The Treatment of Hypertension in Adult Patients With Diabetes

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Hypertension is an extremely common comorbidity of diabetes, affecting 20–60% of people with diabetes. Hypertension is also a major risk factor for cardiovascular events, such as myocardial infarction and stroke, as well as for microvascular complications, such as retinopathy and nephropathy. Cardiovascular disease is the most costly complication of diabetes and is the cause of 86% of deaths in persons with diabetes (1). However, until recently, little research had been done specifically in patients with diabetes and hypertension. In reviewing the literature on diabetes and hypertension, the authors searched MEDLINE for English language articles using keywords “hypertension,” “diabetes mellitus,” “diabetic nephropathy,” and “coronary artery disease/prevention” starting from 1966. Before 1996, most available data come from secondary analysis from studies done in the general population of people with hypertension, observing a subset with diabetes. Recent studies have demonstrated the effectiveness of blood pressure treatment versus placebo in reducing complications of diabetes (2,3), helped to define the optimal level of blood pressure versus placebo in reducing complications of diabetes (2,3), helped to define hypertension in diabetic patients. Studies in the general population indicate an increased risk of cardiovascular disease with an increase in the level of blood pressure. Thus, an increase in diastolic or systolic blood pressure of 5 mmHg is associated with a concomitant increase in cardiovascular disease of 30% (14). Studies in diabetic populations have shown a markedly higher frequency of the progression of diabetic retinopathy when diastolic blood pressure is in excess of 70 mmHg (15). Most epidemiological studies have used a categorical definition of hypertension, using levels of 160 mmHg for systolic and 90 mmHg diastolic blood pressure. Based on the current evidence from clinical trials showing clinically significant benefits of treating diabetic individuals to lower levels of blood pressure, these values are considered too high to serve as a threshold for the definition of hypertension in diabetic patients. In 1997, the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure published revised recommendations (JNC VI) on the management of hypertension in the general population and on diabetic patients that recommended a lower target for patients with diabetes (130/85 mmHg) than for the general population (140/90 mmHg). The standard definition of hypertension is a blood pressure ≥140/90 mmHg (16). Evidence obtained from clinical trials in diabetic patients suggests a continuum of risk and clinically significant benefit in outcomes with reductions of blood pressure below 140 mmHg systolic and 80 mmHg diastolic blood pressure, as will be discussed in this review. For elderly populations with systolic hypertension, benefits have been shown when blood pressure is reduced below systolic levels of 140 mmHg (2,3). Epidemiological studies indicate that there is a benefit to reducing systolic blood pressure still further to 130 mmHg or below (17,18). Therefore, the goal for blood pressure should be ≤130 mmHg for systolic and ≤80 mmHg for diastolic blood pressure.

Prevalence

The prevalence of hypertension in the diabetic population is 1.5–3 times higher than that of nondiabetic age-matched groups (1). The timing and presentation of hypertension differs between type 1 and type 2 diabetes. In type 1 diabetes, hypertension develops after several years of the disease and usually reflects the development of diabetic nephropathy. It ultimately affects ~30% of individuals with type 1 diabetes (18–20). In type 2 diabetes, hypertension may be present at the time of diagnosis or even before the development of hyperglycemia (21). Several confounding factors are present in type 2 diabetes that make the assessment of the prevalence of hypertension attributable to diabetes difficult. Type 2 diabetic patients are older and have a greater degree of ad-
The prevalence of hypertension in Western populations increases with age and degree of obesity (22). Thus, elevated blood pressure in these individuals may represent the aging or obesity of the population. However, after adjusting for age and weight, the prevalence of hypertension is still 1.5 times higher in diabetic groups (21). Approximately 20–60% of patients with type 2 diabetes will develop hypertension, depending on age, ethnicity, and obesity. In some ethnic groups, diabetic nephropathy may be the primary determinant of hypertension in type 2 diabetes. This has been documented in Pima Indians (23). The clustering of hypertension, glucose intolerance or frank type 2 diabetes, hyperlipidemia, central obesity, and insulin resistance has been documented in several populations (22). The pathogenesis of this association is under active investigation. Extensive epidemiological evidence indicates that diabetic individuals with hypertension have greatly increased risks of cardiovascular disease, renal insufficiency, and diabetic retinopathy (24–26). The relationship between diabetic neuropathy and arterial hypertension is less clear. However, some epidemiological studies suggest that hypertension may be a contributory factor for this condition as well (25).

**Pathophysiology**

A detailed review of the pathophysiology of hypertension in diabetes is beyond the scope of this review. In the presence of nephropathy, extracellular fluid volume and total body sodium levels are increased. The activity of the renin-angiotensin-aldosterone system (RAAS) is reduced in these patients, and the hypertension is volume-dependent, similar to other nephropathies (27,28). In the absence of diabetic nephropathy, other factors must play a role in the development of hypertension. These factors are both genetic and acquired. Elevated total body sodium with low or normal activity of the RAAS has been reported (29). Studies in humans with hypertension have found hyperinsulinemia secondary to insulin resistance and decreased insulin clearance (30–32). Hyperinsulinemia may possibly be associated with increased renal sodium resorption and sympathetic nervous system overactivity, leading to hypertension in obese individuals and other insulin-resistant states, such as type 2 diabetes (33,34). Insulin resistance is also associated with a decreased vasodilatory response to insulin in skeletal muscle (35) and an increased vasoconstrictor response to various vasopressors. However, the role of insulin resistance in the etiology and pathogenesis of hypertension is not fully understood.

**SECTION 2: MANAGEMENT OF HYPERTENSION IN DIABETES**

**Screening and initial evaluation**

All patients with diabetes should have blood pressure measured at the time of diagnosis or initial office evaluation and at each scheduled diabetes visit (36). Because of the high cardiovascular risk associated with blood pressure ≥130/80 mmHg in patients with diabetes, 130/80 mmHg is considered to be the cut point for defining hypertension, rather than 140/90 mmHg, as in the general population. Initial assessment of a hypertensive diabetic patient should include a complete medical history with special emphasis on cardiovascular risk factors and the presence of diabetes complications and other cardiovascular complications.

The measurement of blood pressure should ideally be performed in the supine and standing position. Two or more determinations in each position should be obtained using an appropriately sized cuff; obese patients generally require a large arm cuff and sometimes a thigh cuff to ensure accuracy. Cardiovascular autonomic neuropathy with significant orthostatic changes in blood pressure is common in diabetic subjects; can cause falsely low or high readings, depending on the position of the patient when the blood pressure is taken; and should be considered when treating patients (37).

The diagnosis of hypertension in patients with diabetes should be reserved for those individuals whose blood pressure levels exceed 130/80 mmHg on at least two separate occasions separated by at least 1 week. The physical exam should include height, weight, funduscopic examination, and careful evaluation of arterial circulation. Initial laboratory examination should include serum creatinine, electrolytes, A1C test, fasting lipid profile, and urinary albumin excretion (this can be measured by semiquantitative methods as screening tests, by quantitative methods in timed urine samples, or as albumin-to-creatinine ratio in spot samples).  

**Behavioral treatments of hypertension**

Dietary management with moderate sodium restriction has been effective in reducing blood pressure in individuals with essential hypertension (38,39). Several controlled studies have looked at the relationship between weight loss and blood pressure reduction (40,41). Weight reduction can reduce blood pressure independent of sodium intake and can also improve blood glucose and lipid levels. The loss of 1 kg body wt has resulted in decreases in mean arterial blood pressure of ~1 mmHg (42). The role of very low calorie diets and pharmacological agents that induce weight loss in the management of hypertension in diabetic patients has not been adequately studied. Some appetite suppressants, both prescription and over-the-counter, may induce increases in blood pressure levels (43–45) and therefore must be used with care. One over-the-counter appetite suppressant, phenylpropanolamine, has been associated with an increased risk of hemorrhagic stroke (46) in women and has been taken off the market; however, patients may still have supplies of this drug. Therefore, part of history-taking should include the use of over-the-counter drugs. Given the present evidence, weight reduction should be considered an effective measure in the initial management of mild-to-moderate hypertension, and the results could most likely be extrapolated to the diabetic hypertensive population.

Sodium restriction has not been tested in the diabetic population in controlled clinical trials. However, results from controlled trials in essential hypertension have shown a reduction of ~5 mmHg for systolic and ~2–3 mmHg for diastolic blood pressure, with moderate sodium restriction (from a daily intake of 200 mmol [4,600 mg] to 100 mmol [2,300 mg] of sodium per day). A dose-response effect has been observed with sodium restriction. Reductions in daily sodium intake to levels of 10–20 mmol (230–460 mg) per day have resulted in decreases in systolic blood pressure of 10–12 mmHg (38). Even when pharmacological agents are used, there is often a better response when there is concomitant salt restriction caused by the afore-
mentioned volume component of hypertension that is almost always present. The efficacy of these measures in diabetic individuals is not known.

Moderately intense physical activity, such as 30–45 min of brisk walking most days of the week, has been shown to lower blood pressure and is recommended in JNC VI (16). Smoking cessation and moderation of alcohol intake are also recommended by JNC VI to reduce blood pressure (16,47,48).

A number of epidemiological studies suggest an inverse relationship between calcium, magnesium, and potassium intake and blood pressure level (49–51). Most of these studies are cross-sectional, but a few are prospective observational studies. However, none of these studies has analyzed diabetic patients separately from the general hypertension population. Several randomized clinical trials have been published analyzing the effects of calcium supplementation on blood pressure levels. The characteristics of populations studied vary markedly among these studies and include subjects with normal, high-normal, or elevated blood pressure. A meta-analysis of these trials published in 1990 reported a very small blood pressure change (mean reduction in systolic blood pressure 1.8 mmHg and observed reduction in diastolic blood pressure 0.7 mmHg) (50). There are no randomized clinical trials on magnesium supplementation in diabetic subjects with hypertension.

**Drug therapy**

The purpose of antihypertensive treatment is to reduce the morbidity and mortality from cardiovascular complications (congestive heart failure, coronary artery disease, and stroke) and microvascular complications (nephropathy, neuropathy, and retinopathy). Available studies exploring the effects of pharmacological agents on the course of these complications will be reviewed. All available agents produce a similar reduction in systolic and diastolic blood pressure at the doses available for clinical use (10–15 and 5–10 mmHg in systolic and diastolic blood pressure, respectively). The differences among agents observed in comparative efficacy studies (those observing the blood pressure reduction effects) are usually small (52). The effects of these differences on the cardiovascular or microvascular outcomes cannot be adequately evaluated. Many studies have been published on the effects of various antihypertensive agents on metabolic parameters, including lipids, glucose levels, and insulin resistance. Whereas these parameters are known risk factors for cardiovascular complications, the relevance of these findings in terms of clinical outcomes is not clear. Relevant studies in this area will be discussed.

**1. Effects of antihypertensive drugs on microvascular complications**

**Nephropathy.** Approximately 20–30% of patients with type 1 diabetes and 10–20% with type 2 diabetes will develop end-stage renal disease (ESRD) (53). Diabetics now account for ~50% of all new patients with ESRD and is the most common cause of this condition in adults. Among African-Americans, the incidence of ESRD is ~5 times that of whites; Native Americans and Asians also have high rates of ESRD. Familial and genetic factors play an important role in the development of this complication. The purpose of clinical interventions is to reduce the morbidity and mortality from this complication. Few interventional studies have used the development of ESRD as a primary outcome because of the long follow-up period that would be required. However, many studies have analyzed the effects of antihypertensive drugs on surrogate markers for renal damage, mainly urinary excretion of several markers of renal damage, albumin in particular. Because there is not always a correlation between surrogate markers and clinical outcomes, studies assessing clinical outcomes or renal function (glomerular filtration rate [GFR] or creatinine clearance) will be emphasized. The design of the clinical outcomes studies available is not always randomized, and the duration of the studies vary markedly; however, significant evidence is available supporting the aggressive management of hypertension in the prevention of advanced renal disease and its mortality. Normotensive patients with advanced diabetic nephropathy show slower progression compared with hypertensive patients (54). Studies of the impact of antihypertensive treatment on diabetic nephropathy have generally included either type 1 or type 2 patients, but not both. There are also a number of studies of antihypertensive therapy including ACE inhibitors and other drug classes on the progression of nephropathy in patients without hypertension, primarily in type 1 diabetes.

**Type 1 diabetic patients.** A large placebo-controlled clinical trial using the ACE inhibitor captopril (Collaborative Study Group Trial) showed a significant decrease in the progression of diabetic nephropathy in subjects with type 1 diabetes and overt proteinuria (urinary albumin levels >500 mg/24 h) (55). This study was designed to compare the effects of captopril versus other non-ACE inhibitor antihypertensive agents. A total of 409 patients were studied. Patients were randomized to captopril or placebo. Other antihypertensive drugs were allowed to achieve the desired blood pressure level in both groups. Mean baseline blood pressures were 137/85 mmHg in the captopril group and 140/86 mmHg in the placebo group. A total of 75% of the patients were hypertensive, and 60% were receiving antihypertensive medications at baseline. During treatment, the blood pressure averaged 128–134/77–82 mmHg in the captopril group and 129–136/80–84 mmHg in the placebo group. The majority of patients in both groups received diuretics, and 15% in the placebo group and 11% in the captopril group received β-blockers. The rate of decline in renal function in this study was 11% per year in the captopril group and 17% per year in the placebo group. The end points of death, ESRD, or doubling the serum creatinine were reduced by 50% in the captopril group compared with standard antihypertensive treatment. The differences in systolic and diastolic blood pressure levels between the two groups (placebo and captopril) studied were small, suggesting that ACE inhibitors have a renal protective effect independent of their antihypertensive effect. There are studies showing that in patients with microalbuminuria (urinary albumin excretion rate [UAER] 30–300 mg/24 h) and hypertension, ACE inhibitors decrease the progression to overt proteinuria (UAER >300 mg/24 h) (56,57). Also, in studies of type 1 patients with microalbuminuria without a clinical diagnosis of hypertension, several small clinical trials suggest that ACE inhibitors may be beneficial in delaying or preventing the progression of nephropathy (58,59). A recent meta-analysis of raw data obtained for 698 patients enrolled in several small trials has shown a statistically significant decrease in progression to mac-
Table 1—Antihypertensive agents and their effects on adult hypertensive diabetic patients

<table>
<thead>
<tr>
<th>Class</th>
<th>Effects on coronary events rates*</th>
<th>Effects on progression of renal disease</th>
<th>Effects on stroke</th>
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<td>Controversial</td>
<td>Beneficial (A)</td>
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</tr>
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</tr>
<tr>
<td>Angiotensin-2 antagonists</td>
<td>Unknown</td>
<td>Beneficial (A)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*Level of evidence for summary

roalbuminuria and in regression of albuminuria (60).

Type 2 diabetic patients. A multicenter randomized study in type 2 diabetic patients, the U.K. Prospective Diabetes Study (UKPDS)—Hypertension in Diabetes Study (HDS) (4), evaluated the effects of different levels of blood pressure control on diabetic complications. A total of 1,148 patients were included; 758 were allocated to what was designated tight blood pressure control (goal: blood pressure <150/85 mmHg), and 390 were allocated to less tight control (goal: blood pressure <180/105 mmHg). Practitioners could choose any treatment for the “less tight” group, but were to avoid ACE inhibitors and β-blockers. The patients allocated to tight control were subsequently randomized to the ACE inhibitor captopril (400 patients) or the β-blocker atenolol (358 patients). If the target was not met, additional agents were prescribed (loop diuretic, calcium channel blocker, or vasodilator). The baseline blood pressure level was 160/94 mmHg. The patients were followed for a median of 8.4 years. Blood pressure was reduced to 144/82 mmHg in the tight control group and 154/87 mmHg in the less tight control group (P < 0.0001). Tight control was associated with a reduction of 24% in diabetes-related end points, 32% in deaths related to diabetes, and 37% in microvascular end points (nephropathy and advanced retinopathy). Patients assigned to the tight control group had a 29% reduction in the risk of developing urinary albumin levels >50 mg/l at 6 years, but no significant changes were observed in the development of overt proteinuria or increase in plasma creatinine levels between the two groups.

There is little evidence that the use of ACE-inhibitors as prophylactic treatment in type 1 or type 2 patients without microalbuminuria can prevent the development of diabetic nephropathy, although there was a nonsignificant decrease in the development of microalbuminuria in type 2 patients in the MICRO-Heart Outcomes Prevention Evaluation (HOPE) study (61). It should be noted that this was a cardiovascular risk trial, not a hypertensin trial, as a significant portion of the participants did not have hypertension and those who did were managed throughout the study with non–ACE inhibitor medications. The mean blood pressure in this study at baseline was 142/80 mmHg in the ramipril group and 142/79 mmHg in the placebo group. By the end of the study, blood pressure decreased by 1.9 mmHg for systolic and 3.3 mmHg for diastolic in the ramipril group compared with an increase of 0.6 mmHg for systolic and a decrease of 2.3 for diastolic in the placebo group. Even this minimal lowering of blood pressure from the ACE inhibitor may have had some role in producing this result.

Angiotensin receptor blockers (ARBs) have been shown to retard the progression of albuminuria and the development and progression of nephropathy. Losartan, irbesartan, telmesartan, candesartan, eprosartan, and valsartan are effective antihypertensive agents (62,63). They are not associated with cough, like ACE inhibitors. Angiotensin II receptor blockers have been shown to decrease proteinuria (64,65). There are now three recent large, placebo-controlled, multicenter trials examining the renoprotective effects of an ARB in hypertensive patients with type 2 diabetes (already on other hypertensive medications), examining either the development or progression of nephropathy (Table 1). Parving et al. (66) studied 590 hypertensive patients with microalbuminuria, comparing irbesartan (at two different doses) versus placebo. Follow-up was for 2 years. They found that in 5.2% of the 300-mg irbesartan group (P < 0.001) and in 9.7% of the 150-mg irbesartan group (P = 0.08), the primary outcome (time to onset of diabetic nephropathy, defined by persistent albuminuria, with a UAER >200 µg/min and >30% higher than baseline) was achieved, compared with 14.9% of the placebo group. They concluded that irbesartan had a renoprotective effect independent of any blood pressure-lowering effect.

Lewis et al. (67) studied 1,715 hypertensive patients with nephropathy given irbesartan, amlodipine, or placebo. Mean duration of follow-up was 2.6 years. Treatment with irbesartan (300 mg) was associated with a reduction of the risk of the primary composite end point (doubling of serum creatinine, development of ESRD, or death) of 20% compared with the placebo group (P = 0.02) and 23% compared with the amlodipine group (P = 0.006). The risk of doubling serum creatinine was 33% lower compared with the placebo group (P = 0.003) and 37% compared with the amlodipine group (10 mg) (P < 0.001). The relative risk of ESRD was 23% lower in the irbesartan group than in the placebo or amlodipine groups (P = 0.07). These differences were not explained by the blood pressure reduction achieved. There were no significant differences in the rates of death or cardiovascular composite outcomes.

Brenner et al. (68) studied 1,513 hypertensive patients with established nephropathy, comparing losartan (100 mg) with placebo. Mean follow-up was 3.4 years. Patients in the losartan group had a 16% risk reduction in the composite primary end point (doubling of serum creatinine, ESRD, or death) (P = 0.002), a 25% risk reduction in the doubling of serum creatinine (P = 0.006), and a 28% reduction in ESRD (P = 0.002). There was no effect seen for death rate. The composite of mortality and morbidity from cardiovascular causes was similar between the two groups. The benefits exceeded those attributable to changes in blood pressure.
Other microvascular complications. In the UKPDS, there was a significant reduction of 34% in the number of patients requiring photocoagulation and showing deterioration of the retinopathy by two or more steps (4). A 47% reduction in the risk of decreasing vision in both eyes was associated with tight blood pressure control. No differences in blood pressure control were observed between the captopril and the atenolol groups (blood pressure 144/83 and 143/81, respectively). At the end of the study, 78% of the patients assigned to captopril and 65% assigned to atenolol were taking the study medications (P < 0.0001 for captopril vs. atenolol). This difference was attributed to a higher incidence of peripheral vascular problems and bronchial spasm observed with the β-blocker. No difference in study end points was seen between the ACE inhibitor and the β-blocker; both were equally effective in reducing the risk of cardiovascular and microvascular complications. An epidemiological analysis of this study showed that each 10-mmHg decrease in mean systolic blood pressure was associated with relative risk reductions of 12% for any complication of diabetes, 15% for deaths related to diabetes, 11% for myocardial infarction, and 13% for microvascular complications (13). There was no threshold of risk, and the lowest risk occurred in the group with systolic blood pressure <120 mmHg (4,7). Further evidence of reduction in macrovascular disease in the UKPDS will be discussed in the next section.

2. Effects of antihypertensive drugs on cardiovascular disease in diabetic patients

In several recent studies using various antihypertensive drug regimens, indications are that the incidence of cardiovascular events can be effectively reduced in patients with diabetes and hypertension. Three studies, the UKPDSD-HDS (4,7), the Appropriate Blood Pressure Control in Diabetes (ABCD) trial (6), and the Fosinopril versus Amlodipine Cardiovascular Randomized Events Trial (FACET) (9) included only patients with diabetes. The UKPDSD-HDS, the design of which was described in the previous section, was both a study of the effect of tight blood pressure control on microvascular and macrovascular complications of diabetes as well as a comparison of β-blockers (atenolol) versus an ACE inhibitor (captopril) (4,7).

In addition to the decreases in microvascular disease previously described, the tight control group experienced a 24% drop in total diabetes-related end points (CI 8–30%; P < 0.0046), a 32% decrease in deaths related to diabetes (CI 6–51%; P = 0.019), and a 44% decrease in strokes (CI 11–50%; P = 0.0004). There was no difference within the “tight” control group between patients treated with atenolol and patients treated with captopril. After 9 years of follow-up, 29% of patients on the tight control group required three or more drugs to achieve target blood pressures.

Two studies have compared the efficacy of dihydropyridine calcium channel blockers (DCCBs) and ACE inhibitors on cardiovascular events in diabetic patients with hypertension. In the ABCD trial (6), 470 patients with type 2 diabetes and hypertension (diastolic blood pressure ≥90 mmHg) were randomized to nisoldipine (a DCCB) and enalapril (an ACE inhibitor). A similar reduction in blood pressure was observed with both drugs. A slightly higher (but statistically significant) number of patients in the enalapril group received β-blockers and thiazide diuretics. After 5 years of follow-up, 25 patients in the nisoldipine group had developed fatal or nonfatal myocardial infarction compared with 5 patients in the enalapril group (P = 0.002). The results of this study suggest either that enalapril had a marked protective effect beyond its anti hypertensive properties or that nisoldipine has a deleterious effect. Because myocardial infarction was a secondary outcome in this study, these results must be interpreted with caution.

The FACET (9) reported the results of antihypertensive treatment in 380 type 2 diabetic patients with hypertension. Mean follow-up was 2.9 years in the fosinopril (an ACE inhibitor) group and 2.4 years in the amlodipine (a DCCB) group. Cardiovascular events were secondary end points. A total of 27 patients in the amlodipine group and 14 in the fosinopril group developed the combined end point of acute myocardial infarction, stroke, or hospitalization for angina (risk ratio 0.49, 95% CI 0.26–0.95). The number of myocardial infarctions was similar in both groups (13 in the fosinopril group and 11 in the amlodipine group). The differences in outcomes were mainly caused by hospitalization for angina and strokes (more common in the amlodipine group). These two studies suggest that ACE inhibitors may have an advantage over some DCCBs. Interpretation of these studies is controversial and has been the subject of numerous conflicting reviews and commentaries (69–75).

In addition to the clinical trials specifically in patients with diabetes, several studies in the general population of patients with hypertension have included sufficient patients with diabetes to allow analysis of a subgroup with diabetes. These include studies of drug treatment versus placebo in the treatment of isolated systolic hypertension in older patients, studies comparing outcomes in participants assigned to different blood pressure targets, and trials comparing different drugs.

In a post hoc report of the Systolic Hypertension in Europe trial (Syst-Eur) (3), 492 diabetic patients included in the study were separately analyzed. Patients >60 years of age with systolic hypertension, stratified for center, gender, and cardiovascular complications, were randomized to receive a stepped-care regimen with nitrrendipine (as the first step) or placebo. Baseline blood pressure was 175/84 mmHg. After 2 years of follow-up, the blood pressure of patients with diabetes receiving active treatment had decreased by 22.1/6.8 mmHg and by 13.5/2.9 mmHg in the placebo group. Mean differences between the active treatment and placebo groups were 8.6/3.9 mmHg. Cardiovascular mortality and events in the diabetic subjects receiving placebo were approximately twice that of the non diabetic subjects receiving placebo; however, the rate in the diabetic patients receiving active treatment was similar to that of the non diabetic patients. A reduction of 70% in cardiovascular mortality, 62% in all cardiovascular events, 69% in strokes, and 57% in cardiovascular events was associated with active treatment in the diabetic group. The relative benefit of antihypertensive treatment was greater in the group of patients with diabetes compared with the nondiabetic group in terms of overall mortality (P = 0.04 diabetic vs. nondiabetic group), cardiovascular mortality (P = 0.02), and all cardiovascular events combined (P = 0.01). The absolute benefit was also markedly greater for the diabetic patients. For example, 19.5 cardiovascular deaths per 1,000 patient-years were prevented in the diabetic group compared with 1.9 per
1,000 patient-years in the nondiabetic group, and 35.6 cardiovascular events per 100 patient-years were prevented in the diabetic group compared with 7.9 in the nondiabetic group. Although this was a placebo-controlled study and not a drug comparison study, the larger reductions in event rates seen in the group treated with nitrendipine-based therapy suggest that DCCBs, or at least nitrendipine, do not have major deleterious cardiovascular effects in older patients with diabetes and isolated systolic hypertension.

The post hoc analysis of the Systolic Hypertension in the Elderly (SHEP) study included 583 subjects with diabetes >60 years of age (12% of all the study patients) (2). A low-dose thiazide diuretic, chlorthalidone, versus placebo was used, and atenolol or reserpine was used if chlorthalidone alone was not sufficient to control the blood pressure. The goal of the treatment was a reduction in systolic blood pressure of at least 20 mmHg in patients with systolic blood pressure between 160–179 mmHg and a reduction to <160 mmHg in patients with systolic blood pressure >180 mmHg. The actual mean reductions of systolic and diastolic blood pressure were 9.8/2.2 mmHg in the diabetic group and 12.1/4.1 mmHg in the nondiabetic group (n = 4,149). A reduction of 34% (P < 0.05) in cardiovascular events was observed in the diabetic group treated with chlorthalidone compared with the placebo group. This relative reduction was similar to the reduction observed in the group as a whole. These events included major coronary events (fatal and nonfatal myocardial infarction, sudden death, coronary bypass, and angioplasty), cerebrovascular events (stroke, transient ischemic attacks, and carotid endarterectomy), and aortic aneurysm. The rate of coronary artery disease end points in the diabetic group was reduced by 55 vs. 20% in the nondiabetic group (P < 0.05). Because the rate of cardiovascular disease in diabetic patients was twice as high as in nondiabetic patients, the absolute risk reduction in the diabetic group was twice as great in the diabetic group (101 per 1,000 randomized patients).

The Hypertension Optimal Treatment (HOT) trial (5) was a large-scale multinational study that included 18,790 patients, 1,501 of whom had diabetes. One-third of the patients were assigned to each of three different levels of hypertensive control, with treatment targets of diastolic blood pressure ≤90, ≤85, and ≤80 mmHg. The DCCB felodipine was used as initial treatment, followed by a five-step treatment to achieve the goal blood pressures. The baseline diastolic blood pressure was 105 mmHg. Diabetic patients had a rate of cardiovascular events two to three times higher than the group as a whole for the ≤90 and ≤85 mmHg groups. In the ≤80 mmHg group, the rate of cardiovascular disease events in the diabetic group was lower than in the ≤90 mmHg group and approached the lower rate seen in patients without diabetes. In the group as a whole, the lowest incidence of major cardiovascular events was observed at a diastolic pressure of 82.6 mmHg, and the lowest risk of cardiovascular mortality was observed at a diastolic blood pressure of 86.5 mmHg, with no difference among the three groups. Among the diabetic patients, however, the group assigned to a target diastolic blood pressure ≤80 mmHg showed a marked reduction in major cardiovascular events (51%, P = 0.005) and in cardiovascular mortality (43%, P = 0.016) compared with those patients assigned to a target of ≤90 mmHg. The majority of the patients required a combination of at least two drugs (usually felodipine, a DCCB, with an ACE inhibitor, β-blocker, and/or a diuretic) to achieve the targeted level of blood pressure.

Several recent studies primarily aimed at assessing the relative efficacy of different drug classes on cardiovascular outcomes reported separately on patients with diabetes. The Swedish Trial in Old Patients with Hypertension-2 (STOP Hypertension-2) (11) found a significant decrease in myocardial infarction in patients on ACE inhibitors compared with patients treated with the DCCBs felodipine or isradipine, but not compared with β-blockers and diuretics. The International Nifedipine (GITS) study—Intervention as a Goal in Hypertension—found no difference between therapy based on nifedipine, a DCCB, versus amlodipine, a thiazide/potassium-sparing diuretic combination (12). In the Nordic Diltiazem Trial, treatment based on diltiazem hydrochloride, a non-DCCB (NDCCB), was compared with β-blocker/diuretic-based treatment (13). This study found a significantly lower risk of stroke for patients treated with diltiazem-based therapy compared with the β-blocker/diuretic-therapy group but a nonsignificant trend toward higher rates of myocardial infarction, cardiovascular death, and congestive heart failure in the diltiazem group. There were no differences in combined cardiovascular events or mortality. In none of these studies did results differ for participants with diabetes.

In the Captopril Prevention Project (CAPPP), 717 participants with diabetes and treated or untreated hypertension received either the ACE inhibitor captopril or conventional treatment consisting of a β-blocker, diuretic, or both. The study design was an open randomized prospective trial including a total of 10,985 patients with and without diabetes (10). After 6.1 years of follow-up, there was a 14% (95% CI 1.0–26.0) lower rate of the combined outcome of fatal and nonfatal stroke, myocardial infarction, or other cardiovascular death among patients with diabetes in the group taking captopril versus those taking diuretics and β-blockers. In contrast, in the nondiabetic subjects, the only difference in outcomes between groups was an increased relative risk of stroke of 25% (95% CI 1.0–55.0) in the captopril group. Concern has been raised about unbalanced randomization in the nondiabetic group.

Recently, the HOPE study evaluated the effect of an ACE inhibitor, ramipril, on 9,541 patients with a high risk of cardiovascular disease, including 3,378 with diabetes (61). As previously noted, in this non-hypertensive trial, the blood pressure changes were quite small with ramipril treatment. All-cause and cardiovascular mortality as well as cardiovascular events, including myocardial infarction and stroke, were significantly decreased by ramipril treatment.

SECTION 3: REVIEW OF PHARMACOLOGICAL AGENTS IN THE MANAGEMENT OF HYPERTENSION IN DIABETES

The most commonly prescribed antihypertensive agents available in the U.S. and their classification are presented in Table 1. At the doses available for clinical use, most antihypertensives will produce a reduction in systolic or diastolic blood pressure of 5–10% in patients with mild or moderate hypertension.
Thiazide diuretics
Diuretics reduce total body sodium through their natriuretic action (76) and have been shown to have vasodilatory effects as well (77). Treatment with thiazide diuretics at doses equivalent to 25–50 mg of hydrochlorothiazide has been associated with hypokalemia, hypernatremia, volume depletion, hypercalcemia, and hyperuricemia. Potassium supplementation should be used as clinically indicated. Their efficacy in reducing the risk of stroke and congestive failure in large randomized clinical trials including subjects with mild-to-severe hypertension has been demonstrated. In elderly populations with isolated systolic hypertension, thiazides have resulted in decreased cardiovascular morbidity. Evidence from retrospective studies (78,79) suggests increased cardiovascular mortality in diabetic patients receiving diuretics. These studies were not randomized, and significant baseline differences between patients receiving diuretics and the patients not receiving them may have existed. Also, these studies were based on data collected in the 1970s, when high-dose diuretic treatment was the norm. The SHEP study previously described showed that low-dose thiazide treatment of systolic hypertension in older diabetic subjects was associated with a significant reduction in cardiovascular events (2). Thiazides may not be effective in subjects who have significantly decreased renal function (i.e., GFR < 60 ml·min⁻¹·1.73 m⁻²). The effects of thiazide diuretics on the progression of early or advanced diabetic nephropathy have not been studied in large randomized clinical trials.

Insulin sensitivity has been measured in diabetic patients receiving thiazides (80–82). Hydrochlorothiazide at a daily dose of 25 mg or bendroflumethiazide at 1.25 mg daily does not significantly decrease insulin sensitivity. However, bendroflumethiazide at a daily dose of 5 mg caused a significant reduction of in vivo insulin sensitivity (80). Low-dose chlorthalidone in combination with atenolol was associated with low insulin sensitivity and increased triglyceride levels (82). The clinical significance of these metabolic findings is unknown. In diuretic-based therapy, a low-dose thiazide diuretic has been shown to reduce the cardiovascular event rate 34% compared with placebo; the absolute risk reduction was twice as great for diabetic subjects versus nondiabetic subjects (2).

Loop diuretics
The antihypertensive mechanism of loop diuretics is related to a significant decrease in total body sodium; although acutely, these agents also act as vasodilators (83). Furosemide in combination with β-adrenergic blockers was used as the mainstay antihypertensive regimen in a study reported by Parving et al. (84) in the treatment of patients with diabetic nephropathy. This study showed a significant reduction in the rate of deterioration of the GFR in patients with type 1 diabetes treated with an aggressive antihypertensive regimen. Treatment with loop diuretics can be associated with hypokalemia, hypernatremia, and volume depletion (83). Their use is recommended for patients with decreased renal function (GFR < 60 ml·min⁻¹·1.73 m⁻²), usually in combination with other agents.

Adrenergic blockers
1. Centrally acting agents. These drugs effectively lower blood pressure by decreasing central sympathetic outflow (83). However, their effects on the progression or development of microvascular complications or cardiovascular disease have not been studied in detail. They are associated with orthostatic hypotension, and they should be used with caution in patients with cardiovascular autonomic neuropathy. Common side effects are drowsiness, impotence, and dry mouth. Less common effects are depression and Coombs-positive anemia (with α-methyl-dopa) (85).

2. β-Blockers. β-Blockers are competitive inhibitors of the β-adrenergic receptors. Nonselective β-blockers markedly inhibit both the B1- and B2-receptors. Selective β-blockers predominantly inhibit the B1-receptors (86). The initial interventional studies that demonstrated reduced or no β-blockers in insulin-treated patients with hypertension used β-blockers and diuretics as antihypertensive medications, frequently with other drugs (2,4,7,10,12,13,87). In three randomized studies in diabetic hypertensive patients in which proteinuria was examined (88–90), atenolol (a selective B-blocker) produced similar reductions in proteinuria compared with an ACE inhibitor. In a long-term study (43 patients followed for 3.5 years), atenolol and lisinopril produced similar reductions in the decline of the GFR in patients with type 2 diabetes and nephropathy (88).

In the UKPDS-HDS (4,7), the β-blocker atenolol and the ACE inhibitor captopril were equally effective in decreasing the risk of diabetes-related end points (pooling of microvascular and cardiovascular complications) and microvascular events in a large group of subjects with type 2 diabetes. In some patients, atenolol was associated with modest weight gain, the development of side effects (e.g., cold extremities, intermittent claudication, and bronchospasm) and, thus, a slightly lower compliance rate. β-Blockers have demonstrated efficacy in patients with myocardial infarction with relative reductions in mortality of ~25% (86). Because diabetic patients with myocardial infarction have a much higher mortality than nondiabetic individuals, the absolute benefit of a given relative reduction may be greater in diabetic patients.

There has been a long-standing concern about the effect of β-blockers on the perception of and recovery from hypoglycemia, which may be blunted or prolonged by these agents. Nonselective β-blockers are associated with decreased counter-regulatory responses to hypoglycemia, particularly in patients taking insulin (91). However, it is unknown whether this effect is clinically important; the UKPDS study did not show an increased incidence of hypoglycemic episodes in the group treated with β-blockers. It is probably prudent to avoid the use of β-blockers in insulin-using patients who have a history of severe hypoglycemia. In other patients with diabetes, especially patients with a recent myocardial infarction where the benefits are clearly proven, the benefits of β-blockers would appear to outweigh the potential risks.

3. α-Adrenergic blockers. α-Adrenergic blockers are inhibitors of the α-postsympathetic adrenergic receptors (92). The antihypertensive effects of these medications at the doses approved for clinical use are similar to other groups of agents. No long-term randomized clinical trials examining renal or cardiovascular outcomes have been published using this family of drugs. α-Adrenergic blockers have been associated with improved insulin sensitivity in patients with insulin resistance.
associated with essential hypertension (93). A slight decrease in LDL cholesterol has been reported with α-adrenergic blockers in small short-term clinical studies, all involving <25 patients per group (94). The clinical significance of these findings is unclear. Initial doses of these agents, particularly prazosin (92), have been associated with orthostatic hypotension, so this agent should be used with caution in patients with diabetic autonomic neuropathy. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study had an arm comparing an α-blocker, doxazosin, with a β-blocker, a calcium channel blocker, and an ACE inhibitor versus a diuretic. Recently, this part of the study was terminated because of an increased incidence of cardiovascular events, specifically congestive heart failure, in patients receiving the α-blocker. Separate results for patients with diabetes were not reported (95).

Calcium channel blockers
Calcium channel blockers inhibit calcium influx through membrane-bound voltage-dependent calcium channels, resulting in decreased intracellular calcium levels and vasodilation (83). The family of calcium channel blockers is subdivided in three subclasses that have significant differences in their hemodynamic effects (96). The dihydropyridine group (DCCBs) has mainly vasodilatory effects and relatively small effects on cardiac inotropism or atrio-ventricular conduction. Reflex tachycardia can be seen, and edema is the most common side effect. There are many drugs in this group in the U.S., and significant pharmacokinetic differences between agents and pharmacological preparations of a single agent exist. For this reason, it is difficult to assess and generalize results of clinical studies with the DCCB agents. The second group, the benzothiazepines have moderate vasodilatory effects and moderate negative inotropic and chronotropic effects. Diltiazem is the only agent available in this group, and several preparations with different pharmacokinetic profiles exist. The third group, the phenylalkylamines, has similar vascular and cardiac effects as diltiazem. Verapamil is the only agent in this group available in the U.S. It is available in slow- and rapid-release forms with significantly different pharmacokinetics. The benzothiazepine diltiazem and the phenylalkylamine verapamil are referred to as NDCCBs.

1. DCCBs. DCCBs are effective antihypertensive agents. Conflicting evidence exists regarding the safety and efficacy of DCCBs in reducing cardiovascular end points, as has been previously noted. The benefit of DCCBs in decreasing cardiovascular events in hypertensive diabetic patients has been shown in the Syst-Eur and HOT trials (3,5). However, in both trials most patients were also receiving a β-blocker or an ACE inhibitor in order to achieve the goals of therapy. Therefore, it is difficult to judge the effectiveness of monotherapy with these drugs in reducing cardiovascular end points. As mentioned in a previous section, the ABCD and FACET studies suggest a greater benefit of ACE inhibitors over DCCBs with respect to cardiovascular events (6,8,9). A retrospective analysis of patients receiving short-acting nifedipine, a treatment not approved for hypertension in the U.S., suggested an increase in cardiovascular mortality (97). Short-acting dihydropyridines are not approved or labeled for treating hypertension and should not be prescribed for that purpose.

A recent meta-analysis suggests that calcium channel blockers may be equivalent in protecting against stroke but less effective in reducing myocardial infarction and combined major coronary events than ACE inhibitors, β-blockers, or diuretics. All-cause mortality was found to be equivalent among all classes of drugs given equivalent control of blood pressure. These findings did not seem to be affected by the presence of diabetes (98).

Caution should be exerted in the interpretation of clinical trials using DCCBs due to pharmacokinetic differences between these drugs. In the case of the ABCD and FACET, it is not possible to conclude whether the DCCBs increased, decreased, or maintained the level of cardiovascular risk that the patients had before treatment.

Regarding diabetic nephropathy, one study with nifedipine has shown an increase in proteinuria in patients with diabetic nephropathy (57), but the long-term effects of this agent on renal function are unknown. Whereas other studies have not found significant differences between DCCBs and other agents (99–101), a recent study by Lewis et al. (67) (study details of which have been previously described) found amiodipine to be no different from placebo regarding the progression of nephropathy and inferior to irbesartan, an ARB.

The metabolic effects of DCCBs have been investigated in trials in type 2 diabetes and essential hypertension. In general, DCCBs seem to have a neutral effect on metabolic parameters (102).

2. NDCCBs (benzothiazepines and phenylalkylamines). Small studies of short duration using diltiazem and verapamil have been associated with decreased proteinuria in patients with overt diabetic nephropathy (103–105), but long-term studies showing a reduction in the rate of fall of GFR have not been carried out.

ACE inhibitors
These drugs are useful in the management of hypertension in diabetic patients with or without diabetic nephropathy. The UKPDS-HDS showed similar beneficial effects of the ACE inhibitor captopril and the β-blocker atenolol on diabetes-related mortality and microvascular and cardiovascular complications in patients with type 2 diabetes (4,7). They are also effective in decreasing cardiovascular mortality and morbidity in patients with congestive heart failure and post-myocardial infarction (61). ACE inhibitors have been extensively studied in the treatment of diabetic nephropathy and are effective in preventing progression of retinopathy.

The recent HOPE trial (see drug therapy, 2. effects of antihypertensive drugs on cardiovascular disease in diabetic patients) that documented decreased cardiovascular end points despite quite minor changes in blood pressure raises the possibility that ACE inhibitors have benefits for diabetic patients that are independent of their antihypertensive effect (106). Whether this is a class effect or an effect specific to ramipril is unknown. Postulated mechanisms include effects on the endothelium as a result of decreased vascular smooth muscle growth, decreased release of endothelin, increased fibrinolysis, and release of the vasodilating substances nitric oxide and prostacyclin mediated by bradykinin (106).

The most common side effects of ACE inhibitors include cough and, occasionally, acute decreases in renal function. Hyperkalemia can be seen, especially in patients with renal insufficiency, bilateral

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renal artery stenosis, and hyporeninemic hypoaldosteronism (107).

**ARBs**

As has been previously discussed, ARBs have been shown to retard the progression of albuminuria and the development and progression of nephropathy (66–68). Long-term data on cardiovascular outcomes using this class of drugs are limited.

**Combinations of antihypertensive agents**

Many studies of combinations of antihypertensive agents have been published. Diuretic agents in combination with adrenergic blockers have been used in several nephropathy studies and in the UKPDS-HDS and SHEP study. ACE inhibitors have been used in combination with diuretics and calcium channel blockers. Calcium channel blockers in combination with diuretics or ACE inhibitors have been reported. In a small study, dual blockade of the renin-angiotensin system using cardesartan and lisinopril (the Cardesartan and Lisinopril Microalbuminuria [CALM] study) found that the combination of both agents reduced blood pressure and urinary albumin levels to a greater extent than either medication alone (108). In general, combination therapy may help to improve compliance, as one drug may antagonize the adverse effects of another (109). Fixed-dose combinations of many drugs are available and may be appropriate when the patient requires more than one drug, the dosages in the product are appropriate for the patient, and the costs are not greatly increased. The superiority of one combination regime over another has not been documented. However, it is clear that intensive treatment of hypertension, with goals similar to those recommended by the American Diabetes Association’s new target of <130/80 mmHg, will require more than one drug in most patients and three or more in many.

**Blood pressure goals in diabetic patients**

The UKPDS and the HOT study both demonstrate improved outcomes, especially in preventing stroke, in patients assigned to tighter control (HOT, diastolic blood pressure ≤80 mmHg; achieved 81 mmHg; UKPDS, <150/85 mmHg, achieved 144/82 mmHg) and less tight control (HOT, ≤90 mmHg; UKPDS, <180/105 mmHg) (4,5). Optimal outcomes in the HOT study were achieved at a mean diastolic blood pressure of 82.6 mmHg (5). Although patients with diabetes had the best results in the group assigned to a target blood pressure <80 mmHg, the mean result was somewhat higher than this. The ABCD trial, in which the primary outcome measure was decreased creatinine clearance, showed a decrease in all-cause mortality in the group treated to a goal diastolic blood pressure of 75 mmHg (achieved 132/78) vs. 80—89 (achieved 138/86) (6,8). However, this was a secondary outcome, and the study was not powered to detect a decrease in cardiac versus all-cause mortality (6,8). There is support from these randomized clinical trials for reducing systolic blood pressure to ≤140 mmHg and for reducing diastolic blood pressure to ≤80 mmHg. Epidemiological evidence demonstrates that blood pressures ≥120/80 mmHg are associated with increased cardiovascular event rates and mortality in persons with diabetes. Therefore, a target blood pressure goal of ≤130/80 mmHg is reasonable, if it can be safely achieved. A similar target has recently been advocated by the National Kidney Foundation (110). Whether even more aggressive treatment would reduce the risk still further is an unanswered question. There is no threshold value for blood pressure, and risk continues to decrease well into the normal range. Achieving lower levels, however, would increase the cost of care as well as drug side effects and is difficult in practice. Blood pressure goals are outlined in Table 2.

**COST-EFFECTIVENESS**

Until 1998, there were no available cost-effectiveness analyses of treatment of hypertension in diabetes. Several studies (111,112) have examined the cost-effectiveness of hypertension in the general population. In general, the higher the risk, the more cost-effective treatment is, so that elderly patients and those with severe hypertension can be treated at lower cost per quality-adjusted life-year. In 1998, the UKPDS investigators published a cost-effectiveness analysis of patients with diabetes enrolled in the hypertension arm of that study (113). This analysis found that the incremental cost of tight control (<150/85 mmHg blood pressure target) versus less tight control (<200/105 mmHg initially, modified to <180/105 mmHg in 1992) was well within the range of interventions generally considered to be effective. Differences in health care systems make the direct extrapolation to the U.S. health care system somewhat questionable.

Another recent study, using a computer model populated with cost assumptions based on the U.S. health care system and using data from the HOT and UKPDS studies, showed that more intensive treatment of hypertension is potentially cost-saving in persons 60 years of age and over, as long as the incremental treatment cost is less than $414.00/year (U.S. dollars, 1996) (114). It seems likely that hypertension treatment in diabetes is a relatively good value from the standpoint of cost-effectiveness, given the cost-effectiveness of hypertension treatment in the general population and the larger absolute risk reduction seen in patients with diabetes. Special emphasis on the treatment of African-Americans and other groups with very high rates of ESRD in the U.S. would also likely be highly cost-effective (115,116).

**CONCLUSIONS**

All patients with diabetes should have routine blood pressure measurements at each scheduled diabetes follow-up visit. Diabetic patients with blood pressures >130 mmHg systolic or >80 mmHg diastolic are candidates for antihypertensive treatment.
Thiazide diuretics have been shown to improve cardiovascular outcomes and may address the volume or salt-sensitive components of hypertension, complementing the mechanisms of action of other drugs, so these are appropriate choices for a second or third drug and can be used for initial therapy in patients without additional cardiovascular risk factors or proteinuria. The effect of thiazide diuretics on the progression of diabetic nephropathy compared with other drugs is unknown.

NDCCBs can be used when ACE inhibitors, ARBs, or β-blockers are not tolerated or are contraindicated or when a second or third drug is required. There is some evidence that NDCCBs are not as effective in preventing complications, particularly myocardial infarction, heart failure, and nephropathy. However, in studies achieving low-targeted blood pressures with substantial improvements in outcomes, such as the HOT study and the UKPDS, DCCBs were commonly part of an effective multi-drug regimen that also included an ACE inhibitor or a β-blocker, often with a diuretic.

Classes of drugs for which there are no long-term data on efficacy in improving outcomes can be used when there is intolerance to other classes, when there are specific indications for their use apart from treatment of hypertension (for example, α-blockers for patients with benign prostatic hypertrophy and diltiazem for rate control in atrial fibrillation), or when additional drugs are required to achieve the target for blood pressure.

In diabetic patients >65 years of age with isolated systolic hypertension (i.e., >140 mmHg systolic and <80 mmHg diastolic blood pressure), pharmacological treatment should be initiated. Earlier recommendations to treat to a systolic blood pressure <160 have been reduced in order to be consistent with JNC VI and are based on the increased cardiovascular risk of these patients and the results of the SHEP study, in which a systolic blood pressure of 144 was achieved. Combinations of agents are often required. When drug therapy is intensified, patients should be monitored carefully for adverse effects, such as orthostatic hypotension. Finally, it is important to note that in diabetic patients the greatest reduction in cardiovascular mortality occurs at a diastolic blood pressure of ~80 mmHg (3,5,6). Thus, aggressive blood pressure control should be attempted in all diabetic patients.

Treatment decisions should, of course, be individualized based on the clinical characteristics of the patient, including comorbidities as well as tolerability, personal preference, and cost, especially for patients who must pay out of pocket for medications. Fixed-dose combinations of many drugs are available and may help with compliance and be less expensive for patients with a per-prescription co-payment.

SUGGESTIONS FOR FUTURE RESEARCH — Whereas there is ample evidence that the treatment of hypertension in diabetes is important for reducing both cardiovascular and microvascular complications, the ideal strategy for treating hypertension in persons with diabetes is less clear. There are limited head-to-head comparisons of different treatments in the literature, and only a limited number of these report long-term data on significant outcomes such as death, cardiovascular events, and microvascular complications as opposed to short-term effects on metabolic parameters and blood pressure lowering. There are limited data regarding the use of entire classes of antihypertensive agents, such as α-blockers, in the treatment of hypertension in people with diabetes. Often, class effects of drugs cannot be differentiated from particular drug effects because there are no studies available. Studies should include cost comparisons and quality of life measures as well as cardiovascular and microvascular end points. Studies of effects of antihypertensive agents on metabolic parameters may be useful in determining safety but may be misleading if used as a surrogate for clinically significant end points.

The ALLHAT, a large National Heart, Lung, and Blood Institute (NHLBI)-sponsored study, is designed to compare diuretic-based treatment with calcium channel blockers, an ACE inhibitor, and an α-adrenergic blocker as well as to investigate whether lipid-lowering therapy is of value in persons with moderate hypercholesterolemia (117). As previously noted, the α-blocker arm of the study has been terminated because of excess cardiovascular events, especially congestive heart failure, in patients taking an α-blocker versus a diuretic (95). Approximately one-third of the 40,000 patients aimed at lowering blood pressure to <130/80 mmHg. Before beginning treatment, patients with elevated blood pressures should have their blood pressure reexamined within 1 month to confirm the presence of hypertension. In patients with blood pressures between 130/80 and 140/90 mmHg, a behavioral approach may be used for at least 3 months. The behavioral approach should consist of moderate sodium restriction, calorie and alcohol restriction, and increased physical activity. Weight reduction should be the goal in obese patients. If after a trial period of behavioral treatment, blood pressure remains >130 mmHg systolic or >80 mmHg diastolic, pharmacological treatment should be added.

Patients with confirmed blood pressures of ≥140/90 mmHg are candidates for immediate pharmacological treatment in addition to behavioral treatment. Initial drugs for pharmacological treatment include ACE inhibitors, ARBs, low-dose thiazide diuretics, and β-blockers. Because of the large number of studies in patients with diabetes demonstrating improvement in a range of outcomes, including progression of nephropathy, cardiovascular events, and mortality, it is now an established practice to begin hypertensive patients with diabetes and without microalbuminuria on an ACE inhibitor. When microalbuminuria or more advanced stages of nephropathy is present, ACE inhibitors (type 1 diabetes) and ARBs (type 2 diabetes) have been found to be effective in preventing the progression of nephropathy. However, cardiovascular data are limited with ARBs. Although the evidence is not complete, this is certainly a reasonable strategy, as is initial therapy with a β-blocker, unless contraindicated, because the UKPDS study showed β-blockers to be roughly equivalent to ACE inhibitors in improving multiple diabetes-related end points.

If the target blood pressure goal is not obtained with the initial doses of first-line drugs, increases in doses are recommended, or the addition of a second drug from a different group should be considered. Regardless of the initial treatment, it must be emphasized that most patients will require more than one drug to achieve the recommended target of ≤130/80 mmHg, and many will require three or more. Achievement of the target blood pressure may be more important than the particular drug regimen used.
randomized has diabetes. Final results of this study will not be available until March of 2002.

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