Heart Failure and Nephropathy: Catastrophic and Interrelated Complications of Diabetes

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Heart failure (HF) is a major contributor to poor quality of life, a leading cause of hospitalization, and cause of premature death. Both kidney disease and diabetes are major and independent risk factors for the development of heart failure, such that individuals with diabetic nephropathy are at especially high risk. Such patients not only are likely to have coronary artery disease and hypertension but also are likely to have diabetic cardiomyopathy, a distinct pathologic entity that is more closely associated with the microvascular than the macrovascular complications of diabetes. In addition to a better understanding of the epidemiology of HF, advances in noninvasive imaging have highlighted the importance of early cardiac dysfunction in diabetes and the high prevalence of HF with preserved left ventricular systolic function. Although significant renal dysfunction is usually an exclusion criterion in HF trials, diabetes is often a prespecified subgroup so that subanalyses of large multicenter clinical trials do provide some guidance in therapeutic decision-making. However, further therapies for both HF and nephropathy in diabetes clearly are needed, and a number of new therapeutic strategies that target both disorders have already entered the clinical arena.


The global burden of diabetes, estimated to reach 366 million by 2025 (1), brings with it the potential for a catastrophic increase in the prevalence of kidney and cardiovascular disease. Although the increased mortality in patients with diabetes traditionally has been attributed to coronary artery disease, more recent studies have emphasized the importance of chronic heart failure (HF) as a common and deadly comorbidity (2), to which the patient with nephropathy, even in its earliest stages, is especially prone (3). The recognition of such a link between HF and kidney failure in diabetes is supported not only by epidemiologic data but also by shared pathogenetic mechanisms that underlie the development of both disorders and give rise to common therapeutic approaches aimed at slowing their progression.

The studies discussed in this review were based on a search of the Ovid database using the following search terms: Heart failure, diabetes, nephropathy, kidney disease, proteinuria, diastolic dysfunction, and clinical trial.

Epidemiology

Chronic HF is a major and growing public health problem in industrialized nations. In the United States, for instance, the prevalence of HF was 4.9 million in 2002 and is estimated to reach 10 million by 2007 (4), such that at age 40, there will be an approximate one in five lifetime risk for developing new-onset HF in both men and women (5). Despite the advances in therapy, mortality in HF remains high, with a 5-yr age-adjusted death rate of 59% in men and 45% in women (6). Moreover, in addition to its high mortality, HF accounts for considerable morbidity as the leading cause of hospitalizations in those who are older than 65 yr, with almost 1 million admissions each year, making it the US Health Care Financing Administration’s largest, most expensive diagnosis-related group (7), contributing to the estimated direct and indirect costs of HF in the US of $27.9 billion per year (8).

Diabetes and HF

The association between the diabetes and HF was first reported in the Framingham study in 1971, in which the high prevalence of diabetes (14% of men and 26% of women) among patients with HF was noted (9) such that the risk for development of HF in patients with diabetes was increased two- and five-fold in men and women, respectively (10). Similar findings also have been reported by a number of other community-based epidemiologic studies, all of which noted diabetes as an independent risk factor for the development of HF (11–13), and identifying age, diabetes duration, insulin use, ischemic heart disease, and elevated serum creatinine as markers of risk among patients with diabetes (14).

In clinical trials of HF, in which participants are frequently younger than in community-based studies, diabetes is a noted comorbidity in between 10 and >30% of participants (2).
deed, the increased risk for HF conferred by diabetes is especially marked in younger patients (45 to 65 yr), for whom the prevalence of HF is increased five- to eight-fold compared with nondiabetic individuals (Figure 1).

Until very recently, HF in diabetes has received little attention, being omitted frequently in the teaching of lists of diabetic complications, making it “the frequent, forgotten, and often fatal complication of diabetes,” as noted by Bell (15). Indeed, the likelihood of developing HF is similar to the risk for the other micro- and macrovascular problems of the disease. For instance, in the UK Prospective Diabetes Study (UKPDS), the development of HF was examined over a 10-yr period in almost 4000 community-based, middle-aged, patients with type 2 diabetes (16,17). The rate of hospitalization for HF was 3.0 to 8.1 per 1000 patient-years (depending on assigned treatment group), similar to that of nonfatal myocardial infarction (MI), nonfatal stroke, and renal failure at 7.5 to 9.5, 4.0 to 8.9, and 0.6 to 2.3 per 1000 patient-years, respectively, in the same study.

Kidney Failure and HF

Functioning in tandem, the kidney and the heart provide the physiologic regulation of extracellular fluid volume (ECFV), natriuresis, BP, cardiac output, and GFR. The intimate relationship between these two organ systems is also apparent in disease states in which renal and cardiac dysfunction frequently coexist (Figure 2), reflecting common factors in their pathogeneses that include, in addition to diabetes, hypertension, fluid overload, aging, left ventricular hypertrophy, and atherosclerotic vascular disease.

Even mild degrees of renal impairment are associated with an enhanced risk for HF (18) that increases with worsening renal function (19). By the time they reach ESRD, approximately 40% of patients who are on either hemodialysis or peritoneal dialysis have overt HF (20), where it is associated with an especially poor prognosis (20) such that for patients who start ESRD therapy with HF at baseline, the median survival is 36 mo compared with 62 mo in patients without HF (21). Conversely, renal dysfunction (Cockroft-Gault calculated creatinine clearance <60 ml/min) also is a common finding, noted in 20 to 36% of patients with HF (22), for whom its presence is associated with increased mortality, mostly as a consequence of HF progression (22).

HF in Incipient Diabetic Nephropathy

Microalbuminuria (incipient nephropathy) is a well-recognized predictor of increased mortality and cardiovascular risk in diabetes (23–26); however, its value as a predictor of HF has only recently been established. In the Heart Outcomes Prevention Evaluation (HOPE) Study and MICRO (Microalbuminuria, Cardiovascular and Renal Outcomes) HOPE substudy, patients who were at increased cardiovascular risk but without HF at baseline were evaluated over a median of 4.5 yr (27,28). In these studies, the presence of microalbuminuria at baseline (albumin/creatinine ratio ≥2 mg/mmol), noted in 32.6% of participants with diabetes, conferred a 3.7-fold increased risk for hospitalization for HF (3). Indeed, the DIABHYCAR (type 2 Diabetes, Hypertension, Cardiovascular events and Ramipril) Study noted that the presence of HF in the setting of an elevated urinary albumin concentration portends a particularly poor prognosis, with a 10-fold increase in mortality compared with patients who also have a high urinary albumin concentration but not HF (29).

HF in Overt Diabetic Nephropathy

The Irbesartan Diabetic Nephropathy Trial (IDNT) studied patients with type 2 diabetic nephropathy, an elevated baseline serum creatinine (1.0 to 3.0 mg/dl in women, 1.2 to 3.0 mg/dl in men), overt proteinuria, and hypertension, excluding patients with symptomatic HF because of their absolute requirement for an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) (30). Despite this, over a median follow-up period of 2.6 yr, hospitalization for HF was the most commonly reported cardiovascular event, occurring in 13% of study participants, compared with MI (6%) and stroke (4%) (31). Likewise, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study, with similar entry and exclusion criteria, reported HF hospitalizations in 14% of patients (32).
**Proteinuria**

The magnitude of proteinuria not only is an important marker of progressive renal dysfunction but also predicts an increased likelihood of cardiovascular events, including HF (33). For instance, in the RENAAL study, baseline proteinuria was found to be the strongest predictor of HF (34), with an almost linear relationship between the two such that an increase of 1.0 g/g proteinuria was associated with 26% (95% confidence interval 18 to 34%) risk for HF (34) (Figure 3). Furthermore, the extent to which proteinuria was reduced in the trial also had an impact on the likelihood of HF events, even after adjustment for other risk markers (Figure 3), leading the authors to suggest that reduction in albuminuria may achieve cardiovascular benefits beyond BP lowering (34).

**GFR**

As with proteinuria, the extent to which GFR is impaired also is an important predictor of HF in diabetic nephropathy (35) such that in the RENAAL Study, the incidence of HF hospitalization increased with tertiles of serum creatinine, rising from 11.1% (lowest tertile; serum creatinine 0.9 to 1.6 mg/dl) through 15.0% (middle tertile; serum creatinine 1.6 to 2.0 mg/dl) to 16.4% (highest tertile; serum creatinine 2.1 to 3.6 mg/dl) (35).

**Cause of HF in Diabetes and the “Toxic Triad”**

The mechanisms underlying the development of HF in patients with diabetes, particularly those with nephropathy, are multiple and interrelated, including not only the pathophysiologic changes, which develop as a direct consequence of hyperglycemia and of renal dysfunction, but also those related to the common comorbidity of the metabolic syndrome. Such patients exhibit what has been termed a “cardiotoxic triad” of cardiac ischemia, hypertension, and diabetic cardiomyopathy (15), together resulting in a poorly compliant, fibrotic, hypertrophied, and ultimately dysfunctional myocardium.

**Coronary Artery Disease**

Patients with diabetes characteristically develop premature atherosclerotic coronary artery disease, which often is widespread, is asymptomatic, presents late, and tends to involve multiple and distal coronary segments (36). Furthermore, patients with diabetes develop fewer collateral vessels in response to ischemia (37), possibly reflecting impaired production of or responsiveness to vascular endothelial growth factor (38,39). Not only are patients with diabetes at higher risk for coronary artery disease, but also their outcome after MI is considerably worse than in nondiabetic patients (40,41), as is their response to both percutaneous (42,43) and surgical revascularization (44,45). As might be expected from these findings, patients with diabetes are also two to three times more likely to develop HF after MI, and women with diabetes are at particularly high risk (46).

Painless ischemia is very common in patients with diabetes such that dyspnea may be both the presenting symptom of acute ischemia and the result of chronic, incremental loss of myocardium (47). Because patients with diabetes and HF may derive benefit not only from medical anti-anginal therapy but also from percutaneous or surgical revascularization, investigation for underlying coronary artery disease routinely should be undertaken.

As with diabetes, renal function, even when mildly impaired, also is an important predictor of adverse outcome after MI. For instance, in the Valsartan in Acute Myocardial Infarction Trial (VALLANT), in which patients whose plasma creatinine at entry was >2.5 mg/dl (0.22 mmol/L) were excluded, the likelihood of developing HF increased incrementally with the extent of renal impairment as assessed by estimated GFR, with an approximate three-fold increase of HF in patients with GFR <45 ml/min per 1.73 m² compared with those whose GFR was >75 ml/min per 1.73 m² (48). However, the likelihood of previous HF, diabetes, and hypertension also increased with worsening baseline renal function such that it is difficult to assess the impact of the renal dysfunction per se. Nevertheless, the presence of renal dysfunction does identify patients who are at high risk for HF after MI, and it seems likely that this risk might be magnified in the presence of diabetes as a comorbidity.

**Diabetic Cardiomyopathy**

In 1972, Rubler et al. (49) reported a postmortem case series of four patients with diabetic nephropathy and HF in the absence...
of valve disease, significant coronary atherosclerosis, hypertension, or alcohol excess. All had advanced HF with pathologic examination revealing cardiac fibrosis and hypertrophy. More recent biopsy-based studies have indicated that cell loss as a result of apoptosis and necrosis of cardiac myocytes and endothelial cells also are prominent features of diabetic cardiomyopathy (50), along with a range of microvascular abnormalities that include capillary microaneurysm formation (51), arteriolar thickening, and reduced capillary density. Together, these histopathologic features of diabetic cardiomyopathy of fibrosis, atrophy, and hypertrophy are similar to those found in the diabetic kidney, where enlarged and sclerotic glomeruli are found among alternately hypertrophied and atrophic tubules surrounded by a fibrotic interstitium.

In addition to the structural changes of fibrosis, apoptosis, and hypertrophy, a number of pathophysiologic perturbations that contribute to the development of diabetic cardiomyopathy also have been elucidated. These include both changes in cardiac myocytes such as altered substrate metabolism and depressed cardiac myocyte energetics as well as extramyocardial abnormalities such as endothelial dysfunction and autonomic neuropathy (52). Although a detailed exposition of these is not possible in this report, the mechanisms that underlie the development of diabetic cardiomyopathy have been the subject of several recent excellent reviews (15,53–55).

Thus, although still the subject of controversy, clinical, histopathologic, and experimental data all support the existence of a diabetic cardiomyopathy as a cause of systolic and diastolic dysfunction and impaired exercise tolerance in patients with diabetes (56). From a clinical perspective, diabetic cardiomyopathy is a diagnosis of exclusion, defined as cardiac dysfunction in a patient with diabetes that cannot be explained by coronary artery disease, hypertension, or other known cardiac disease (56). In many patients with diabetes, diabetic cardiomyopathy will present subclinically as impaired exercise capacity. Although this often is presumed to be a consequence of obesity and aging, echocardiography frequently will identify diastolic dysfunction in such patients. With more advanced disease, patients will present with overt HF and show evidence of diastolic and/or systolic dysfunction on echocardiography.

Hypertension

Hypertension, another risk factor for the development of HF, is common in patients with diabetes and, as would be expected, increases with the severity of nephropathy. Thus, on the basis of a BP >140/90 mmHg or the receipt of antihypertensive therapy, hypertension is present in 71, 90, and 93% of patients with diabetes and normo-, micro-, and macroalbuminuria, respectively (57).

As in nephropathy, the coexistence of hypertension has an important influence on the extent of cardiac injury in diabetes. For instance, in an autopsy-based study that examined the heart of patients with hypertension, diabetes, or both, the extent of cardiac fibrosis was lowest in the heart of patients with hypertension, mid-range in those with diabetes, and highest in hypertensive patients with diabetes and was significantly greater in those with HF (58). More recently, in a biopsy-based study, Frustaci et al. (50) examined cardiac pathology in patients who had diabetes and HF and no evidence of coronary artery disease on angiography, reporting that the extent of fibrosis, apoptosis, and hypertrophy all were greater in hypertensive patients with diabetes compared with those with diabetes alone.

Diabetes and Diastolic and Subclinical Systolic HF

The ability to assess noninvasively cardiac systolic function with left ventriculography and echocardiography has brought with it the realization that approximately 30 to 50% of hospitalizations for HF occur in patients with preserved left ventricular systolic function, mostly as a result of diastolic dysfunction of the left ventricle (59), a condition to which patients with diabetes are especially prone. Although mortality rates for diastolic HF (DHF) are lower than in systolic HF (SHF), particularly in younger (<65 yr) patients (60), hospitalization rates are similar (60). Risk factors for the development of DHF in patients with diabetic nephropathy include in addition to renal dysfunction and diabetes per se, advancing age, hypertension, and coronary artery disease (61).

Diagnosis

Despite its clinical importance, the criteria that are used to make a diagnosis of DHF are still debated. The “gold standard” for the assessment of left ventricular diastolic function requires cardiac catheterization. However, in most cases, this is not practicable and a combination of clinical and noninvasive cardiac imaging techniques are used to make a diagnosis of DHF. For instance, a patient who presents in pulmonary edema would be referred to as having “probable” DHF if left ventricular function, measured within 72 h of presentation, is preserved (left ventricular ejection fraction [LVEF] >0.50), requiring, in addition, evidence of diastolic dysfunction as measured by noninvasive techniques to make a diagnosis of “definite” DHF according to Vasan and Levy (62). Furthermore, an important caveat in the evaluation of a patient who has symptomatic HF and whose systolic function is preserved is that episodic painless cardiac ischemia may cause transient systolic dysfunction, such that the underlying diagnosis is ischemic heart disease rather than DHF.

Echocardiography in DHF

The tremendous advances in echocardiography and tissue Doppler imaging over the past 10 yr, particularly with regard to the assessment of diastolic function (63), have witnessed an avalanche of echocardiographic studies performed in asymptomatic patients with diabetes. However, although greatly advancing our knowledge in the area, the parameters detailed in such studies, are not those routinely reported in the clinical setting and thus are not well understood by internists, diabetologists, and nephrologists who commonly treat patients with DHF. Accordingly a brief outline of echocardiography as it pertains to the study of DHF and compensated SHF in diabetes is given below.

There are two components to diastolic function: Active and passive. Whereas the active phase involves energy-dependent
relaxation, the passive phase predominantly reflects the viscoelastic properties of the heart. The conventional technique for the assessment of these functions involves the interrogation of transmitral flow during diastole using Doppler echocardiography. This first focuses on the early diastolic flow that occurs when the mitral valve opens (E wave), that serves as an index of left ventricular relaxation, compliance, and atrial pressure. The E wave then is followed by the A wave of atrial contraction that heralds the end of diastole. With early diastolic dysfunction, left ventricular relaxation is slowed and the amplitude of the E wave is diminished while the contribution of atrial contraction is increased, together resulting in a reduced E:A ratio (Figure 4). However, with advancing disease, left atrial and ventricular pressure both rise, increasing the magnitude of the E wave, giving a normal E:A ratio (pseudonormal pattern) that can be unmasked by the Valsalva maneuver. With even further progression, abnormal left ventricular compliance in addition to impaired relaxation gives rise to a restrictive pattern (E:A >2). Using criteria based on these measurements, including the use of the Valsalva maneuver (64), two studies of normotensive men with well-controlled type 2 diabetes found evidence of diastolic dysfunction in 47 and 60% of patients (65,66). Furthermore, although diastolic dysfunction also is a common finding in patients with chronic kidney disease (CKD), patients with diabetic nephropathy have an even greater degree of impairment than is present in nondiabetic kidney disease (67) (Figure 5).

Tissue Doppler Imaging

Although useful, a major caveat, particularly in the setting of renal disease, is the dependence of conventional echocardiographic measurements of transmitral flow on preload (volume status). Accordingly, more recent studies have used tissue Doppler imaging to provide load-independent assessments of cardiac relaxation. These include the myocardial relaxation velocity during early diastole (E’ or E_n), a measurement that is frequently expressed in relation to peak early diastolic transmitral flow (E) as the E/E’ ratio to provide a more preload independent index of left ventricular filling pressure. These studies not only have confirmed evidence of diastolic dysfunction in asymptomatic patients with diabetes but also have

![Figure 4](image-url)  
*Figure 4.* In mild diastolic dysfunction, slowed ventricular relaxation reduces the velocity of early diastolic filling (E wave) and an increase in flow velocity, with atrial contraction leading to a reduced E:A ratio. With more advanced disease, the left atrial and transmitral pressure rise, giving an E:A ratio that is similar to normal individuals (pseudonormal pattern) and that can be unmasked by the Valsalva maneuver. With further progression, left ventricular compliance is increased and a restrictive pattern is seen (156).
shown a direct relationship between the extent of diastolic dysfunction and glycemic control (68) (Figure 6). Consistent with this, studies that have examined the effects of improved metabolic control with pancreas transplantation noted reversal of diastolic abnormalities in recipients of a combined kidney-pancreas transplant over a 4-yr period but not in patients with kidney transplantation alone (69).

Compensated Systolic Dysfunction
In addition to being able to assess diastolic relaxation, tissue Doppler is useful in the examination of cardiac contraction in systole. In particular, this technique is able to differentiate radial systolic function, as a result mainly of contraction of circumferential fibers, from the longitudinal motion that occurs as a consequence of contraction of longitudinal fibers in the subendocardium (70), a region that seems especially vulnerable to ischemic injury and fibrotic repair (71). Indeed, a number of recent studies have shown that subclinical left ventricular systolic dysfunction is a common finding in diabetes, reporting a reduction in longitudinal contraction that is compensated for by increased radial contraction so that global function is preserved (72–74). These findings suggest that both disordered diastolic and systolic function, although mostly asymptomatic, occur early in the course of diabetes.

Brain Natriuretic Peptide in Screening for Left Ventricular Dysfunction in Diabetes
There is considerable controversy regarding the clinical utility of brain natriuretic peptide (BNP) in identifying patients with asymptomatic cardiac disease among patients with diabetes. BNP is a 39–amino acid peptide that is released predominantly by the ventricle in response to intracardiac pressure and stretch. As such, it is a highly sensitive and reasonably specific marker of left ventricular systolic (and to a lesser extent diastolic) dysfunction. Accordingly, in patients with overt symptomatic HF (either diastolic or systolic), BNP is markedly elevated (75).

The role of BNP measurements in the diagnosis, prognosis, and assessment of response to therapy in HF has been the subject of intensive investigation, with recent consensus statements and critical reviews providing useful guidelines (76–78). It is in the first of these roles (diagnosis) where BNP has been evaluated the most extensively. BNP has been found to be of high sensitivity and moderate specificity (i.e., high negative predictive value) in diagnosing HF among patients with undifferentiated dyspnea in the emergency department, outpatient, and general practice settings (79,80), although potential confounders include acute conditions such as coronary syndromes and pulmonary embolism (81).

As diabetes is a known and independent risk factor for the development of HF, it has been proposed that BNP could be used to screen for and aid in the detection of subclinical left ventricular dysfunction in such patients. However, findings using this approach have been somewhat conflicting. For instance, some groups have noted that BNP can reliably screen patients with diabetes for the presence or absence of left ventricular dysfunction even in the absence of clear indications for echocardiography such as symptoms (82,83). However, a number of other groups have suggested that BNP is not capable of identifying mild left ventricular diastolic dysfunction in asymptomatic patients with diabetes, particularly when these patients do not have evidence of macrovascular disease (84,85). Moreover, kidney disease per se, in the absence of either diabetes or HF, results in elevated BNP, adding further difficulties in the interpretation of these clinical studies.

Treatment
Consistent with the common pathologic features of diabetic kidney disease and HF, the treatment of these two complications is also similar. However, whereas there is substantial information regarding the treatment and prevention of SHF in diabetes, there is a dearth of trial data in DHF.

Glycemic Control
Good glycemic control reduces the development and progression of nephropathy in type 1 and type 2 diabetes (16,86–88). Although neither the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes nor the UKPDS in type 2 diabetes showed a reduction in cardiovascular events with intensive glycemic control (16,86), a prospective, observational component of UKPDS revealed a continuous relationship between glycemic exposure and the development of HF with no threshold of risk, such that for each 1% (absolute) reduction in glycosylated hemoglobin (HbA1c), there was an associated 16% decrease in hospitalization for HF (Figure 7) (89). Similar findings also were reported recently in a large cohort study from the US (90).

Despite the absence of definitive interventional studies, these studies suggest that attaining optimal glycemic control should be a goal in both the treatment and the prevention of HF in patients with diabetes. However, the choice of oral hypoglycemic agent that may be used is restricted. For instance, metformin is contraindicated in the presence of either renal impairment or HF, and precautions also apply to the use of the thiazolidinediones (TZD).

Figure 6. Relationship between glycosylated hemoglobin (HgbA1c) and left ventricular diastolic function in patients with type 1 diabetes and without overt HF ($r = 0.68$, $P < 0.0002$) (68).
TZD

The TZD are agonists of the peroxisome proliferator–activated receptor-γ (PPAR-γ), a nuclear receptor that modulates transcription of genes that are related not only to glucose and lipid metabolism but also to adipogenesis and inflammatory signaling (91). In addition to their ability to lower blood glucose by increasing insulin sensitivity, a number of rodent and small clinical studies have shown a beneficial effect of PPAR-γ agonists in diabetic nephropathy (92,93). Similarly, studies of TZD in animals and small human studies using surrogate markers of cardiovascular injury have reported beneficial effects, with larger phase III studies, assessing the effects of TZD on the progression of atherosclerosis, as measured by intravascular ultrasound (APPROACH: Rosiglitazone versus a Sulfonurea on Progression of Atherosclerosis in Patients with Cardiovascular Disease and Type 2 Diabetes, and PERISCOPE: Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation), currently in progress.

Among their multiple effects, TZD also induce fluid retention by mechanisms that are incompletely understood but include the regulation of renal sodium transport (94). Accordingly, patients with New York Heart Association (NYHA) class III or IV HF were not included in the major clinical trials of rosiglitazone and pioglitazone, so these drugs are not recommended in such patients. Although the expansion of ECFV is usually well tolerated, patients with known cardiovascular disease seem to be at increased risk for developing HF with TZD use. For instance, in patients with acute MI, TZD were associated with an increased likelihood of hospital readmission, predominately as a result of HF (95). More recently, in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events), in which patients with diabetes and known macrovascular disease were randomly assigned to receive either pioglitazone or placebo and followed for a mean of 35 mo, has been reported (96). As pointed out in the accompanying editorial (97), although pioglitazone reduced the composite of all-cause mortality, nonfatal MI, and stroke by approximately 16%, its use was associated with an increase in HF that was two-fold greater than the reduction in incidence of cardiovascular events.

BP

The UKPDS examined the effect of BP control on the development of HF in patients with type 2 diabetes in the community setting. “Tight” BP control (achieved BP 144/82 mmHg) was associated with a 56% reduction in the risk for HF compared with less tight control (achieved BP 154/87 mmHg; P = 0.004) (17). The UKPDS further noted a significant association between HF and systolic BP (SBP), such that a 10-mmHg decrease in SBP was accompanied by a 12% decrease in HF, with no apparent threshold of risk (99). More recently, the relationship between achieved BP and cardiovascular outcomes in patients with diabetic nephropathy was examined in IDNT. This post hoc analysis showed that the effects of achieved BP were independent of treatment assignment (irbesartan, amiodipine, and placebo) (100) and that as in UKPDS, SBP and HF hospitalization were directly related such that achieving a 20-mmHg lower SBP was associated with a 25% reduction in HF events (100) (Figure 8).

ACE Inhibition and ARB

A large body of clinical trial data provides important evidence for the routine use of ACE inhibitors and ARB in the treatment of both diabetic nephropathy and HF. Accordingly, more recent trials have examined the use of such treatment in the prevention of HF as well as the effects of combination of ACE inhibitor and ARB with each other or with mineralocorticoid receptor blockade. Both the IDNT and RENAAL trial reported a reduction in hospitalization for new-onset HF in patients who had overt nephropathy and had received ARB.

In the setting of diabetic nephropathy, in which many patients likely will have asymptomatic diastolic dysfunction, an increase in ECFV potentially may precipitate pulmonary edema as a consequence of the steep pressure–volume relationship that characterizes diastolic disease. TZD, if used in such patients, should be administered with caution, commencing with low doses, careful observation, and slow, cautious dose escalation (98).
therapy (31,32), apparently independent of their effects on BP (31).

**Combined ACE Inhibitor and ARB**

Although effective, the response to treatment with an ACE inhibitor or an ARB is incomplete, leading to the speculation that a more complete blockade of the renin-angiotensin-aldosterone system (RAAS), by synergistically combining the two classes of drugs, may be more effective than either when used as a single-agent therapy. This hypothesis is fueled by the concept of “RAAS escape.” According to this hypothesis for which some supportive data exist, constant treatment with an ACE inhibitor or an ARB eventually leads to the return of angiotensin II and aldosterone to their pretreatment levels and limiting of their long-term efficacy (101). The corollary is that dual blockade with an ACE inhibitor and an ARB should limit the reactive activation of the RAAS that results from single-agent treatment. To date, a number of studies of such dual therapy have been conducted in kidney disease. The largest study, the Combination Treatment of Angiotensin II Receptor Blocker and Angiotensin Converting Enzyme Inhibitor in non-diabetic renal disease (COOPERATE), found a beneficial effect of the combination in patients with nondiabetic kidney disease independent of any change in BP (102). Studies in diabetic nephropathy have shown reductions in proteinuria with combination therapy that have been associated with and without BP-lowering effects (103,104). Most recently, the Candesartan and Lisinopril Microalbuminuria II (CALM II), a follow-up to the first study to examine combination therapy in diabetic nephropathy, compared double-dose ACE inhibitor (lisinopril 40 mg) with dual therapy (lisinopril 20 mg with candesartan 16 mg), reporting similar reductions in BP and albuminuria with both treatment regimens (105). Thus, in diabetic nephropathy, in the absence of a definitive study with a renal function outcome, the renoprotective effects of combination therapy, beyond higher dose single-agent treatment or BP reduction, remains highly controversial.

**Combination ACE Inhibitor and ARB for HF**

Two major studies have explored the utility of combining ACE inhibitor with ARB in patients with HF; the CHARM-Added study (106) and the Val-HeFT (107) study. In CHARM-Added, 2548 patients who had symptomatic HF and a LVEF <40% and were treated with ACE inhibitors were assigned to 32 mg of candesartan or placebo. The primary outcome variable of cardiovascular death and HF hospitalization was met with a hazard ratio of 0.85 favoring candesartan. Although various subgroups were analyzed in the primary results manuscript, no subgroup analysis has been published yet according to presence or absence of background diabetes, which comprised 30% of the study population.

In the Val-HeFT study, patients with symptomatic HF and LVEF <40% and left ventricular internal diastolic diameter >2.9 cm/m² were randomly assigned to valsartan (up titrated to 320 mg/d) or placebo. Overall, the co-primary end point of mortality was not met in this study. However, the second co-primary end point of mortality and morbidity (defined as incidence of cardiac arrest and resuscitation, hospitalization for HF, or receipt of intravenous inotropic or vasodilator therapy for at least 4 h) was met with a 13.2% risk reduction with valsartan (relative risk 0.87; P = 0.009). Subgroup analysis according to presence or absence of diabetes was reported in the primary manuscript. Overall, approximately 25% of patients had diabetes in this study. There was no heterogeneity in response according to presence or absence of diabetes at baseline. However, there was a trend for less benefit (although not significantly) in patients who had diabetes at baseline.

**Mineralocorticoid Receptor Antagonism**

Beyond the actions of angiotensin II as the effector molecule of the RAAS, there is increasing evidence that aldosterone also contributes to heart and kidney disease (108). In the Randomized Aldactone Evaluation Study (RALES) of patients with NYHA class III to IV HF, treatment with the nonselective mineralocorticoid receptor antagonist spironolactone led to a 30% reduction in mortality at 2 yr (109). Furthermore, in patients with proteinuric renal disease in general (110) and early diabetic nephropathy in particular, spironolactone was shown to reduce proteinuria (111). However, spironolactone is a non-specific mineralocorticoid receptor antagonist with unwanted affects on gonadal steroid receptors leading to gynecomastia as a frequent adverse effect. In contrast, eplerenone, a specific mineralocorticoid receptor antagonist, recently approved by the Food and Drug Administration, does not cause gynecomastia. In the Eplerenone Post Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), eplerenone reduced mortality with no heterogeneity in effect between subgroups with and without diabetes (110). Moreover, the effects of eplerenone in combination with ACE inhibition have also been examined in patients with early diabetic nephropathy, and although only published in abstract form, these studies showed a greater reduction in albumin:creatinine ratio in patients who were treated with the combination of eplerenone and enalapril than those who were treated with either drug as monotherapy (112) (Figure 9). Hyperkalemia, however, led to

![Figure 9. Percentage change in urinary albumin:creatinine ratio at week 24 in patients who were treated with eplerenone, enalapril, or their combination. P < 0.001 versus baseline (108,112).](image-url)
withdrawal from the study in 14 (21%) patients who received combination therapy, compared with six (8%) patients in the eplerenone group and 2 (3%) in those who were treated with enalapril (108,112). Whether the risk for hyperkalemia can be managed by careful patient selection, dietary potassium restriction, kaliuretic agents, and even ion exchange resins in a manner that might permit the wider use as dual cardiorenoprotective therapies remains to be determined.

β-Blockers

As in other groups, β-blockers also exert substantial cardioprotective effects in patients with diabetes and with kidney disease. For instance, in a meta-analysis of HF trials in which β-blockers were added to an ACE inhibitor or an ARB, patients with diabetes derived a clear beneficial effect (113). Similarly, β-blocker use in long-term dialysis patients improved survival in patients with dilated cardiomyopathy (114) and also reduced risk for new-onset HF in patients without pre-existing HF (115). However, despite compelling data in HF and ischemic heart disease, β-blockers have traditionally been avoided in patients with diabetes because of adverse effects that include hypoglycemic awareness, increased insulin resistance, dyslipidemia, and exacerbation of peripheral arterial disease. However, such risks, which mostly can be managed, need to be balanced against the significant reductions in morbidity and mortality afforded by these drugs. Indeed, the risks of hypoglycemia with β-blockers is no greater than with ACE inhibitors (116), and the newer vasodilatory β-blockers such as carvedilol, which inhibit not only β1 but also β2 and α1 receptors, seem not to have the adverse metabolic effects that beset conventional β-blockers (116) and may even reduce the likelihood of new-onset diabetes (117).

Anemia

Anemia, HF, and CKD are linked components in a vicious circle of chronic disease whereby HF leads to CKD and anemia, CKD leads to anemia and CHF, and anemia leads to HF and CKD (118). Whereas each disorder is associated with increased mortality, their combination further exacerbates risk, suggesting that optimal therapy in each condition should include treatment for all three (118).

In addition to being a common feature of CKD that parallels falling GFR, the prevalence of anemia (Hb <12 g/dl) increases with the severity of HF, reaching 79% in those with NYHA class IV disease (119). Patients with diabetes and impaired renal function may be particularly prone to anemia such that 35 to 55% of patients with diabetes and creatine clearance was <60 ml/min per 1.73 m² are anemic (120). Indeed, for any level of renal dysfunction, diabetic subjects have lower Hb levels than their nondiabetic counterparts.

A number of small studies have examined the effects of anemia correction with erythropoietin (EPO), reporting improvements in renal and cardiac parameters (122). In a study of 179 patients with resistant HF and mild to moderate chronic kidney failure, half of whom had diabetes, the effects of correcting mild anemia (Hb 9.5 to 11.5 g/dl) with EPO and iron were examined. Among patients with diabetes, Epo-Fe treatment was associated with a mean 2.7-g/dl increase in Hb, 35% improvement in NYHA functional class, 7.4% improvement in LVEF, and a 96% reduction in the number of hospitalizations along with stabilization in the previously declining renal function (123). A large prospective study, the Anemia Correction in Diabetes (ACORD) study, is also under way to examine the use of subcutaneous epoietin-β in patients with diabetic nephropathy, comparing early treatment with a target Hb of 13 to 15 g/dl to a conventional target of 10.5 to 11.5 g/dl, with therapy initiated once Hb has fallen to <10.5 g/dl (124).

DHF and Diabetes

To date, almost all large-scale clinical trials in HF have examined patients with systolic dysfunction. However, with the realization of the contribution of HF with preserved systolic function to HF hospitalizations, recent trials have begun to explore treatment in this important group. In the CHARM-Preserved (125) study, 3023 patients with symptomatic HF and LVEF >40% were randomly assigned to candesartan (target 32 mg once daily) or placebo. There was no significant difference in the primary end point of time to cardiovascular death or hospital admission for HF between the two groups or a significant difference in mortality. Although roughly 28% of patients had diabetes in that study, there as yet has been no publication of results according to the presence or absence of diabetes in this population.

The SENIORS (126) study examined the β-blocker/vasodilator nebivolol in 2128 elderly patients with both SHF and DHF. In this study, the overall group was examined according to the presence or absence of baseline diabetes. Diabetes was present in approximately 26% of patients. Although there was no heterogeneity in the response according to presence of baseline diabetes, patients with diabetes did not seem to derive benefit from nebivolol. These analyses have not been subdivided further according to patients with SHF versus DHF as their primary condition.

The Digoxin Intervention Group (DIG) study (127) examined digoxin versus placebo in patients with predominantly SHF and DHF. In that group, there seemed to be a similar response to digoxin to those with impaired systolic function, i.e., reduced hospitalizations and pump failure death offset by an increase in sudden death. None of these differences was statistically significant between digoxin and placebo. Diabetic responses within the preserved systolic function group have not been reported.

New Therapies

In addition to currently marketed treatments, a range of novel therapies are undergoing clinical development for the prevention and treatment of diabetic complications. As might be expected from the common pathology of diabetic nephropathy and cardiomyopathy, these new strategies have the potential to provide new therapeutic options in the management of both kidney disease and HF in diabetes. Among the most advanced in clinical development are agents that modulate
advanced glycation end products (AGE) and the activity of protein kinase C (PKC).

AGE

AGE formation results from a series of nonenzymatic reactions in which sugar derivatives covalently bind to proteins, forming irreversible cross-links that may accumulate in long-lived proteins such as collagen. The quantity of AGE increases as a function of time and glucose concentration (128) such that their abundance increases in diabetes and with age. The accumulation of AGE within tissues leads to alterations in structure and function, with experimental evidence implicating implicating them in the pathogenesis of diabetic complications, including those of the kidney and the heart. As a consequence, strategies to attenuate the pathogenic influence of AGE include prevention of AGE formation, blockade of AGE receptors, and breakers of AGE–protein cross-links.

In experimental animal models of diabetic kidney and cardiovascular disease, blockade of AGE formation with agents such as aminoguanidine (pimagedine) results in attenuation of the disordered structure and function that develops as a consequence of aging and/or diabetes (129–131). Two clinical trials of aminoguanidine have been conducted, both in patients with diabetic nephropathy. In the aminoguanidine in overt type 1 diabetic nephropathy trial (ACTION I), which included 690 patients with type 1 diabetes, nephropathy, and retinopathy, the treated group showed a nonsignificant reduction in the primary end point of time to doubling serum creatinine, although significant reductions in secondary outcomes measures such as proteinuria and progression of retinopathy were noted (132). At the higher of the two doses used in ACTION I (150 mg twice daily and 300 mg twice daily), three study patients developed antineutrophil cytoplasmic antibody–positive crescentic glomerulonephritis, two of whom developed ESRD (132). ACTION II, a 599-patient trial in patients with type 2 diabetes, was stopped prematurely on the recommendation of the data and safety monitoring board because of adverse events (133).

In an attempt to avoid the potential toxicity of aminoguanidine, a number of other inhibitors of AGE formation have been synthesized and are undergoing preclinical and early-phase clinical evaluation. Strategies to block AGE receptor–mediated effects are also in clinical development. However, trials using compounds that can break the covalent AGE cross-links, with their potential to reverse established disease, seem to be the most advanced. These agents that include alagebrum chloride (ALT 711; Alteon Inc., Parsippany, NJ), a stable derivative of N-phenacylthiazolium bromide (134), is under investigation for a range of potential indications that include DHF and diabetic nephropathy. Indeed, the findings of a small 23-patient DHF study were published recently showing that after 16 wk, alagebrum reduced left ventricular mass along with a trend to improvement in E/E’ (135).

PKC

PKC is a ubiquitously expressed, large family of serine-threonine kinases that transduce a wide range of cell-signaling processes by catalyzing substrate-specific phosphorylation. Those of particular relevance to cardiac and renal disease include PKC-mediated increases in TGF-β and matrix–protein expression, activation of mitogen-activated protein kinase, and phenotypic changes in endothelial and smooth muscle cells. At present, there are several PKC inhibitors in preclinical and clinical development that differ in their specificity and mechanisms of action (136). To date, the PKC inhibitor that has been studied most extensively in renal disease is ruboxistaurin (LY 333531; Eli-Lilly and Co., Indianapolis, IN), a specific inhibitor of the PKC-β isoform (137). In studies in diabetic rodents, ruboxistaurin was shown not only to reduce TGF-β and collagen expression (138) but also to attenuate mesangial expansion (139) and albuminuria (137) with evidence of renoprotection despite the presence of continuing hyperglycemia and hypertension (140,141).

In a recently reported pilot phase 2 clinical study, patients with type 2 diabetes and nephropathy were administered ruboxistaurin 32 mg/d along with continued ACE inhibitor and/or ARB for 12 mo, noting a significant decrease in albumin/creatinine ratio from baseline of 24% (P = 0.02) that did not change in the placebo group (−9%; P = 0.33) (142). Furthermore, estimated GFR fell over 1 yr in placebo-treated patients (modified Modification of Diet in Renal Disease −4.8 ± 1.8 ml/min per yr; P = 0.009) but not in the ruboxistaurin-treated group (−2.5 ± 1.9 ml/min per yr; P = 0.185).

In addition to its effects in the kidney, a number of preclinical and human studies suggest a role for PKC-β in the pathogenesis of HF. For instance, PKC-β expression is significantly increased in the failing human heart (143), and mice that overexpress PKC-β in their myocardium exhibit changes similar to those of diabetic cardiomyopathy with left ventricular hypertrophy, myocyte necrosis, cardiac fibrosis, and decreased left ventricular function (144). Moreover, treating rats with ruboxistaurin after MI reduces both cardiac fibrosis and the progressive decline in cardiac function (71). However, although encouraging, to date, the effects of ruboxistaurin in humans with HF have not been examined.

Antifibrotic Therapies

Myocardial fibrosis is a key feature of both diabetic cardiomyopathy and nephropathy. In the heart, fibrosis leads to reduced myocardial elasticity, impaired contractility, and overt cardiac dysfunction (65,66,145,146), and in the kidney, the extent of both glomerulosclerosis and tubulointerstitial fibrosis are closely related to declining renal function (147,148). Accordingly, strategies that reduce the pathologic accumulation of extracellular matrix have been advocated as potential therapies for the treatment and prevention of HF and kidney failure in both diabetic and nondiabetic states. Among potential therapies are tranilast (n-[3,4-dimethoxycinnamoyl] anthranilic acid), an antifibrotic compound that is used in Japan for the treatment of hypertrophic scars (149) and also has been shown to reduce cardiac (150,151) and renal pathology (152,153) in experimental studies, with a pilot clinical trial suggesting a beneficial effect on the progression of renal dysfunction in patients with diabetic nephropathy when added to an ACE inhibitor or an ARB (154).
Conclusion

HF is an important comorbidity in patients with diabetic nephropathy, with common pathogenetic processes underlying both disorders. Although agents that block the RAAS are routinely used in managing chronic kidney and heart disease, β-blockers remain underused, despite their proven benefit in patients with diabetes and HF. In the same way that microalbuminuria is used as an early indicator of nephropathy, it is possible that in the future, sensitive echocardiographic or other noninvasive measurements might become more widely available for the diagnosis of preclinical cardiac dysfunction in diabetes. Such measurements may pave the way for studies that examine new therapies that prevent the progression of both kidney and cardiac dysfunction in diabetes.

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We regret that because of space constraints, we were not able to cite the excellent work of many investigators in the field.

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Most patients with ESRD who are maintained on dialysis or with a successful transplant have increased risks for coronary artery disease cardiomyopathy and subsequent mortality. This is particularly true in diabetics. An article by Kasiske et al. (pages 900–907) in this month’s JASN discusses risk factors after transplant for acute myocardial infarction compared to patients on the waiting list.