Diabetes, Hypertension, and Cardiovascular Disease
An Update

James R. Sowers, Murray Epstein, Edward D. Frohlich

Abstract—Cardiovascular diseases (CVDs) are the major causes of mortality in persons with diabetes, and many factors, including hypertension, contribute to this high prevalence of CVD. Hypertension is approximately twice as frequent in patients with diabetes compared with patients without the disease. Conversely, recent data suggest that hypertensive persons are more predisposed to the development of diabetes than are normotensive persons. Furthermore, up to 75% of CVD in diabetes may be attributable to hypertension, leading to recommendations for more aggressive treatment (ie, reducing blood pressure to <130/85 mm Hg) in persons with coexistent diabetes and hypertension. Other important risk factors for CVD in these patients include the following: obesity, atherosclerosis, dyslipidemia, microalbuminuria, endothelial dysfunction, platelet hyperaggregability, coagulation abnormalities, and “diabetic cardiomyopathy.” The cardiomyopathy associated with diabetes is a unique myopathic state that appears to be independent of macrovascular/microvascular disease and contributes significantly to CVD morbidity and mortality in diabetic patients, especially those with coexistent hypertension. This update reviews the current knowledge regarding these risk factors and their treatment, with special emphasis on the cardiometabolic syndrome, hypertension, microalbuminuria, and diabetic cardiomyopathy. This update also examines the role of the renin-angiotensin system in the increased risk for CVD in diabetic patients and the impact of interrupting this system on the development of clinical diabetes as well as CVD. (Hypertension. 2001; 37:1053-1059.)

Key Words: diabetes ■ cardiovascular diseases ■ hypertension, essential ■ blood pressure

Hypertension in the Diabetic Patient

The subject of diabetes mellitus as a comorbid disease that frequently confounds hypertension, adding significantly to its overall morbidity and mortality,1,2 will be updated in the present review. Among the complications of diabetes, cardiovascular and renal vascular diseases are among the most costly in terms of human suffering and national healthcare costs. Over the past several years, since the publication of these foregoing reviews, a number of controlled multicenter clinical trials have demonstrated the safety and efficacy of specific antihypertensive therapeutic programs that can significantly alter the outcomes of these cardiovascular and renal complications. The present report summarizes these advances as well as newer fundamental findings that add importantly to our overall knowledge of the cardiovascular complications of diabetes mellitus.

In a recent, large, prospective cohort study that included 12,550 adults, the development of type II diabetes was almost 2.5 times as likely in persons with hypertension than in their normotensive counterparts.3 This, in conjunction with considerable evidence of the increased prevalence of hypertension in diabetic persons,1,2 suggests that these 2 common chronic diseases frequently coexist. Moreover, each pathophysiologic disease entity, although independent in its own natural history, serves to exacerbate the other.1,2 In a recent report of Gress et al,3 hypertensive patients who were taking β-blockers had a 28% higher risk of diabetes than did those taking no medication. In contrast, patients with hypertension who received thiazide diuretics, ACE inhibitors, or Ca2+ antagonists were found not to be at greater risk for subsequent diabetes than were patients who were not receiving any antihypertensive medications. However, that study was not prospective or randomized,3 and other randomized prospective trials have not shown an increase in the development of diabetes with β-blocker or low-dose diuretic treatment of hypertension.4–6 Recent studies have reported that ACE inhibitor therapy reduced the propensity of hypertensive patients to develop type 2 diabetes by 11%7 and 34%8 in trials extending for 6 and 4 years, respectively, suggesting that antihypertensive treatment may have a significant impact on the propensity for the development of diabetes in this population.9 These observations are in contrast to a recent report3 in which no reduction in progression to diabetes on ACE inhibition therapy was observed. Thus, more controlled ran-
domized prospective trials are required to address the potential for ACE inhibitor therapy to reduce the rate of development of diabetes in hypertensive patients.

There is an increasing body of data from controlled clinical trials indicating that rigorous control of arterial pressure to levels <140/90 mm Hg markedly reduces cardiovascular disease (CVD) morbidity and mortality and the development of end-stage renal disease in persons with type 2 diabetes.\textsuperscript{6–13} In the Systolic Hypertension in the Elderly Program (SHEP) study,\textsuperscript{4} elderly persons with type 2 diabetes derived more benefit from aggressive systolic blood pressure lowering in reduction of CVD than did those without diabetes. Baseline therapy in the SHEP study used a low-dose diuretic, which is often a necessary component of the antihypertensive regimen because of the sodium sensitivity and expanded plasma volume that is often present in diabetic patients.\textsuperscript{14} Data from the subset analysis of type II diabetes in the Hypertension Optimal Treatment (HOT) trial\textsuperscript{10} suggest that reduction in diastolic pressures from <90 mm Hg to values <85 mm Hg is beneficial in reducing CVD events. The initial drug therapy in HOT was with a dihydropyridine Ca\textsuperscript{2+} antagonist, but >70% of diabetic patients required at least 3 drugs to control the diastolic pressure to levels <85 mm Hg. Special benefits of aggressive blood pressure lowering in the diabetic population was observed in a subanalysis of this cohort in the Systolic Hypertension in Europe (Syst Eur) Trial.\textsuperscript{11} In that trial, although systolic pressure was reduced by a comparable amount in each group (~22.0±16 mm Hg [nondiabetic group] versus ~22.1±14 mm Hg [diabetic group]), the risk reduction in mortality from CVD was 13% in nondiabetic patients versus 76% for the diabetic patients.\textsuperscript{11} Again, diabetic patients required more antihypertensive treatment to achieve goal blood pressures, with up to two thirds requiring ≥2 medications as previously observed.\textsuperscript{4,10} Moreover, the benefit confirmed per mm Hg blood pressure reduction was greater in diabetic patients than in those patients with hypertension but without concomitant diabetes mellitus, providing further evidence for rigorous reduction of arterial pressure in diabetic patients.

United Kingdom Prospective Diabetes Study Group

In the United Kingdom Prospective Diabetes Study (UKPDS) group,\textsuperscript{12,13} blood pressure lowering was similarly effective for captopril- and atenolol-based regimens in reducing the incidence of both microvascular and macrovascular diabetic complications. Many of these type 2 diabetic patients required both drugs plus a diuretic for “tight control” of pressure (ie, 144/82 mm Hg). The necessity for use of at least 3 drugs for tight control was also observed in the diabetic cohorts of the HOT and Syst Eur studies as well.\textsuperscript{10,11} In the UKPDS, reductions in risk in the group assigned to tight control were 24% in diabetes-related end points, 32% in death-related end points to diabetes, 44% in strokes, and 37% in microvascular end points, especially diabetic retinopathy. Moreover, in the UKPDS trial, the relative benefit on CVD risk reduction was conferred in a far more powerful fashion by intensive blood pressure reduction rather than by tight glucose control.\textsuperscript{12}

\textbf{Figure 1.} Algorithm for antihypertensive therapy in the diabetic individual. “An adequate response indicates that goal blood pressure is achieved or considerable progress is made.

ACE inhibitors are currently recognized as first-line antihypertensive therapy in diabetic persons with proteinuria,\textsuperscript{2,15,16} and these agents afford unique benefits in modifying the progression and severity of CVD as well as of diabetic nephropathy (Figure 1). Indeed, a cardioprotective effect of ACE inhibitors has been suggested from results of the Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET),\textsuperscript{17} the Captopril Prevention Project (CAPPP),\textsuperscript{7} the Heart Outcomes Prevention Evaluation (HOPE) trial,\textsuperscript{8} and the Shunt Thrombotic Occlusion Prevention by Picotamide (STOP)-2 Hypertensive Trial.\textsuperscript{6} FACET\textsuperscript{16} was an open-label single-center trial designed to compare the effects of fosinopril and amlodipine on serum lipids and glycemic control. Patients were assigned to treatment with either amlodipine or fosinopril; if blood pressure was not controlled, the other drug was added. The incidence of CVD events was less in the fosinopril-treated group than in the amlodipine-treated group, but the incidence was least in the group that received both antihypertensive agents.\textsuperscript{18} Furthermore, it should be noted that there was no placebo group in the FACET study, so that the impact of Ca\textsuperscript{2+} antagonists alone could not be ascertained. These results, as well as those of the Syst Eur\textsuperscript{13} and HOT\textsuperscript{10} studies, suggest that the combination of a dihydropyridine Ca\textsuperscript{2+} antagonist (such as amlodipine or nitrendipine) and an ACE inhibitor is an acceptable approach to the treatment of this high-risk population. It is clear from these recent studies that reaching goal blood pressure in diabetic patients, especially if they have renal disease, will require treatment with several antihypertensive agents. Results of the SHEP\textsuperscript{8} and the UKPDS\textsuperscript{12} trials suggest that diuretics and β-blockers as well as ACE inhibitors are also useful therapeutic agents in
diabetic hypertensive patients who often require ≥2 drugs to control blood pressure adequately19 (Figure 1).

**CAPP Trial**

CAPP7 was an unblinded prospective trial that enrolled 10,985 patients aged 25 to 66 years with diastolic pressure of at least 100 mm Hg. Patients were randomized to receive either captopril (in 1 or 2 doses up to 100 mg/d), with a thiazide diuretic added if necessary, or the clinician’s choice of a thiazide diuretic or β-blocker, with the alternative agent as add-on therapy if necessary. Over a follow-up period of ≈6.1 years, in part because of inadequate randomization for baseline blood pressure, there was a small increase in stroke in the captopril group and a slight reduction in myocardial infarction and other cardiovascular deaths in this treatment group for the nondiabetic cohort. However, the risk of developing new diabetes was 11% less in the captopril-treated group. In diabetic patients (n=572), there was a reduction in the CVD end points (P=0.02) in the group receiving captopril. In the diabetic cohort, there was a better outcome with regard to all outcomes in patients randomized to captopril. The study suggested that although overall events may be similar to β-blocker/diuretic treatment compared with an ACE/diuretic regimen, there appears to be an advantage to the latter regimen in diabetic persons.

**HOPE Trial**

HOPE was a randomized double-blind evaluation of the ACE inhibitor ramipril in patients at high risk for vascular disease complications but without clinically evident heart failure.8 The HOPE trial tested the hypothesis that ACE inhibitors in general, and ramipril in particular, have beneficial effects on vascular disease complications above and beyond their effects on blood pressure. However, the small reduction in blood pressure with ramipril may have contributed to its beneficial effects.8

All patients enrolled in the HOPE trial had documented vascular disease, ie, a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes, with 1 additional cardiovascular risk factor. A total of 9,297 patients were randomized to either ramipril or matching placebo and were followed for a mean duration of 5 years. The primary end points were myocardial infarction, stroke, or death from a cardiovascular cause. Secondary outcomes were death from all causes, need for coronary artery revascularization, hospitalization for unstable angina, heart failure, and complications related to diabetes.

The 3,577 diabetic patients enrolled in the HOPE trial were also examined separately in a substudy of microalbuminuria and cardiovascular and renal outcomes (MICRO-HOPE).20 In keeping with the findings of the major trial, the primary outcome (a composite of myocardial infarction, stroke, or death from a cardiovascular cause) was reduced by 25% (95% CI 12% to 36%, P<0.0004) in diabetic patients treated with ramipril compared with diabetic patients receiving placebo. Secondary outcomes of total mortality and need for revascularization were also significantly lower among diabetic patients receiving ramipril. Admissions to the hospital for unstable angina or heart failure did not differ between patients receiving ramipril and those receiving placebo. However, there was a significant 16% reduction in progression to overt nephropathy (95% CI 1% to 29%, P=0.036), and there were nonsignificant trends toward less laser therapy for retinopathy and less progression to end-stage renal disease in the ramipril group as well.

One of the most striking observations from the HOPE trial is that relatively large reductions in risk were achieved in the face of comparatively small reductions in blood pressure. Patients enrolled in the HOPE trial were not required to be hypertensive, and the average blood pressure on admission was 139/79 mm Hg. By 2 years, when the trends in end points first reached statistical significance, the average reduction in blood pressure was only 3/2 mm Hg. This striking finding points toward possible direct effects of ramipril (and ACE inhibitors as a class) on the heart and vasculature in addition to their additional effect on blood pressure. In the HOPE trial, diabetic patients derived an even greater reduction in CVD than did the rest of the high-risk population.8

The HOPE study also showed a 34% reduction in the development of diabetes in those patients without diabetes at the onset of the study. Furthermore, in another study, the ACE inhibitor perindopril was reported to reduce insulin resistance in obese hypertensive patients without diabetes.21 Thus, the lessons learned from these 3 studies suggest that ACE inhibitor therapy can improve insulin sensitivity and also delay the development of diabetes in patients at high risk for the development of this disease. The mechanism whereby ACE inhibitors improve glucose metabolism and protect against the development of clinical diabetes may involve the improvement of blood flow through the microcirculation to fat and skeletal muscle tissue and/or the improvement of insulin action at the cellular level (by interfering with the angiotensin II [Ang II] antagonism of insulin signaling) (Figure 2). The fact that ACE inhibitors, but not Ang II receptor antagonists, improve insulin resistance21 suggests that their action on glucose metabolism may be mediated via (at least in part) bradykinin metabolism. Significant improvement of insulin responsiveness, which was achieved by the addition of an ACE inhibitor to a tissue culture,22 indicated
that the protective effect of ACE inhibition on diabetes is not
(or is not solely) related to changes in blood flow. This
improvement is also likely mediated at a cellular level, as
shown by increases in glucose transporter (GLUT-4) protein
and the activity of hexokinase, one of the major enzymes of
GLUT-4. Proinsulin, one of the major enzymes of
glucose metabolism, in skeletal muscle of obese rats treated
with an ACE inhibitor (Figure 2).

Interrupting the effects of the renin-angiotensin system
(RAS) may improve the cellular actions of insulin by several
mechanisms. Ang II in vascular and heart tissue interferes
with insulin stimulation of phosphatidylinositol 3-kinase
(PI3-kinase) activation, a major pathway for insulin signal
transduction.23–25 (Figure 2). The relationship between the
RAS and insulin is complex and includes several intracellular
mechanisms and signaling pathways. Normally, insulin binds
to its receptor (IR) on the surface of the insulin-sensitive cell
and triggers autophosphorylation of the IR β-subunit, which,
in turn, phosphorylates tyrosine in the IR substrate (IRS)
molecules. This allows the regulatory p85 subunit of PI3-
kinase to connect to the IRS-1 and form an IRS-1/PI3-kinase
complex, which is involved in many of the actions of insulin,
including chemotaxis, translocation of cellular elements, and
insulin vesicle transport.26 This pathway has also been implicated in
mediating the activation of NO synthase and the Na+ pump
activity in vascular tissue26,27 and in facilitating vascular
relaxation.

Ang II, acting via an Ang II type 1 G-protein–linked
receptor, phosphorylates a number of proteins, including
IRS-1 and -2. Such phosphorylation, leads to the activation of
catalytic activity of the p110 subunit of PI3-kinase, the same
enzyme that is involved in insulin-signaling pathways. Para-
doxically, this process interferes with insulin-dependent
activation of PI3-kinase and, therefore, inhibits this major
pathway of insulin signaling and decreases the ability of the
cell to consume glucose in response to insulin.12 Precise
mechanisms of such inhibition remain unclear, but it has been
shown that Ang II inhibits the insulin-stimulated association
between IRS-1 and -2 and the regulatory p85 subunit of PI3-kinase
by 30% to 50% in a dose-dependent manner.23,24 A recent
population-based study showed that CVD mortality
was 7.5 times greater among persons with type 2 diabetes
without a previous myocardial infarction than in those with-
out diabetes31 (Figure 3). Furthermore, the incidence of CVD
mortality was 3-fold higher among individuals with diabetes
who had suffered a myocardial infarction than among nondi-
abetic individuals.33 Diabetes is associated with a relatively
greater risk for CVD in women than in men.32 Moreover,
diabetes negates the normal gender differences in the preva-
ence of CVD, and when adjusted for other risk factors, the
risk rate for increased mortality is 2.4 times greater for
diabetic men and 3.5 times greater for diabetic women.32,33

A number of factors, in addition to hypertension, contrib-
ute to the high prevalence of CVD in type 2 diabetic persons.
Within the Multiple Risk Factor Intervention Trial (MR-
FIT),34 >5000 diabetic patients were followed for 12 years
and were compared with >350 000 persons without diabetes.
The occurrence of CVD death at the 12-year follow-up was
≈3 times more in diabetic men than in their nondiabetic
controls, regardless of systolic pressure, age, cholesterol,
ethnic group, or use of tobacco. This study also confirmed
that systolic hypertension, elevated cholesterol, and cigarette
smoking were independent predictors of mortality and that
the presence of ≥1 of these risk factors had a greater impact
on increasing CVD mortality in persons with diabetes than in
those without diabetes.

Other risk factors that are involved in the cardiometabolic
syndrome, which includes persons with prediabetes, include
the following: obesity, hyperlipidemia, hyperuricemia, and albuminuria. The hyperuricemia that occurs in essential hypertension (when not ascribed to gout, diuretic therapy, or other factors known to produce hyperuricemia) is related to reduced renal blood flow and increased renal vascular resistance. This elevation in serum uric acid not only accompanies the vascular alterations associated with nephrosclerosis but also follows the development of left ventricular hypertrophy (echocardiographically) and accompanies the foregoing renal hemodynamic involvement in patients with the early stages of essential hypertension, even before the development of proteinuria or impaired renal excretory function. On the other hand, microalbuminuria has been reported to develop before any clinical evidence of coronary heart disease (eg, myocardial infarction and cardiac failure) or intrarenal vascular disease in patients having diabetes with or without hypertension. Nephrosclerosis associated with hypertension and renal diabetic vascular disease affects the intrarenal arterioles, whereas CHD, associated with occlusive epicardial coronary artery disease, as manifested by myocardial infarction, is an arterial disease. In the case of the latter, both hypertension and diabetes exacerbate the atherosclerotic occlusive disease.

Diabetic Cardiomyopathy
Diabetic cardiomyopathy, a diabetes-related myopathic state, is characterized mainly by impaired diastolic function. In experimental diabetes, the mechanical properties of the myocardium and cardiomyocytes in vitro involve prolongation of contraction and relaxation as well as considerable slowing in relaxation velocity. Diabetic cardiomyopathy is observed in chemically induced insulinopenic as well as in genetically predisposed insulin-resistant rodent models. Potential abnormalities underlying this cardiomyopathic state include altered K⁺ channel function, alterations in Na⁺ pump function, alterations in sarcoplasmic (endoplasmic) reticulum Ca²⁺-ATPase, Na⁺-Ca²⁺ exchanger function, and abnormalities of protein kinase C metabolism.

Diabetic cardiomyopathy may be associated with a balance between the cardiac RAS and the autocrine/paracrine actions of insulin-like growth factor (IGF)-1. The peptides, Ang II and IGF are generated by cardiomyocytes and exert pleiotropic effects in an autocrine/paracrine fashion. IGF-1 also has been demonstrated to increase myocardial contractility by increasing [Ca²⁺], and cardiomyocyte myofilament Ca²⁺ sensitivity. IGF-1 is synthesized by cardiomyocytes under the control of insulin, Ang II, mechanical stress, and increased total peripheral resistance. IGF-1 and Ang II have opposing actions on key signaling pathways of the heart but work synergistically in promoting growth. One of the major pathways of IGF-1 signaling involves the activation of the PI3-kinase/IRS-1 complex. The PI3-kinase pathway is known to mediate many insulin/IGF-1 actions, including receptor trafficking, glucose transport, cytoskeletal reorganization, the Na⁺,K⁺-ATPase and K⁺ channel expression/activity, and myofilament-Ca²⁺ sensitivity.

Ang II, acting via its G-protein–linked receptor, also induces tyrosine phosphorylation of IRS-1. In cardiac tissue in contrast to insulin/IGF-1, Ang II acutely inhibits basal as well as insulin/IGF-1–stimulated PI3-kinase activity (Figure 2). Thus, it has been proposed that overexpression of the RAS, as occurs in the diabetic heart, would predispose one to a resistance to the actions of insulin/IGF-1 on the PI3-kinase–mediated activation of K⁺ channel and Na⁺ pump expression/activation as well as myofilament-Ca²⁺ sensitivity. Indeed, reduced cardiomyocyte glucose transport and attenuated PI3-kinase response to insulin-IGF-1 have been observed in insulin-resistant rodent models. These abnormalities are associated with decreased expression/activation of the K⁺ channel and Na⁺ pump in both type 1 and type II diabetic states. Resistance to the PI3-kinase–mediated actions of IGF-1 and insulin could explain the abnormalities of both diastolic and systolic function and left ventricular hypertrophy, which characterize “diabetic cardiomyopathy.” However, unabated action of both IGF-1 and Ang II could help explain why patients with diabetes appear to have greater left ventricular mass than do nondiabetic cohorts with comparable blood pressures.

Microalbuminuria and CVD in Diabetes
There is considerable evidence that the presence of hypertension in type 1 diabetes is a consequence rather than a cause of renal disease. For example, with low levels of microalbuminuria, the arterial pressure remains normal, a finding that suggests that nephropathy precedes the raise in blood pressure. Regardless of whether hypertension in type 1 diabetics who develop this complication and that nephropathy and hypertension exacerbate each other. On the other hand, microalbuminuria is an independent risk factor for the development of CVD and a predictor of cardiovascular mortality in the diabetic population. It is associated with insulin resistance, atherogenic dyslipidemia, central obesity, and the absence of nocturnal drop in both systolic and diastolic pressures and is a part of the metabolic cardiovascular syndrome associated with hypertension (Table). Because microalbuminuria is part of the cardiometabolic syndrome and is related to endothelial dysfunction and increased oxidative stress, it is not surprising that diabetic glomerulosclerosis parallels diabetic atheroscle-
nosis and is a very powerful risk factor for coronary heart disease and stroke in diabetic persons.15,16,57

Therapeutic Implications
It is clear from the foregoing review of newer information concerning the CVD complications of diabetes mellitus and their interaction with hypertension and its complications that the recent national recommendations concerning the treatment of patients with hypertension19 are all the more important. Thus, although there is a necessity for risk stratification of patients with hypertension according to the stage of blood pressure elevation, it is apparent that the inclusion of all patients with hypertension whose systolic and diastolic pressures exceed 130 and/or 85 mm Hg, respectively, should probably receive antihypertensive drug therapy. Although a goal blood pressure of 130/85 mm Hg is relatively arbitrary, it is also recognized by other organizations, such as the Canadian Hypertension Society,58 as a reasonable goal to maximally preserve function and reduce CVD morbidity and mortality. Clearly, lifestyle modifications are important for all patients with diabetes, but in those with even high normal levels of blood pressure elevation, pharmacotherapy of hypertension is particularly important. It is further evident from these Joint National Committee-6 recommendations and recent clinical trial data cited in the present report that the first choice in antihypertensive agents is the selection of an ACE inhibitor. Indeed, ACE inhibitor therapy has been shown to reduce the progression of renal disease20,59 and CVD in diabetic persons with “normal blood pressure.”7

Although it is clearly not our purpose to review the pharmacological treatment of diabetes and hypertension, a few compelling observations are in order. A review of recently completed clinical trials indicates that >65% of people with diabetes and hypertension will require ≥2 different antihypertensive medications to achieve the new suggested target blood pressure of <130/85 mm Hg.19 ACE inhibitor therapy should be an integral component of any antihypertensive regime in patients with diabetes, inasmuch as these agents have been demonstrated to reduce CVD7,8 and renal disease53 in this population. Not every patient with diabetes and hypertension can take an ACE inhibitor either because of specific side effects from therapy or because of absolute contraindications. Thus, if a persistent cough secondary to the ACE is intolerable and precludes its further use, then selection of an Ang II (type 1) receptor antagonist appears appropriate. A number of multicenter trials are ongoing and are directed to support this recommendation. However, because results supporting their use are not yet available, it is not unreasonable to conclude that Ang II receptor antagonists are appropriate choices. Other complications of ACE inhibitor therapy, particularly in patients with diabetes, may be the progression of renal functional impairment and/or hyperkalemia. In these patients, a number of studies have supported the use of Ca2+ antagonists.19 Finally, the use of ACE inhibitors or Ang II antagonists in any pregnant woman (including one with diabetes) is definitely contraindicated.

Over and above the foregoing therapeutic recommendations, it is also important to assess the status of the diabetic patient’s serum concentration of LDL cholesterol and glycated hemoglobin.1,2,10,19,59 Thus, in those patients with an LDL cholesterol of 100 mg/dL and glycated hemoglobin of ≥6.5, more vigorous control of both lipids and of glycated hemoglobin levels is particularly indicated. Finally, all diabetic patients should receive aspirin unless there is absolute contraindication.60

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