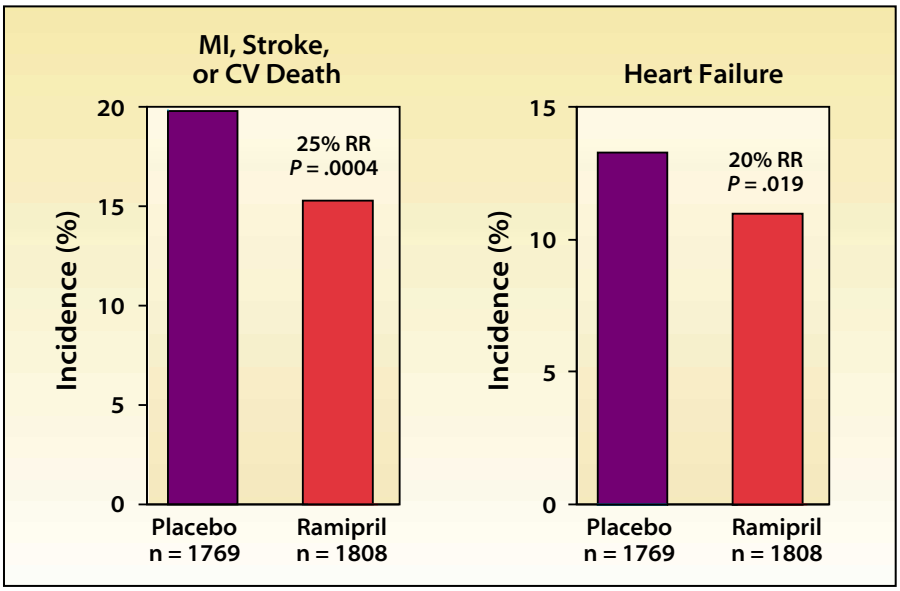


Figure 3. *Effect of angiotensin-converting enzyme inhibition with ramipril on incidence of major cardiovascular events and incidence of heart failure in diabetic patients. MI, myocardial infarction; CV, cardiovascular; RR, risk reduction. Data from Heart Outcomes Prevention Evaluation Study Investigators.*[16]

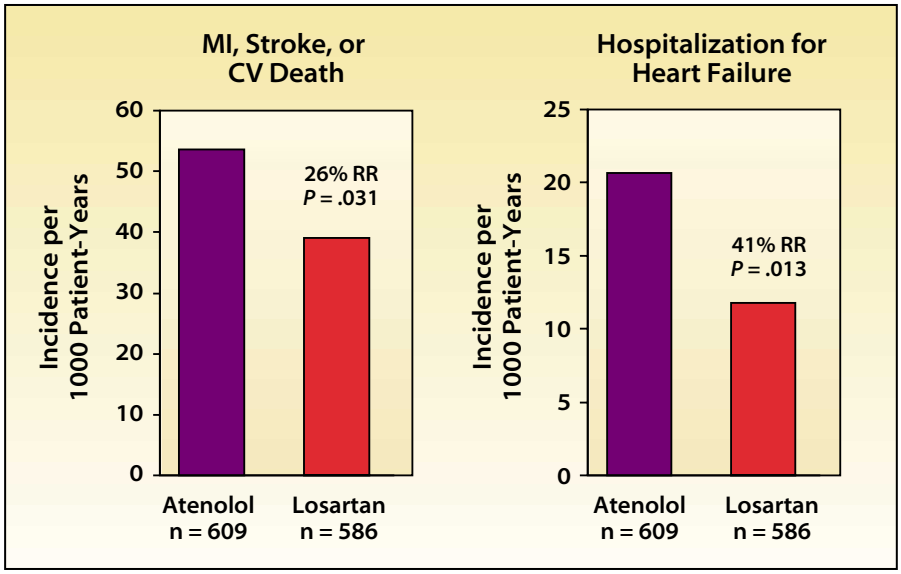
with heart failure, it can be associated with acute renal failure, especially in patients who are hypotensive or who are volume depleted.[17] Serum potassium levels should be monitored carefully, because hyperkalemia has been reported in diabetic patients and those with heart failure.[17]

Angiotensin II–Receptor Blockers. Angiotensin II–receptor blockers (ARBs) interrupt the renin-angiotensin system by blocking the type 1 angiotensin II receptor. In two major studies in patients with chronic heart failure, ARBs have been roughly equivalent to ACE inhibitors in preventing morbidity and mortality associated with heart failure.[18,19] In the VALsartan HEart Failure Trial (Val-HeFT), valsartan added to conventional treatment (which could include an ACE inhibitor) significantly reduced the combined end point of death or heart failure morbidity by 13.2% (P = .009) over placebo.[19] However, this beneficial effect was smaller (about 5%) and not statistically significant in the diabetic cohort.

The Valsartan in Acute Myocardial Infarction (VALIANT) trial compared captopril to valsartan and to combined captopril plus valsartan in 13,703 patients with AMI complicated by clinical or radiologic signs of heart failure. For both the diabetic subset and the total study population, valsartan was equivalent to both captopril and combination therapy in preventing the combined end points of cardiovascular death, MI, or heart failure.

Two recent studies of the ARB losartan suggest that this pharmacological class may prevent heart failure in type 2 diabetes. In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study,[21] type 2 diabetic patients with nephropathy and no history of heart failure were randomly assigned to receive losartan or placebo in addition to conventional antihypertensive therapy. In addition to slowing the progression of kidney failure over the 4-year study, the incidence of heart failure was reduced by 32% in the losartan group (P = .005). In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, 1195 diabetic patients with hypertension and signs of left ventricular hypertrophy were randomly assigned to either losartan or atenolol as the primary antihypertensive agent and were followed for an average of 4.7 years.[22] Not only was the incidence

Figure 4. *Incidence of new heart failure in diabetic hypertensive patients treated with losartan versus atenolol. MI, myocardial infarction; CV, cardiovascular; RR, risk reduction. Data from Lindholm et al.*[22]



of the primary composite end point (cardiovascular death, myocardial infarction, or stroke) reduced with losartan, but hospitalizations for heart failure were reduced by 41% (P = .013) (Figure 4).

ARBs are remarkably well tolerated and have an excellent safety record. Unlike ACE inhibitors, the incidence of cough is no higher than in patients treated with placebo, and angioedema has rarely been reported. However, despite these advantages, until results of clinical studies clearly demonstrate superiority or equivalence to ACE inhibitors, ARBs should be reserved for those patients who are unable to tolerate ACE inhibition.

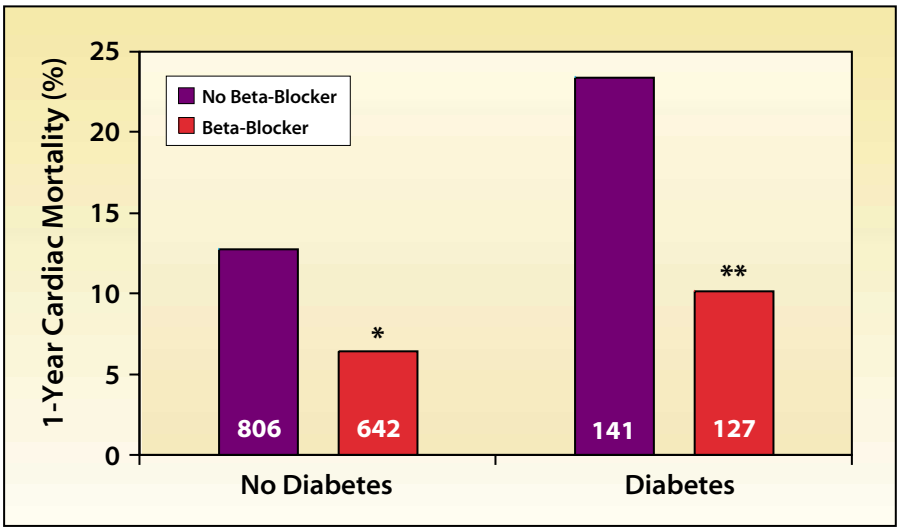


Figure 5. *One-year mortality with chronic ß-blocker use in diabetic and nondiabetic patients following an acute myocardial infarction. *P < .01, **P < .001 compared with no beta-blocker. Data from Kjekshus et al.*[27]

ß-Adrenergic Blockers. ß-Blockers reduce morbidity and mortality when used chronically following an acute myocardial infarction,[23,24] and in recent clinical trials have been shown to have a similar benefit in patients with heart failure of various severities.[25,26] However, the use of most ß-blockers (excluding carvedilol) in the diabetic population has been controversial because of the potential of some to reduce sensitivity to hypoglycemic symptoms, to precipitate glucose intolerance, to inhibit the release of insulin, and to adversely affect plasma lipid profile.[27] Despite these concerns, treatment of diabetic patients with ß-blockers following myocardial infarction has successfully reduced mortality. Evidence of this beneficial effect of ß-blockade comes primarily from retrospective subgroup analyses of larger trials and from observational cohort studies.[28-30] For example, Kjekshus and colleagues followed a multicenter sample of 1716 patients who had survived an acute myocardial infarction and determined the effect of diabetes and ß-blocker use on 1-year survival.[28] As illustrated in Figure 5, the chronic use of ß-blockers (propranolol was used in 80% of the cases) was associated with a significant reduction in 1-year mortality in patients with and without diabetes.

Treatment of diabetic patients with beta-blockers following myocardial infarction has successfully reduced mortality.

Jonas and associates[29] followed a group of 2723 patients for 3 years; these patients had type 2 diabetes and confirmed coronary artery disease (a myocardial infarction between 6 months and 5 years before study entry or stable angina pectoris during the preceding 2 years). Although the patients receiving ß-blockers were more likely to be hypertensive than those not taking ß-blockers (52% vs 38%, P < .05), both total mortality and cardiac mortality were significantly reduced by ß-blockers. Three-year cardiac mortality was 8.4% in subjects not treated with a ß-blocker and 4.9% in those treated with a ß-blocker (P < .005). A similar cardioprotective effect in elderly diabetic patients (mean age 79 years) has recently been reported by Aronow and Ahn.[30] During the average 29 months of follow-up, 87% to 90% of those not treated with a ß-blocker suffered a new coronary event, whereas in the patients treated with a ß-blocker, the new event rate was only 61% (P < .0001).

The beneficial effect of ß-blockers in the treatment of heart failure in the general patient population also extends to the treatment of heart failure in the diabetic population. For example, in the MEtoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT–HF),[31] the risk of death or hospitalization for worsening heart failure was reduced by 31% (95% CI, 20%–40%) in all patients receiving the study medication (n = 1990) compared with those receiving placebo (n = 2001). In the diabetic subpopulation (about 25% of the total), the reduction in risk was 25%

(95% CI, 11%–48%). In the U.S. Carvedilol Heart Failure Study, diabetic patients made up 28% of the total study population, and although the analysis was not prespecified, the reductions in morbidity and mortality were similar in both the diabetic and nondiabetic subgroups.[32] When the effect of ß-blockers in diabetic patients with coronary artery disease described by Jonas and coworkers was analyzed according to New York Heart Association (NYHA) functional capacity, the beneficial effect on mortality was seen in those with NYHA class I to III heart failure (Figure 6).[29] The magnitude of the mortality effect in the Kjekshus study[28] was similar in those with and without radiologic evidence of heart failure, but the small number of patients with heart failure may have kept the effect in this subgroup from reaching statistical significance.

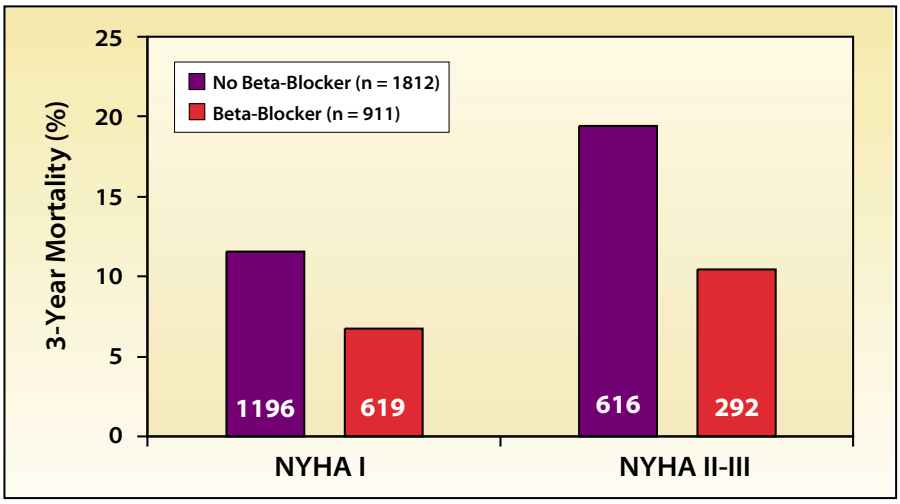


Figure 6. *Effect of beta-blocker treatment on mortality in patients with type 2 diabetes and heart failure by New York Heart Association (NYHA) functional capacity. P values calculated from data presented in the text (chi-square). Adapted from Jonas et al.[29]*

The mortality benefit in patients with heart failure has been seen with nonselective ß-blockers, cardioselective ß-blockers, and a nonselective ß-blocker that also blocks α_1-adrenergic receptors (carvedilol [Coreg,® GlaxoSmithKline, Philadelphia, PA][25,26]). ß-Blockers with intrinsic sympathomimetic activity may be contraindicated in patients with heart failure, and particularly in diabetic patients with heart failure. In the Australian-Swedish study in which pindolol was started 1 to 21 days after an acute myocardial infarction, not only was there no significant survival benefit in those without diabetes, mortality was nearly doubled in those with diabetes.[33] Carvedilol may be the preferred ß-blocker for diabetic patients following an acute myocardial infarction or with heart failure because of its favorable effects on insulin sensitivity and plasma lipid profile in patients with type 2 diabetes,[34] as well as its peripheral vasodilating activity.[32] Despite the continuing growth of evidence regarding their efficacy and safety in the diabetic patient, ß-blockers continue to be underprescribed in this group. In a recent case-control study

Main Points

- Diabetes increases the risk of heart failure and adversely affects the prognosis once heart failure develops.
- The response of diabetic patients to drug therapies for heart failure is similar to, if not better than, that of nondiabetic patients.
- Inotropic agents do not improve survival in diabetic patients and should not be used in diastolic heart failure.
- Carvedilol may be the preferred ß-blocker for diabetic patients following an acute myocardial infarction or with heart failure because of its favorable effects on insulin sensitivity and plasma lipid profile in patients with type 2 diabetes, as well as its peripheral vasodilating activity.
- Clinical trials of angiotensin-converting enzyme (ACE) inhibitors in diabetic patients with heart failure have demonstrated a reduction in mortality, a slowing in the progression to severe heart failure, and a primary prevention of heart failure in high-risk diabetic patients. ACE inhibitors should be used in all diabetic patients with signs of left ventricular dysfunction or overt heart failure.
- Beta-blockers are as effective in diabetic patients as in nondiabetic patients with heart failure in reducing mortality and slowing progression; yet they remain underused because of concerns that they reduce sensitivity to hypoglycemic symptoms, inhibit the release of insulin in type 2 diabetics, and adversely affect plasma lipid profile.

of prescribing practices following a first myocardial infarction, failure to prescribe a ß-blocker, despite no contraindications, was twice as common in diabetic patients as in nondiabetic patients.[35]

Summary and Conclusions

Diabetes is an independent risk factor for the development of heart failure, and those with diabetes who develop heart failure have a much poorer prognosis than those without diabetes. Both the increased incidence and poorer prognosis are likely due to a distinct diabetic cardiomyopathy, which is characterized by morphological and functional changes to the myocardium and coronary vasculature. These changes render the myocardium more susceptible to ischemia and less able to recover following an ischemic insult.

Once heart failure develops, the goals of treatment are the same in the diabetic as in the nondiabetic patient: relieving congestion, slowing the progression of the disease, and prolonging survival. The clinical response of diabetic patients to drugs used to treat heart failure is similar, if not superior, to that of nondiabetic patients. ACE inhibitors should be used in all diabetic patients with signs of left ventricular dysfunction or overt heart failure. In patients who are unable to tolerate ACE inhibitors, ARBs should be initiated. Although they may adversely influence glucose tolerance and reduce the awareness of hypoglycemia, ß-blockers have a proven survival benefit in diabetic patients with heart failure and should be used unless contraindicated. ■

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