Heart Failure

The frequent, forgotten, and often fatal complication of diabetes

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There is a high frequency of heart failure (HF) accompanied by an increased mortality risk for patients with diabetes. The poor prognosis of these patients has been explained by an underlying diabetic cardiomyopathy exacerbated by hypertension and ischemic heart disease. In these patients, activation of the sympathetic nervous system results in increased myocardial utilization of fatty acids and induction of fetal gene programs, decreasing myocardial function. Activation of the renin-angiotensin system results in myocardial remodeling. It is imperative for physicians to intercede early to stop the progression of HF, yet at least half of patients with left ventricular dysfunction remain undiagnosed and untreated until advanced disease causes disability. This delay is largely because of the asymptomatic nature of early HF, which necessitates more aggressive assessment of HF risk factors and early clinical signs. Utilization of β-blockade, ACE inhibitors, or possibly angiotensin receptor blockers is essential in preventing remodeling with its associated decline in ventricular function. β-Blockers not only prevent, but may also reverse, cardiac remodeling. Glycemic control may also play an important role in the therapy of diabetic HF. The adverse metabolic side effects that have been associated with β-adrenergic inhibitors in the diabetic patient may be circumvented by use of a third-generation β-blocker. Prophylactic utilization of ACE inhibitors and β-blockers to avoid, rather than await, the need to treat HF should be considered in high-risk diabetic patients.

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Heart failure (HF) is a common and serious comorbidity of diabetes. This review examines the increased incidence of HF, the possible reasons for this increase, and the poor prognosis associated with HF in diabetic patients. The potential therapies and prophylactic strategies to improve clinical outcomes in diabetic patients with HF are also discussed.

EPIDEMIOLOGY — The Framingham Heart Study showed HF to be two times as common in diabetic men and five times as common in diabetic women ages 45–74 years than in age-matched control subjects. The association was even stronger in younger patients (ages ≤65 years), being fourfold higher in diabetic male patients and eightfold higher in diabetic female patients than in nondiabetic subjects (1).

In a recent health maintenance organization study of nearly 10,000 type 2 diabetic patients, 12% had HF at entry (2). Independent risk factors for HF in this group were older age, longer duration of diabetes, use of insulin, and lower BMI (2). Furthermore, of the >8,000 diabetic patients without HF at entry, HF developed at a rate of 3.3% per year. Although the risk factors were the same as above, they also, paradoxically, reported a reduction in HbA_{1c} levels. However, only those patients with incident chronic heart failure (CHF) were more likely to have had follow-up HbA_{1c} tests than those free of CHF (2).

In a study of elderly nursing home residents initially free of HF, 39% of those with diabetes vs. 23% of those without diabetes had developed HF after 43 months of follow-up, a relative risk of 1.3 (3). A cross-sectional Italian study found the prevalence of diabetes to be 30% in an elderly HF population (4). This is also supported in the U.K. Prospective Diabetes Study, which found that the prevalence of HF rose with an elevation of HbA_{1c}, without an upper or lower threshold (5).

Patients with diabetes account for >33% of all patients requiring hospitalization for HF (6). In Alabama during the year 2000, 38% of patients admitted to a tertiary care hospital with a primary diagnosis of HF also had diabetes, a rate that was similar to that found in a statewide quality assurance audit of HF admissions from July to December 1998, in which 33.6% of admissions with HF had diabetes (7).

Conversely, the presence of HF is an independent risk factor for developing diabetes. During a 3-year follow-up of nondiabetic HF patients, diabetes developed in 29% compared with 18% of matched control subjects; multivariate analysis also showed HF to be an independent risk factor for the development of diabetes (4). Diabetic subjects make up ~25% of all patients enrolled in large-scale clinical trials evaluating treatments for HF: 23% in the Cooperative North Scandinavian Enalapril Survival Study, 25% in SOLVD (Studies of Left Ventricular Dysfunction), 20% in the Vasodilation Heart Failure Trial II, 20% in ATLAS (Assessment of Treatment with Lisinopril and Survival), and 27% in RESOLVD (Randomized Evaluation for Strategies of Left Ventricu-

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Abbreviations: ANG-II, angiotensin-II; ANP, atrial natriuretic peptide; ATLAS, Assessment of Treatment with Lisinopril and Survival; BNP, brain natriuretic peptide; CHF, chronic heart failure; CPT-1, carnitine palmityl transferase 1; DIGAMI, Diabetes Insulin Glucose in Acute Myocardial Infarction; FFA, free fatty acid; HF, heart failure; MHC, myosin heavy chain; MI, myocardial infarction; RAS renin-angiotensin system; RESOLVD, Randomized Evaluation for Strategies of Left Ventricular Dysfunction; SERCA-2, sarcoplasmic reticular Ca^{2+} ATPase; SNS, sympathetic nervous system; SOLVD, Studies of Left Ventricular Dysfunction; TZD, thiazolidinedione.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

lar Dysfunction) (8–12). Diabetic patients with HF may actually have been underrepresented in these clinical trials, as exclusion criteria such as impaired renal function are often used, resulting in a bias selection against diabetic subjects.

The dire prognosis of the diabetic patient with HF is well known. In the SOLVD and RESOLVD trials, diabetes was an independent risk factor for death (9,12). In the Diabetes Insulin Glucose in Acute Myocardial Infarction (DIGAMI) study of myocardial infarction (MI) in diabetic patients, HF was the most common cause of mortality, accounting for 66% of deaths in the year following the first MI (13). Key points concerning the epidemiology of HF in diabetic patients are presented in Table 1.

Table 1—*Epidemiology of heart failure in diabetic patients*

- HF is two times as common in diabetic men and five times as common in diabetic women as in age-matched nondiabetic subjects.
- About 12% of type 2 diabetic subjects have established HF.
- About 3.3% of type 2 diabetic subjects develop HF each year.
- Elderly diabetic subjects have a 1.3-fold greater risk of developing HF than nondiabetic subjects.
- Prevalence of HF in elderly diabetic subjects is 39%.
- 1% rise in HbA_{1c} is associated with a 15% increased risk of HF in elderly diabetic patients.
- Diabetic patients account for 25% of all patients enrolled in large HF trials.

ETIOLOGY — Although epidemiological studies carried out over the last 3 decades have established the association between diabetes and HF, the underlying pathophysiological explanation for this common comorbidity is less clear. Several theories characterizing specific cellular or metabolic derangements linking diabetes and HF have been investigated, including a triad of overlapping cardiotoxic and cellular maladaptive alterations comprising a specific diabetes-related cardiomyopathy, association with coronary artery disease, distorted gene expression, and alteration in autonomic activity. These theories are reviewed below.

The cardiotoxic triad

The coexistence of myocardial ischemia, hypertension, and a specific diabetic cardiomyopathy seems to independently and cooperatively contribute to biochemical, anatomic, and functional alterations in cardiac cells and tissues that impair cardiac function. Results from a series of animal research studies, supported by clinical studies in humans, point to a role for these overlapping influences in patients with diabetes and HF.

The high incidence and poor prognosis of HF in diabetic patients have been linked in part to the presence of an underlying diabetic cardiomyopathy characterized by myocellular hypertrophy and myocardial fibrosis (14). Diabetic cardiomyopathy has been found to be associated with depressed mechanical function, electrophysiological abnormalities, defects in subcellular organelles, and receptor downregulation because of chronically elevated catecholamine levels (15). Experimentally induced diabetes in animal models causes changes in myocardial cellular calcium transport and contractile proteins, which result in subclinical systolic and diastolic dysfunction (16,17). The increased myocardial collagen content associated with diabetic cardiomyopathy further worsens diastolic dysfunction (18).

Hypertension, another frequent comorbidity of diabetes, may further damage myocardial contractile proteins, induce increased myocardial fibrosis, and generate a hypertrophic state, which results in mild clinical systolic and diastolic dysfunction (19). Furthermore, the addition of myocardial ischemia may change a mildly dysfunctional myocardium, caused by diabetes or a moderately dysfunctional myocardium caused by the combined effects of diabetes and hypertension, to a severely dysfunctional myocardium and even terminal HF (20). The end result of diabetes, hypertension, and myocardial ischemia is a fibrotic, noncompliant myocardium, initially with diastolic and later with systolic dysfunction. In addition, papillary muscle fibrosis can lead to a mitral insufficiency that adds a mechanical burden to the already dysfunctional myocardium (21).

Although severe myocardial dysfunction in the diabetic patient is often caused by a combination of diabetic cardiomyopathy, hypertension, and/or myocardial ischemia, any one of these factors may dominate. The appropriate management of diabetic patients with severe HF requires evaluation for coronary artery disease. The absence of significant coronary obstructions in a subset of patients with diabetic HF has suggested the possibility of a diabetic microangiopathy as an underlying etiology, although microvascular ischemia has generally been excluded by the absence of increased lactate production during rapid atrial pacing (22). However, it is still possible that in the insulin-resistant or diabetic patient, endothelial dysfunction could lead to repeated episodes of vasoconstriction, with subsequent reperfusion injury and myocardial dysfunction (23). Furthermore, the increased small vessel permeability associated with endothelial dysfunction could lead to interstitial edema, fibrosis, and myocardial dysfunction (24). It is also possible that a defect in the angiogenic response to ischemia that has been reported in diabetic patients could also play a role (25).

Autonomic dysfunction

Animals with experimental diabetic cardiomyopathy exhibit biochemical and molecular abnormalities resembling those seen in human myocardial failure stemming from hemodynamic overload (26), which potentially contribute to HF. Hyperglycemia has been shown to activate the same intracellular signaling pathways (e.g., protein kinase C and mitogen-activated protein kinase) as mechanical stretch or increased ventricular wall stress. Regardless of the setting, impaired myocardial performance would eventually require activation of the neurohormonal compensatory systems, including the renin-angiotensin system (RAS) and the sympathetic nervous system (SNS), to avoid systemic hypoperfusion. Activation of these and other autocrine and paracrine systems leads to the progressive loss of cardiac myocytes because of accelerated apoptosis and necrosis, eventuating in further myocardial dysfunction and the downward spiral of cardiac failure. Similarly, activation of the RAS and SNS leads to compensatory changes in the size and shape of the cardiac chambers through cellular hypertrophy, or "remodeling." Even though this process involves increased cardiac muscle mass, the change in cellular and noncellular composition, geometry, and energetics leads to further

decreases of ventricular function and even greater increases in neurohormonal activation (27). Based on this proposed scenario, the HF in diabetic cardiomyopathy would appear to follow the same pattern of initially adaptive but eventually harmful compensatory mechanisms leading to progressive ventricular dysfunction, as recognized in HF of other etiologies.

At a cellular level, activation of the RAS and SNS leads to defects in β-adrenergic receptor signal transduction and induction of the fetal gene program (28–30). An important metabolic consequence of β-adrenergic receptor signaling is increased stimulation of carnitine palmityl transferase 1 (CPT-1) activity. CPT-1 is a mitochondrial enzyme that plays a key role in transporting long-chain acyl-CoA compounds into the mitochondria, promoting myocardial fatty acid rather than glucose utilization. Increased myocardial use of free fatty acids (FFAs) results in the uncoupling of oxidative phosphorylation, inhibition of membrane ATPase activity, increased myocardial oxygen consumption, myocardial ischemia, impaired myocardial function, and cardiac arrhythmias (31). Inhibition of CPT-1 is one mechanism through which β-blockade may be cardioprotective (32).

Altered gene expression

Another change brought about through β-adrenergic receptor signal transduction abnormalities, and one believed to contribute to HF progression, is an alteration of gene expression to what has been called the fetal gene program. Atrial natriuretic peptide, which is ordinarily limited to atrial muscle, is re-expressed in the ventricle, as it was in fetal life. The proportions of the fast (α) and slow (β) isoforms of myosin heavy chain (MHC) are changed into a more fetal-like pattern with higher β-MHC and lower α-MHC. The skeletal muscle α actin gene, which is not expressed in cardiac muscle after birth, is also re-expressed in the heart along with the normal cardiac actin gene. As these genes are being re-expressed, there is a downregulation of the gene encoding a key inotropic protein, sarcoplasmic reticular Ca^{2+} ATPase (SERCA-2). The net effect of these changes in gene expression is an overall decrease in both diastolic and systolic ventricular function, which may be an adaptive mechanism to protect the surviving myocardium by reducing its energy expenditure (33).

Table 2—*Etiology of heart failure in diabetic patients*

Diabetic cardiomyopathy
Hypertension
Myocardial ischemia
Coronary artery disease
Possible diabetic microangiopathy
Possible endothelial dysfunction
Activation of RAS and SNS
Cardiac remodeling
Increased FFA utilization
Induction of fetal gene program

Altered gene expression is also reversed by β-blockade. Studies in diabetic rats have shown improvement in SERCA-2 expression, as well as other aspects of fetal gene activation, with β-adrenergic inhibition (34,35). In humans, β-blockers have been shown to produce a time-dependent improvement in myocardial contractile function by stopping and even reversing the remodeling process (27,36). Indeed, the prophylactic use of β-blockers in patients with diabetes, hypertension, or ischemic heart disease has the potential to prevent the initiation of the remodeling process. See Table 2 for a list of key points outlining the etiology of HF in diabetic patients.

The relative impact and exact therapeutic potential of these suggested contributors to the development and progression of HF in diabetic individuals remain to be established and are the subject of ongoing research.

RISK FACTORS, SCREENING, AND DIAGNOSIS FOR HF

Risk factors

The high prevalence and significant morbidity and mortality of HF mandate early identification of risk factors and clinical signs to deliver appropriate and timely therapy. Although treatment has been shown to reduce the complications of HF, ~50% of individuals with left ventricular systolic dysfunction—the antecedent to HF—remain undiagnosed and untreated (37). Early diagnosis and immediate treatment can help to delay or prevent the progression of this debilitating disease.

Risk factor identification may be the most reliable indicator of subclinical myocardial dysfunction. The most prominent risk factors for HF in both diabetic and nondiabetic individuals include prior MI (especially anterior or Q-wave) (38), angina pectoris, hypertension (39), and valvular deformity. Diabetes has such an important influence on the development of HF that it has been incorporated as a risk factor for HF in the American College of Cardiology /American Heart Association HF guidelines (40). In the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the guidelines state that patients with diabetes are automatically placed in the highest risk category for HF, even with high-normal blood pressure and no target organ damage (41). Older age, longer duration of diabetes, use of insulin, and increasing body weight independently contribute to the risk of HF (42). The macrovascular and microvascular risks associated with type 2 diabetes are strongly associated with an increased blood pressure (43).

Diagnosis and screening

A careful history will detect symptoms of dyspnea on effort, orthopnea, nocturnal cough or wheezing, easy fatigability, and nocturia. However, as discussed by Marantz et al. (44), many patients with left ventricular systolic dysfunction do not report symptoms (e.g., 20% of those with an ejection fraction <40%). In many cases, however, this may be because of absolute inactivity; a simple in-office exercise tolerance exam—time to dyspnea can be judged by simply walking the patient or observing the patient on a graded exercise test—can be very revealing (45).

Physical examination, no matter how skilled the examiner, may not show signs of HF. In the SOLVD study, among those subjects with an ejection fraction <45%, 32% were observed to have rales; 26%, edema; 26%, jugular vein distention; and 17%, a third heart sound (46).

Therefore, the diagnosis of HF in the diabetic patient may require further testing. Although electrocardiogram and chest X-ray may be helpful in demonstrating hypertrophy, present in 32% of diabetic patients, or left ventricular enlargement (47), two-dimensional and pulsed Doppler echocardiography is needed to visualize the cardiac structural and functional changes that underlie HF and is the recommended test if HF is suspected (48). An economical test to prescreen patients for left ventricular dysfunction and the need for echocardio-

graphic evaluation is the plasma level of brain natriuretic peptide (BNP). Like atrial natriuretic peptide (ANP), BNP is elevated with increased cardiac filling pressure, but unlike ANP, it is not affected by hyperglycemia (49). Used as a screening test in patients over age 55 years, BNP had a sensitivity of 92% and a specificity of 72% (50). Therefore, plasma BNP level may be an excellent and economic test to identify diabetic patients who should be further evaluated for HF with echocardiography.

TREATMENT AND PREVENTION

Although diuretics and digoxin improve the clinical manifestations of HF and improve the quality of life for the HF patient, their use has demonstrated no effect on mortality (51). To improve mortality, the remodeling process must at least be halted and preferably reversed. Evidence from large clinical trials has shown that remodeling can be attenuated, ventricular function improved, and mortality and morbidity reduced by drugs that interfere with the enhancement of the neurohormonal systems, the RAS, and the SNS (27). In the diabetic patient, glycemic control plays an important role.

Glycemic control

Glycemic control can benefit cardiac metabolism and performance in the diabetic patient with HF by decreasing myocardial FFA oxidation and increasing glucose utilization. In patients with HF, dichloroacetate has been shown to increase stroke volume and left ventricular performance by reducing myocardial FFA utilization and increasing glucose oxidation and lactate extraction. Dichloroacetate stimulates pyruvate dehydrogenase, the pivotal enzyme connecting glycolysis with the Krebs cycle (52). The clinical consequences of this shift in metabolic substrate utilization were suggested by the DIGAMI study. A group of diabetic patients who had sustained an acute MI received an intravenous insulin infusion followed by multiple daily subcutaneous insulin injections. Mortality risk in these patients, who sustained a first myocardial infarct and had no previous history of HF, was diminished. Although FFAs were not measured, there may have been a shift in myocardial substrate utilization from FFA to glucose. It is believed that increased levels of FFAs depress myocardial contractility and increase myocardial oxygen consumption without a concomitant increase in myocardial work (13,53,54).

Better glycemic control improves myocardial function in HF by reducing serum FFAs and tissue triglycerides. In the Zucker diabetic fatty rat, cardiac dilatation, impaired contractility, and increased fibrosis resulted from triglyceride overloading of the myocardium. Triglyceride overloading occurs because of the underexpression of FFA oxidative enzymes by their transcription factor, peroxisome proliferator–activated receptor α. Levels of ceramide (a mediator of apoptosis) and DNA laddering (an indicator of apoptosis) are both increased. The thiazolidinedione (TZD) troglitazone was shown to reduce myocardial triglyceride and ceramide levels, reverse the apoptotic loss of cardiac myocytes, and prevent the degradation of cardiac function in obese rats (55).

The cardiotoxicity of elevated FFA levels has also been linked to the disruption of plasma membrane structure and function and to an increase in intracellular calcium and cardiac work load (56,57). Finally, high FFA levels themselves are known to increase cardiac sympathetic activity in healthy adults (58).

The potential of glycemic control in improving the outcome of diabetic patients with HF has never been fully examined. However, based on pathophysiological, epidemiological, and clinical observation evidence, aggressive glycemic control might be considered as part of a comprehensive management strategy for HF in diabetic patients.

Use of thiazolidinediones

TZDs are widely used in the treatment of type 2 diabetes in the U.S. There is some concern about TZD use in patients with or at high risk for HF because of the potential of these drugs to induce edema. Although few data have been published, in the author's experience, only a minority of the edema cases are associated with HF; those few cases are possibly attributable, at least in part, to an increased permeability of the microvasculature, secondary to a reduction in insulin resistance, and thus are resistant to diuretic action with only a partial response expected. By reducing insulin resistance, the effect of insulin on capillary dilatation and, in some cases, permeability is increased (59,60). Permeability is also increased by increasing endothelin-1 levels, which are stimulated by insulin and an increase in vascular endothelial growth factor and calcium channel blockade caused by the TZD (61–64). Higher catecholamine levels can also increase capillary pressure by their opposing effects on pre- and postcapillary sphincters (65).

The net result of increased capillary permeability and dilatation is a volume-related stimulus to the neurohormonal compensatory systems, including the RAS and the SNS, to increase plasma volume. If this hypothesis is correct, in a situation of subclinical ventricular dysfunction, any increase in plasma volume or stimulation of the RAS and sympathetic systems can be enough to cause further myocardial decompensation and clinically apparent CHF. Under these circumstances, induction of and survival from HF may be paradoxically fortuitous, as left ventricular dysfunction is unexpectedly diagnosed, instigating treatment with ACE inhibitors and β-blockers, which will improve survival. Undiagnosed left ventricular dysfunction, even in asymptomatic patients, is associated with an increased incidence of sudden death caused by arrhythmias (66).

With the diagnosis of HF, the question of whether TZD use should continue in addition to optimal HF therapy is unanswered. Based on the package inserts of both rosiglitazone and pioglitazone, TZDs can be used for class 1 and class 2 New York Heart Association HF (i.e., the patient can walk 200 yards without dyspnea). Many physicians believe that with the improvements in cardiac risk factors, especially endothelial dysfunction, diastolic blood pressure, C-reactive protein levels, microalbuminuria, plasminogen activator inhibitor and adhesion molecule levels, increase in LDL and HDL particle size, and decreased vascular smooth muscle cell proliferation, cautious and closely monitored continuation of TZD therapy should be considered (67–69). Pending recommendations from ongoing studies of TZD use in HF, TZDs should at this time be used with extreme caution in the diabetic patient with HF (i.e., starting with a lower-than-recommended dosage and conservative dosage increases).

ACE inhibition

ACE inhibition exerts its cardiovascular benefits primarily by blocking the conversion of angiotensin-I to angiotensin-II

(ANG-II), thereby decreasing the circulating level and tissue concentration of ANG-II. In addition to being a potent vasoconstrictor, ANG-II induces the protein synthesis involved in cardiac myocyte hypertrophy as well as collagen production by cardiac fibroblasts, leading to myocardial fibrosis (70–72). ACE inhibitors also attenuate cardiac myocyte hypertrophy and myocardial fibrosis by raising bradykinin and prostacyclin levels and mediating the release of nitric oxide (an endothelium-derived growth factor) (73). Unlike ACE inhibitors, ANG-II receptor blockers do not increase bradykinin levels and therefore may be less effective in impacting mortality caused by HF (40). The results of the recent RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) trial (74) revealed, for example, no benefit to overall or cardiovascular mortality related to ANG-II receptor blockade with losartan (in combination with conventional antihypertensive therapies) in 1,513 patients with type 2 diabetes and nephropathy. However, this therapy did improve the time to the doubling of the serum creatinine (risk reduction 25%; $P = 0.006$), reduce the incidence of end-stage renal disease (risk reduction 28%; $P = 0.002$), and reduce the rate of first hospitalization for HF (risk reduction 32%; $P = 0.005$), suggesting potential benefits that justify further investigation of this class of drugs. A recent study has shown that the addition of the ANG-II receptor blocker, valsartan, to HF patients already treated with ACE inhibitors and β-blockers resulted in an increased mortality. Thus, in the treatment of HF, the addition of an adrenergic receptor binder to ACE inhibition and sympathetic blockade may be counterproductive (75).

ACE inhibitors can reduce mortality and limit cardiac morbidities, including HF, in diabetic patients with or without systolic dysfunction (76). One of the mechanisms for improvement is through the prevention of myocardial remodeling. In patients with anterior or inferior wall MIs, increases in left ventricular chamber dimensions and sphericity occurring between 3 weeks and 1 year post-MI (remodeling) can be prevented by ACE inhibition. However, the degree of protection depends on how soon after the onset of MI ACE inhibitors are initiated (77,78). In addition, ACE inhibition lowers pulmonary wedge pressure and increases exercise tolerance.

Diabetic patients who suffer an MI have an increased mortality and morbidity from HF, presumably because of the more severe left ventricular dysfunction. It is therefore extremely important that an ACE inhibitor be initiated early following an MI in diabetic patients, so that HF can be avoided.

ACE inhibitors are at least as effective in reducing mortality risk in diabetic as in nondiabetic patients. The ATLAS trial compared high and low dosages of the ACE inhibitor lisinopril in New York Heart Association classes II–IV HF patients, including 611 diabetic subjects (11). Although the overall mortality was higher among diabetic subjects, the risk of death was reduced by more than half in the group of diabetic subjects receiving a high dosage of lisinopril. In the Survival and Ventricular Enlargement study, although not powered for subgroup analysis, captopril therapy appeared to reduce the combined end point of cardiovascular morbidity/mortality in both diabetic and nondiabetic individuals (79). Similarly, in the GISSI-3 (Italian Study Group for Streptokinase in Myocardial Infarction 3) study, lisinopril therapy yielded a significantly greater mortality risk reduction among diabetic patients than among nondiabetic patients ($P < 0.025$) (80). Therefore, although the data are incomplete, ACE inhibitors are clearly of value in treating diabetic patients with HF and are at least as efficacious as in nondiabetic patients.

β-Blockers

Heart failure is associated with the harmful effects of chronic SNS activation. Norepinephrine, acting through α_1-, downregulated β_1-, and mildly upregulated β_2-receptors, causes direct myocardial toxicity and stimulates altered gene expression and remodeling (81,82). This is exacerbated in diabetes, wherein insulin resistance and hyperinsulinemia are associated with increased sympathetic tone, as indicated by an elevated heart rate (83). Furthermore, high ANG-II levels also increase norepinephrine production, whereas ANG-II itself has a direct toxic effect on cardiomyocytes (84,85). To prevent cardiac remodeling most effectively, both neurohormonal systems must be therapeutically blocked. β-Blockade, particularly with nonselective agents, is an effective intervention to inhibit sympathetic activation at both α- and β-receptors and prevent the deleterious effects of norepinephrine on cardiac cells and tissues.

There are three generations of β-blocking agents. The first-generation agents, such as propranolol and timolol, are contraindicated in HF patients because of their myocardial depressant effects. Second-generation β-blockers, including metoprolol and bisoprolol, are safe to use in HF, but are selective for β_1 activity and therefore of limited efficacy. The third-generation β-blocking agents were developed specifically to act nonselectively to provide more comprehensive benefit, each with a different specificity for β_1-, β_2-, and α_1-receptors.

This newer concept of using nonselective adrenergic-blockade for HF was based on a correction of the prior misconception that among the adrenergic receptors, only β_1 activity contributed to myocardial dysfunction in the failing heart. In addition, several of these newer β-blockers have additional beneficial features. Labetalol, a third-generation β-blocker with a higher affinity for α_1-receptors than β_1- or β_2-receptors and, therefore, a potent vasodilatory effect, has been shown to improve myocardial function in hypertensive cardiomyopathy (86), although it has not been directly studied in HF patients. Nebivolol, with high β_1 selectivity but vasodilator activity related to potentiation of nitric oxide in controlling cellular proliferation, has had some, albeit limited, clinical success in HF (86). The most reliable information on the use of nonselective β-blockade in the management of HF has come from the experience with carvedilol, which has antioxidant activity and excess adrenergic activities that prevent adrenergic receptor upregulation (87). This β-blocker has been widely studied in HF and has exhibited 2.5- and 7-fold selectivity for β_1- versus α_1- and β_2-receptors, respectively.

In over 15 placebo-controlled studies involving more than 2,000 HF patients, β-blockade has resulted in enhanced myocardial contractility, indicated by improvement in left ventricular ejection fraction. Although acute β-blockade causes a decrease in the ejection fraction, ventricular function starts to improve after 1 month of therapy and is significantly improved by 3 months, accompanied by reduced ventricular volumes.

After 18 months of therapy with the third-generation β-blocker carvedilol, left ventricular mass is decreased and the spherical ventricle returns to its normal elliptical shape (88). Thus, unlike ACE inhibitors, β-blockers may be able to actually reverse the remodeling process. This effect was seen after 4 months of therapy with carvedilol (89). Improvement in left ventricular function has also been observed with metoprolol (90,91), but was significantly greater with carvedilol (87).

Diabetic subjects comprised 25–30% of patients enrolled in the pivotal β-blocker HF clinical trials. In both the U.S. Carvedilol and Copernicus studies, the mortality and morbidity outcomes for the diabetic subjects were at least as good as those of the nondiabetic subjects, and in the MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure), diabetic patients treated with metoprolol CR/XL showed a trend in a similar direction. In the large U.S. Carvedilol Heart Failure Study, treatment with a β-blocker decreased overall mortality by 65% ($P < 0.001$) (92). Randomized clinical trials support the position that β-blockers should be used in all HF patients and that there is no contraindication to their use.

Compared with the general population, diabetic individuals are at high risk for MI. Data from a Finnish population-based cohort study showed that this risk is as great in the diabetic population without previously recognized ischemic heart disease as in the nondiabetic population with a history of MI. Accordingly, based on the clinical assumption that all diabetic patients over age 35 years should be treated as if they have coronary artery disease (93), a reasonable case can be made to apply guideline recommendations for post−myocardial ischemia therapy that include a combination of ACE inhibitors and β-blockers (94). Conversely, a study conducted in Tayside, Scotland, concluded that patients with type 2 diabetes were at lower risk of suffering an MI than those who had established coronary artery disease; however, the diabetic cohort consisted of newly diagnosed type 2 diabetic subjects, suggesting that the duration of diabetes may be a factor in assessing the risk of cardiovascular outcomes (95).

To most physicians, ACE inhibitor therapy has been accepted for diabetic patients, whereas β-blockers may often be withheld. Many reasons have been postulated for this reluctance to treat with the latter drug, despite β-blockers having been proven efficacious for risk reduction in this population. For example, it is feared that β-blockade may impair the recognition and prolong the duration of hypoglycemia in patients receiving insulin or a sulfonylurea. However, although it is true that hypoglycemia may be a problem with β-blockers in type 1 diabetes, it is seldom a concern for type 2 diabetic patients (96). Physicians may also be concerned about peripheral vasoconstriction as well as adverse effects on carbohydrate and lipid metabolism. Both first-generation nonselective and second-generation β_1 selective antagonists decrease peripheral blood flow, increase insulin resistance, worsen glycemic control, and induce a more atherogenic lipid profile by elevating the proportion of small LDL particles and triglycerides and lowering levels of HDL cholesterol (97).

There is evidence that many of these problems may be avoided by using third-generation β-blockers. For example, carvedilol, a nonselective β-blocker with α_1-blocking properties, maintains insulin sensitivity and glucose disposal, while lowering triglycerides, raising HDL levels, and vasodilating peripheral vasculature (98). See Table 3 for a list of key points outlining the treatment and prevention of HF in diabetic patients.

Table 3—*Treatment and prevention of heart failure in diabetic patients*

Glycemic control
ACE inhibitors
Block RAS
Prevent cardiac remodeling
Improve left ventricle function
Reduce risk of death
β-Blockers
Block β-adrenergic stimulation
Prevent cardiac remodeling
Reverse cardiac remodeling
Improve left ventricle function
Reduce risk of death
Adverse side effects of β-blockers
Peripheral vasoconstriction
Loss of glycemic control
Increased insulin resistance
More atherogenic lipid profile
Avoided by use of "third-generation" β-blocker
ACE inhibitors and β-blockers may prevent HF in high-risk diabetic patients: prophylactic use

CONCLUSIONS — An estimated 77% of U.S. hospitalizations for complications of diabetes are linked to cardiovascular disease. Diabetic patients have a high frequency of HF and subsequent poor clinical prognosis because of the combination of diabetic cardiomyopathy, hypertension, and ischemic heart disease. The lack of patient awareness of the association between diabetes and CVD contributes to the risk of HF in the diabetic population, as does the asymptomatic yet progressive nature of early stage HF. This should necessitate physicians to consider the risk of this comorbidity and use appropriate screening tests to achieve early identification and initiate preventive strategies. There is evidence suggesting that glycemic control may improve cardiac metabolism and myocardial function in diabetic patients with HF. Improvements in cardiac function engendered by neurohumoral inhibition are associated with a decrease in mortality that is at least as great in the diabetic patient as it is in the nondiabetic HF patient. However, it should be mentioned that certain medical interventions that are efficacious in general populations do not always seem appropriate for diabetic subjects. Thus physicians should be encouraged to use therapies tested in the diabetic population, such as β-blockers and ACE inhibitors. Overall, it appears that diabetic patients would benefit from more aggressive preventive programs that set more stringent standards likely to reduce the incidence of cardiovascular morbidity and mortality in this high-risk population.

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