Treatment of Hypertension in Type 2 Diabetes Mellitus: Blood Pressure Goals, Choice of Agents, and Setting Priorities in Diabetes Care

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Background: **Hypertension in patients with type 2 diabetes mellitus is a prevalent condition that leads to substantial morbidity and mortality.**

Purpose: **To evaluate the goals and optimal agents for treatment of hypertension in type 2 diabetes.**

Data Sources: **Review of the medical literature**

Study Selection: **Randomized trials that evaluated the pharmacologic treatment of hypertension in patients with diabetes and reported microvascular and macrovascular outcomes.**

Data Extraction: **Studies were identified by using the Cochrane Library, MEDLINE, meta-analyses, review articles, and expert recommendation. The searches of the Cochrane Library and MEDLINE were performed in May 2000 and updated in April 2002. Data were abstracted to standardized forms by a single reviewer and were confirmed by a second reviewer.**

Data Synthesis: **Treatment of hypertension in type 2 diabetes provides dramatic benefit. Target diastolic blood pressures of less than 80 mm Hg appear optimal; systolic targets have not been as rigorously evaluated, but targets of 135 mm Hg or less are reasonable. Studies that compare drug classes do not suggest obviously superior agents. However, it is reasonable to conclude that thiazide diuretics, angiotensin-II receptor blockers, and perhaps angiotensin-converting enzyme (ACE) inhibitors may be the preferred first-line agents for treatment of hypertension in diabetes. β-Blockers and calcium-channel blockers are more effective than placebo, but they may not be as effective as diuretics, angiotensin-II receptor blockers, or ACE inhibitors; however, study results are inconsistent in this regard.**

Conclusions: **Treatment of hypertension in type 2 diabetes, with blood pressure goals of 135/80 mm Hg, provides dramatic benefits. Thiazide diuretics, angiotensin II receptor blockers, and ACE inhibitors may be the best first-line treatments, although other agents are usually necessary and goals may not be achieved even with three or four agents. Aggressive blood pressure control may be the most important factor in preventing adverse outcomes in patients with type 2 diabetes.**

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Type 2 diabetes mellitus is a common disease with substantial associated morbidity and mortality (1, 2). Most adverse diabetes outcomes are a result of vascular complications, both at a macrovascular level (coronary artery disease, cerebrovascular disease, or peripheral vascular disease) and a microvascular level (retinopathy, nephropathy, or neuropathy) (3). Macrovascular complications are more common; up to 80% of patients with type 2 diabetes will develop or die of macrovascular disease (4–12), and the costs associated with macrovascular disease are an order of magnitude greater than those associated with microvascular disease (13).

Because diabetes is defined by blood glucose levels, much of the attention in diabetes care focuses on the management of hyperglycemia. This has been magnified by the causal link between hyperglycemia and microvascular outcomes (3, 14). However, while some observational evidence suggests that level of glycemia is a risk factor for macrovascular disease (15–18), experimental studies to date have not clearly shown a causal relationship between improved glycemic control and reductions in serious cardiovascular outcomes (3, 14). Given these results and the epidemiologic characteristics of diabetes complications, it would seem more logical to focus diabetes care on prevention of macrovascular complications rather than on glucose control and microvascular complications. Indeed, the importance of preventing the macrovascular complications of type 2 diabetes has started to receive greater attention. In particular, several trials have examined the benefit of management of highly prevalent risk factors, such as hypertension. Hypertension is extremely common in patients with type 2 diabetes, affecting up to 60% (2), and there are a growing number of pharmacologic treatment options.

The goals of this paper are to review the literature to evaluate effects of management of hypertension on the complications of type 2 diabetes and, based on this literature, to determine optimal blood pressure goals and choice of agents. This will provide an evidence base to guide clinicians in setting hypertension treatment goals and priorities in patients with type 2 diabetes.

METHODS

The literature review was limited to randomized, controlled trials that included patients with diabetes. Only studies that measured major clinical end points were included. We defined four classes of clinical end points: all-cause mortality, cardiovascular mortality, major cardiovascular events (that is, myocardial infarction or stroke), and advanced microvascular outcomes (photocoagulation or visual loss, nephropathy or end-stage renal disease, neuropathy, or amputation).

We separated the literature review into two categories. The first category evaluated the effects of hypertension control if the comparison examined an antihypertensive drug versus placebo or the effects of different target blood

Table 1. **Primary Trials of Hypertension Control in Diabetes***

Trial	Intervention and Primary Agents	Primary or Subgroup Analysis	Total Cardiovascular Events	
			Relative Risk	Absolute Risk Reduction
SHEP	Thiazide diuretic vs. usual care	Subgroup	0.66 (0.46 to 0.94)	0.08 (0.01 to 0.14)
Syst-Eur	Calcium-channel blocker vs. placebo	Subgroup	0.38 (0.20 to 0.81)	0.08 (0.03 to 0.13)
HOPE	ACE inhibitor vs. placebo	Subgroup	0.75 (0.64 to 0.88)	0.05 (0.02 to 0.07)
RENAAL	Angiotensin II receptor blocker vs. placebo	Primary	0.90†	0.02 (−0.03 to 0.07)
IPDM	Angiotensin II receptor blocker vs. placebo	Primary	Not reported	Not reported
HOT	Target diastolic blood pressure <80 mm Hg or <90 mm Hg; agents = felodipine, then ACE inhibitor or β-blocker	Subgroup	0.49 (0.14 to 0.78)	0.05 (0.02 to 0.08)
UKPDS	Target blood pressure <180/105 mm Hg vs. <150/85 mm Hg; agents = captopril or atenolol	Primary	0.66‖	Not reported
ABCD	Target diastolic blood pressure 75 mm Hg vs. 80–89 mm Hg; agent = nisoldipine or enalapril	Primary	No difference	Not reported

* Values in parentheses are 95% CIs. ABCD = Appropriate Blood Pressure Control in Diabetes; ACE = angiotensin-converting enzyme; HOPE = Heart Outcomes and Prevention Evaluation study; HOT = Hypertension Optimal Treatment; IDPM = Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria; RENAAL = Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; SHEP = Systolic Hypertension in the Elderly Program; Syst-Eur = Systolic Hypertension in Europe; UKPDS = United Kingdom Prospective Diabetes Study.
† $P > 0.2$.
‡ Renal outcomes (doubling of serum creatinine concentration and risk for end-stage renal disease).
§ Comparison for 300-mg dose of irbesartan; 150-mg dose did not significantly reduce risk; risk is for progression of nephropathy.
‖ $P = 0.019$.
¶ No combined end point reported. Relative risks for individual end points comparing intensive with moderate blood pressure control were as follows: progression from normoalbuminuria to microalbuminuria, 1.38 (CI, 0.84 to 2.27); progression from microalbuminuria to overt albuminuria, 0.70 (CI, 0.36 to 1.36); retinopathy progression, 0.88 (CI, 0.68 to 1.15); and neuropathy progression, 1.30 (CI, 1.01 to 1.66).

pressure levels. The second category evaluated the effects of different classes of drugs. We used several sources to identify the relevant literature. For older literature, we started with the Cochrane Collaboration Diabetes Group report on treatment of hypertension in diabetes, which was published in 1997 (19). This report has now been withdrawn because it is out of date, but it served as a reasonable starting point to identify pre-1997 literature. We then performed a MEDLINE search in May 2000 and updated it in April 2002. We used the keywords *exp diabetes mellitus* and *exp hypertension[therapy or prevention and control]* and limited the search to randomized, controlled trials. The final search produced 322 results. Of these, most were discarded because they did not measure major clinical outcomes, were observational in nature, were reviews or editorials, or did not primarily address the issue of treatment of hypertension. We then updated the search through consultation with experts and through examining references from meta-analyses and review articles.

Data were extracted from the primary study reports by the primary author and were reviewed by the senior author. Accuracy and quality of the abstraction were confirmed through reabstraction and comparison with the original abstraction. The outcomes were broken into categories as described, and data on absolute and relative risk reduction and numbers needed to treat for benefit were derived from the primary reports or were calculated in standard fashion (20).

RESULTS

Benefits of Blood Pressure Control

The results of the studies of blood pressure control versus placebo, or of different blood pressure targets, are outlined in **Table 1**. The Systolic Hypertension in the Elderly Program (SHEP) enrolled a diabetes subgroup totaling 583 patients and randomly assigned these patients to chlorthalidone plus atenolol or reserpine versus placebo and usual care (21). The intensive group had a 9.8–mm Hg decrease in systolic blood pressure and a 2.2–mm Hg decrease in diastolic blood pressure, as well as a significant decline in total cardiovascular events and a nonsignificant trend for lower all-cause mortality.

The Systolic Hypertension in Europe (Syst-Eur) study (22) randomly assigned elderly patients (≥60 years of age) with systolic hypertension to nitrendipine or placebo. The mean decreases in systolic blood pressure and diastolic blood pressure were 8.6 and 3.9 mm Hg in the intervention group compared with the placebo group. In the subgroup of 492 patients with diabetes, this led to an improvement in the risk for cardiovascular death, all cardiovascular events, and stroke. There was no significant difference in overall mortality in unadjusted analyses; however, after adjustment for baseline differences between groups, there was a 55% reduction in overall mortality in the active treatment group ($P = 0.04$).

The Heart Outcomes and Prevention Evaluation (HOPE) study evaluated the cardiovascular effects of the angiotensin-converting enzyme (ACE) inhibitor ramipril (23, 24). Patients with diabetes and at least one other cardiovascular risk factor ($n = 3577$) were randomly assigned to the ACE inhibitor ramipril or placebo. The participants had only mild elevations in systolic blood pressure at baseline, and blood pressure differences at the final visit were small (systolic blood pressure, 2.4 mm Hg lower; diastolic blood pressure, 1 mm Hg lower). The ramipril group had significantly lower risks for cardiovascular outcomes, total mortality, and microvascular diabetes complications. The

Table 1—**Continued**

Total Mortality		Microvascular End Points	
Relative Risk	**Absolute Risk Reduction**	**Relative Risk**	**Absolute Risk Reduction**
0.74 (0.46 to 1.18)	0.02 (−0.04 to 0.08)	Not reported	Not reported
0.59 (0.31 to 1.09)	0.05 (−0.01 to 0.09)	Not reported	Not reported
0.76 (0.63 to 0.92)	0.03 (0.01 to 0.05)	0.84 (0.71 to 0.99)	0.03 (0.00 to 0.05)
1.02 (0.73 to 1.19)	−0.01 (−0.05 to 0.03)	0.79 (0.66 to 0.95)‡	0.04 (0.00 to 0.09)‡
Not reported	Not reported	0.30 (0.14 to 0.61)§	0.10 (0.04 to 0.16)§
0.56 (0.31 to 1.02)	0.03 (0.00 to 0.05)	Not reported	Not reported
0.82 (0.63 to 1.08)	0.04 (−0.01 to 0.09)	0.63 (0.44 to 0.89)	0.05 (0.01 to 0.09)
0.51 (0.27 to 0.97)	0.05 (0.00 to 0.10)	No difference¶	No difference¶

lower cardiovascular risk persisted after adjustment for blood pressure differences, suggesting that ACE inhibitors may confer a benefit independent of blood pressure control. Furthermore, several smaller or short-term studies suggest that ACE inhibitors may have a renoprotective effect in patients with type 2 diabetes compared with placebo; this effect may be independent of blood pressure control and may occur regardless of whether albuminuria is present (25–32).

Several studies have also evaluated the effectiveness of angiotensin II receptor blockers on outcomes in patients with type 2 diabetes. In the Reduction of Endpoints in

Table 2. **The Effectiveness of Hypertension versus Glucose Control in the United Kingdom Prospective Diabetes Study***

End Point	Strategy	Tight Blood Pressure Control†‡			Tight Glucose Control†		
		8.4-y Event Rate, *n/n*	10-y Absolute Risk Reduction	10-y NNT_B	10-y Event Rate, *n/n*	10-y Absolute Risk Reduction	10-y NNT_B
Any diabetes end point	Conventional	170/390	–	–	438/1138	–	–
	Intensive	259/758	0.112 (0.05 to 0.17)§	8.9	963/2729	0.032 (0.00 to 0.07)§	31.2
Diabetes-related death	Conventional	62/390	–	–	129/1138	–	–
	Intensive	82/758	0.061 (0.02 to 0.11)§	16.4	285/2729	0.009 (−0.01 to 0.03)	112.1
All-cause mortality	Conventional	83/390	–	–	213/1138	–	–
	Intensive	134/758	0.043 (−0.01 to 0.10)	23.3	489/2729	0.008 (−0.02 to 0.04)	125.3
Myocardial infarction	Conventional	69/390	–	–	186/1138	–	–
	Intensive	107/758	0.043 (−0.01 to 0.09)	23.3	387/2729	0.022 (0.00 to 0.05)	46.2
Stroke	Conventional	34/390	–	–	55/1138		
	Intensive	38/758	0.044 (0.01 to 0.08)§	22.7	148/2729	−0.006 (−0.02 to 0.01)	169.40‖
Peripheral vascular death or amputation	Conventional	8/390	–	–	18/1138	–	–
	Intensive	8/758	0.012 (−0.01 to 0.03)	83.3	29/2729	0.005 (0.00 to 0.01)	192.7
Microvascular	Conventional	54/390	–	–	121/1138	–	–
	Intensive	68/758	0.058 (0.02 to 0.10)§	17.2	225/2729	0.024 (0.00 to 0.05)§	41.9

* Values in parentheses are 95% CIs. NNT_B = number needed to treat for benefit.
† Achieved mean blood pressure was 154/87 mm Hg in the control group versus 144/82 mm Hg in the tight blood pressure control group; achieved mean hemoglobin A_{1c} level was 7.9% in the control group versus 7.0% in the tight glucose control group.
‡ Mean follow-up in the blood pressure trial was 8.4 years; the crude event rate is presented for this 8.4-year follow-up, while the absolute risk reduction and the number needed to treat for benefit are standardized to a 10-year time frame to allow a more direct comparison with intensive blood glucose control (20).
§ Statistically significant relative risk reduction in primary data.
‖ For stroke, intensive glucose control led to a trend toward harm rather than benefit. As a result, the presented statistic is number needed to harm.

Table 3. **Effects of Different Drug Classes in Treatment of Hypertension in Diabetes***

Trial	Intervention	Primary or Subgroup Analysis	Total Cardiovascular Events	
			Relative Risk	Absolute Risk Reduction
ABCD	Enalapril vs. nisoldipine	Primary	0.43 (0.25 to 0.73)	0.09 (0.04 to 0.13)
FACET	Fosinopril vs. amlodipine	Primary	0.49 (0.26 to 0.95)	0.07 (0.01 to 0.13)
CAPPP	Captopril vs. thiazide diuretic or β-blocker	Subgroup	0.59 (0.38 to 0.91)	Not reported
UKPDS	Captopril vs. atenolol	Primary	1.29 (0.92 to 1.81)	Not reported
NORDIL	Diltiazem vs. β-blocker or diuretics	Subgroup	1.01 (0.66 to 1.53)	−0.01 (−0.06 to 0.04)
INSIGHT	Nifedipine GITS vs. coamilozide	Subgroup	0.99 (0.69 to 1.42)	0.00 (−0.03 to 0.03)
STOP-2 (3 groups)	Calcium-channel blocker vs. diuretics or β-blockers	Subgroup	0.91 (0.66 to 1.26)	0.03 (−0.06 to 0.11)
	ACE inhibitor vs. diuretics or β-blocker		0.85 (0.62 to 1.18)	0.04 (−0.04 to 0.12)
	ACE inhibitor vs. calcium-channel blocker		0.94 (0.67 to 1.32)‡	0.01 (−0.07 to 0.10)
IDNT (3 groups)	Irbesartan vs. placebo	Primary	0.91 (0.72 to 1.14)	0.02 (−0.04 to 0.07)
	Amlodipine vs. placebo		0.88 (0.69 to 1.12)	0.03 (−0.02 to 0.08)
	Irbesartan vs. amlodipine		1.03 (0.81 to 1.31)	−0.01 (−0.06 to 0.04)
LIFE	Losartan vs. atenolol	Secondary	0.76 (0.58 to 0.98)	0.05 (0.01 to 0.10)
ALLHAT (3 groups)	Lisinopril vs. chlorthalidone	Secondary	1.08 (1.00 to 1.17)	Not reported
	Amlodipine vs. chlorthalidone		1.06 (0.98 to 1.15)	Not reported

* Values in parentheses are 95% CIs. ABCD = Appropriate Blood Pressure Control in Diabetes; ACE = angiotensin-converting enzyme; ALLHAT = Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; CAPPP = Captopril Prevention Project; FACET = Fosinopril versus Amlodipine Cardiovascular Events Trial; GITS = gastrointestinal therapeutic system; IDNT = Irbesartan Diabetic Nephropathy Trial; INSIGHT = International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment; LIFE = Losartan Intervention for Endpoint Reduction; NORDIL = Nordic Diltiazem; STOP-2 = Swedish Trial in Old Patients with Hypertension-2; UKPDS = United Kingdom Prospective Diabetes Study.
† Brown M. Personal communication.
‡ The risk for myocardial infarction in the ACE inhibitor group was 0.51 (CI, 0.28 to 0.92) compared with the calcium-channel blocker group.
§ Composite microvascular end point = doubling of serum creatinine concentration + development of end-stage renal disease + all-cause mortality; individually, only doubling of the serum creatinine concentration was statistically significantly lower with irbesartan compared with either placebo or amlodipine.
‖ Risk for microalbuminuria was lower in the losartan group, although the risk/hazard ratio is not presented ($P = 0.002$).

NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study (33), 1513 participants with type 2 diabetes and nephropathy were randomly assigned to losartan or placebo. There were minimal differences in blood pressure. Losartan led to a reduction in the risk for the primary end point of combined doubling of the creatinine concentration, end-stage renal disease, or death; there was no difference in combined cardiovascular end points.

The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IPDM) Study (34) randomly assigned 590 hypertensive patients with type 2 diabetes and microalbuminuria to irbesartan, 300 mg or 150 mg daily, or placebo. There were small but significant reductions in systolic blood pressure with irbesartan. Compared with the placebo group, systolic blood pressure was 3 mm Hg lower in the 300-mg group and 2 mm Hg lower in the 150-mg group. The risk for overt nephropathy was 0.30 (95% CI, 0.14 to 0.61) in the 300-mg group and 0.61 (CI, 0.34 to 1.08) in the 150-mg group. In both RENAAL and IPDM, the differences in outcomes persisted after adjustment for blood pressure differences and baseline level of microalbuminuria, suggesting a benefit that is independent of systemic blood pressure.

Several studies have specifically compared the effects of different blood pressure targets on diabetes outcomes. The Hypertension Optimal Treatment (HOT) study included a subgroup of 1501 patients with diabetes; participants were randomly assigned into three groups with target diastolic blood pressures of 90, 85, and 80 mm Hg (35). There were substantial improvements in diastolic blood pressure in these groups (20.3, 22.3, and 24.3 mm Hg, respectively, with achieved diastolic blood pressure of 85.2, 83.2, and 81.1 mm Hg). In patients with diabetes, the group randomly assigned to a diastolic blood pressure target of 80 mm Hg had a significantly reduced risk for cardiovascular death and major cardiovascular events and a nonsignificant trend toward improved overall mortality compared with those who had a target diastolic blood pressure of 90 mm Hg.

The United Kingdom Prospective Diabetes Study (UKPDS) of hypertension randomly assigned 1148 patients with newly diagnosed type 2 diabetes to a "less tight" target blood pressure of 180/105 mm Hg or to a "tight" control target of 150/85 mm Hg (36). The achieved blood pressure was 154/87 mm Hg in the less tight control group and 144/82 mm Hg in the tight control group. In the tight control group, there were substantial reductions in risk for any diabetes end point, deaths related to diabetes, and stroke but a nonsignificant change in all-cause mortality. There was also a significant reduction in risk for microvascular disease, most of which was due to reduction in retinal photocoagulation. In addition, at 7.5 years of follow-up, visual acuity had improved in the tight blood pressure control group. Of interest, similar improvements in vision were not found after 10 years in the glycemic control group of the UKPDS (3). The UKPDS results allow an

Table 3—**Continued**

Total Mortality		Microvascular End Points	
Relative Risk	**Absolute Risk Reduction**	**Relative Risk**	**Absolute Risk Reduction**
0.77 (0.36 to 1.67)	0.02 (−0.03 to 0.06)	Not reported	Not reported
0.81 (0.22 to 3.02)	0.01 (−0.03 to 0.04)	Not reported	Not reported
0.54 (0.31 to 0.96)	Not reported	Not reported	Not reported
1.14 (0.81 to 1.61)	−0.02 (−0.08 to 0.03)	1.29 (0.80 to 2.10)	−0.02 (−0.06 to 0.02)
1.07 (0.63 to 1.84)	−0.01 (−0.05 to 0.03)	Not reported	Not reported
0.75† (0.52 to 1.09)	Not reported	Not reported	Not reported
0.79 (0.54 to 1.14)	0.05 (−0.03 to 0.12)	Not reported	Not reported
0.88 (0.62 to 1.26)	0.03 (−0.05 to 0.10)	Not reported	Not reported
1.14 (0.78 to 1.67)	−0.02 (−0.10 to 0.05)	Not reported	Not reported
0.92 (0.69 to 1.23)	0.01 (−0.03 to 0.06)	0.80 (0.66 to 0.97)§	0.06 (0.01 to 0.12)
0.88 (0.66 to 1.19)	0.02 (−0.03 to 0.06)	1.04 (0.86 to 1.25)§	−0.02 (−0.08 to 0.04)
1.04 (0.77 to 1.40)	0.00 (−0.05 to 0.04)	0.77 (0.63 to 0.93)§	0.09 (0.03 to 0.14)
0.61 (0.45 to 0.84)	0.06 (0.02 to 0.10)	‖	‖
1.02 (0.91 to 1.13)	Not reported	Not reported	Not reported
0.96 (0.87 to 1.07)	Not reported	Not reported	Not reported

interesting opportunity to compare the effects of intensive glycemic and hypertension control on diabetes outcomes. The benefits of intensive hypertension control (diastolic blood pressure, 87 mm Hg vs. 82 mm Hg) dramatically outweighed those of intensive glucose control (mean hemoglobin A_{1c} level, 7.9% vs. 7.0%), with substantially greater (by two- to fivefold) absolute risk reductions and much lower numbers needed to treat for benefit for all published outcomes (**Table 2**).

The Appropriate Blood Pressure Control in Diabetes (ABCD) trial was primarily designed to evaluate renal end points with intensive hypertension control in patients with type 2 diabetes (37). Four hundred seventy patients with diabetes and hypertension were randomly assigned to one of two treatment goals: a target diastolic blood pressure of 75 mm Hg or of 80 to 89 mm Hg. Achieved blood pressure was 132/78 mm Hg in the intensive group and 138/86 mm Hg in the moderate group. At 5 years of follow-up, groups did not differ in progression of normoalbuminuria, microalbuminuria (relative risk [RR], 0.76 [CI, 0.36 to 1.36]), diabetic retinopathy (RR, 0.88 [CI, 0.68 to 1.15]), or neuropathy (RR, 1.30 [CI, 1.01 to 1.66]). However, total mortality was 5.5% in the intensive group and 10.7% in the moderate group (RR, 0.51 [CI, 0.27 to 0.97]). Of interest, no differences in myocardial infarction, congestive heart failure, or stroke explained this mortality difference.

Pharmacologic Class Effects in Hypertension and Diabetes

Studies comparing the effects of specific classes of drugs in the management of hypertension in patients with diabetes are summarized in **Table 3**. Several studies have compared ACE inhibitors with calcium-channel blockers. In a substudy of the ABCD trial (38), 470 hypertensive patients with diabetes were randomly assigned to treatment with nisoldipine or enalapril; the achieved blood pressure was equivalent. In intention-to-treat analyses, the nisoldipine group had a substantially higher rate of myocardial infarction (RR, 5.5 [CI, 2.1 to 14.6]) but not of other events or total mortality. The Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET) (39) was an open-label study that randomly assigned 380 patients with type 2 diabetes and hypertension to fosinopril or amlodipine. At the end of the study, systolic blood pressure control was better in the amlodipine group than in the fosinopril group, while diastolic blood pressure was similar. Despite the higher systolic blood pressure, patients randomly assigned to fosinopril had significantly fewer combined cardiovascular events, although total mortality and changes in albumin excretion or renal function did not differ.

In the Swedish Trial in Old Patients with Hypertension-2 (STOP-2), three drug groups were compared for the treatment of hypertension: calcium-channel blockers, ACE inhibitors, and β-blockers plus diuretics (40). In a post hoc subgroup analysis of patients with type 2 diabetes, blood

pressure was equal in the treatment group and there were no differences in the risks for total cardiovascular events or total mortality. However, as in the ABCD trial, risk for myocardial infarction was lower in patients treated with ACE inhibitors than in those treated with calcium-channel blockers (RR, 0.51 [CI, 0.28 to 0.92]). Similarly, the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) compared ACE inhibitors, calcium-channel blockers, and thiazide diuretics (41). Blood pressure control was slightly but significantly different between groups; systolic blood pressure was best in the diuretic group, while diastolic blood pressure was best in the calcium-channel blocker group. In a prespecified subgroup analysis of 12 063 patients with type 2 diabetes, no significant differences were seen between the groups in the primary outcomes of nonfatal myocardial infarction plus coronary heart disease death or all-cause mortality. However, the risk for heart failure was lowest in the diuretic group (RR with calcium-channel blocker, 1.42 [CI, 1.23 to 1.64]; RR with ACE inhibitor, 1.22 [CI, 1.05 to 1.42]). In addition, the ACE inhibitor group had a borderline elevated risk for combined cardiovascular disease compared with the diuretic group (RR, 1.08 [CI, 1.00 to 1.17]). Renal outcomes have not yet been reported from ALLHAT. However, in small studies that have measured renal outcomes (primarily albumin excretion), no clear data suggest that ACE inhibitors are superior to calcium-channel blockers in patients in type 2 diabetes (42–45).

In addition to STOP-2 and ALLHAT, two studies have compared ACE inhibitors with traditional β-blocker or diuretic-based therapy. The Captopril Prevention Project (CAPPP) trial randomly assigned patients with hypertension to captopril or treatment with β-blockers or diuretics; target diastolic blood pressure was less than 90 mm Hg (46). A subgroup analysis was performed on 572 patients with diabetes. Blood pressure control was similar. However, in the captopril group, risk for all-cause mortality, cardiovascular events, and myocardial infarction was lower (RR, 0.34 [CI, 0.17 to 0.67]). Captopril led to an increase in risk for stroke in the nondiabetic patients but not in the diabetic patients. This study has been criticized because randomization was unbalanced, subgroup analyses were done post hoc, and the diastolic blood pressure goal was only 90 mm Hg. The UKPDS included a substudy in which patients in the intensive control group (target blood pressure $<$ 150/85 mm Hg) were randomly assigned to atenolol or captopril (47). Achieved blood pressure was similar in both groups (143/81 mm Hg vs. 144/83 mm Hg). In contrast to the CAPPP trial, but in accord with STOP-2, there were no differences in any of the aggregated or individual macrovascular or microvascular events between the groups. However, patients taking β-blockers gained more weight and required more frequent addition of new glucose-lowering agents than those taking ACE inhibitors. In sum, the results of the UKPDS and STOP-2 raise doubt about whether ACE inhibition produces superior macrovascular or microvascular outcomes compared with β-blockade. Indeed, even in terms of renal outcomes, small or short-term studies of ACE inhibitors versus β-blockade have yielded inconsistent results (48–50).

In addition to STOP-2 and ALLHAT, two other studies have directly compared calcium-channel blockers and traditional treatment with β-blockers and diuretics. The Nordic Diltiazem (NORDIL) trial compared treatment with diltiazem and treatment with β-blockers or diuretics (or both) (51). Blood pressure was similarly reduced in both groups. In the subgroup of 727 patients with type 2 diabetes, there were no differences in combined cardiovascular end points or total mortality. The International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) study compared treatment with long-acting nifedipine with coamilozide (52). Blood pressure reduction was similar in both groups. In the subgroup of 1302 patients with diabetes, there were no differences in the risk for cardiovascular end points or in total mortality.

Two studies have compared angiotensin II receptor blockers and other drugs in treating hypertension in diabetes. The first, the Irbesartan Diabetic Nephropathy Trial (IDNT), randomly assigned 1715 patients with diabetes, hypertension, and nephropathy into three groups: irbesartan, amlodipine, and placebo (53). Irbesartan was more effective than amlodipine or placebo in preventing the primary end point of doubling of serum creatinine concentration, development of end-stage renal disease, or death (RR vs. placebo, 0.80 [CI, 0.66 to 0.97]; RR vs. amlodipine, 0.77 [CI, 0.63 to 0.93]). Of interest, no differences were seen between amlodipine and placebo in any of the outcomes or between any of the groups in the secondary outcomes of risks for cardiovascular events or total mortality. The second major trial, the Losartan Intervention for Endpoint Reduction (LIFE) study, randomly assigned patients with hypertension and signs of left ventricular hypertrophy on electrocardiography to an angiotensin II receptor blocker (losartan) or a β-blocker (atenolol) (54). In a prespecified subgroup analysis of 1195 patients with diabetes, the losartan group had a substantially lower risk for cardiovascular end points and total mortality. Risk for microalbuminuria was also lower in the losartan group (P = 0.002).

Discussion

Studies of hypertension control in diabetes show a clear and consistent effect: Improved control of blood pressure leads to substantially reduced risks for cardiovascular events and death (19, 21, 22, 35–37, 55). In addition, findings suggest that in patients with diabetes, aggressive hypertension control also reduces the risk for microvascular events, including end-stage functional impairment (such as decreased visual acuity and end-stage renal disease) (33, 34, 36, 53).

The risk reduction seen with hypertension control in patients with diabetes is substantially greater than that seen in persons in the general population who have similar blood pressure levels (35). It is also clear that blood pressure targets for patients with diabetes should be more aggressive. In the HOT study, a four-point difference in diastolic blood pressure (85 mm Hg vs. 81 mm Hg) resulted in a 50% decrease in risk for cardiovascular events in patients with diabetes (35). In contrast, HOT study participants without diabetes received no benefit. Therefore, tight blood pressure goals should not be extended to the average nondiabetic patient with uncomplicated hypertension.

The current experimental evidence suggests that the diastolic blood pressure goal in patients with type 2 diabetes should be 80 mm Hg; ongoing studies may suggest an even lower diastolic target. Systolic target goals have not been specifically tested in trials, but a 10-point reduction in the UKPDS (154 mm Hg vs. 144 mm Hg) and a four-point reduction in the HOT trial (144 mm Hg vs. 140 mm Hg) led to substantial decreases in diabetes-related mortality and end points (36). While the optimal level of systolic blood pressure control has not been as rigorously established, it may be reasonable to target systolic blood pressures of 135 mm Hg. We could find no evidence from randomized trials supporting the commonly recommended blood pressure goal of less than 130 mm Hg. Indeed, a less stringent goal of 140 mm Hg could be supported given the current evidence.

We caution clinicians about the need to clearly distinguish between blood pressure targets and quality standards (56). For example, although the target diastolic blood pressure in the intensive group of the HOT study was 80 mm Hg, the mean achieved blood pressure was 81 mm Hg; thus, more than 50% of patients did not achieve the target, even in a volunteer population with intensive follow-up. Performance and quality standards should allow goals to be tempered by clinical discretion and a realization that many, or perhaps most, patients with diabetes and hypertension will not achieve aggressive goals, even while taking three or four antihypertensive agents.

Choice of initial blood pressure agent in patients with diabetes is difficult to define precisely. It could be argued, given the conflicting available evidence, that there are no obviously superior agents. It is clear, however, that most patients will require more than one blood pressure agent (22, 35–37, 55). The weight of current evidence suggests that thiazide diuretics and angiotensin II receptor blockers, and perhaps ACE inhibitors, are reasonable first-choice agents, although angiotensin II receptor blockers and ACE inhibitors are considerably more expensive than diuretics (some ACE inhibitors are now off patent). However, high doses of thiazide diuretics can worsen important metabolic variables, including glucose and lipid levels (57–59).

Available data suggest that angiotensin II receptor blockers have impressive benefits. They clearly reduce the risk for renal end points (33, 34, 53), and the LIFE study suggests that they are superior to β-blockers in reducing cardiovascular events and mortality, at least in patients with evidence of left ventricular hypertrophy on electrocardiography (54). However, the evidence comparing ACE inhibitors, diuretics, and β-blockers is much less definitive. Indeed, although ALLHAT found that diuretics were equivalent to ACE inhibitors for most outcomes and were superior for heart failure, the CAPPP trial found that ACE inhibitors were superior to β-blockers and diuretics. The UKPDS and STOP-2 found that ACE inhibitors were equivalent to β-blockers and diuretics (40, 41, 46, 47). Some have argued for the use of ACE inhibitors as first-line agents based on the HOPE study, which showed a hypertension-independent benefit on mortality. However, these benefits were not apparent in ALLHAT, which suggests that the HOPE study may have been little more than a trial of blood pressure treatment versus placebo in high-risk patients (23, 24, 41). Some limited evidence shows that ACE inhibitors may have hypertension-independent renoprotective effects in patients with diabetes (25, 26, 28–32), although this is tempered by the at best inconsistent data comparing ACE inhibitors with other drugs for preventing progression of renal disease (37, 39, 42–45, 47–50). There are as yet no long-term trials comparing angiotensin II receptor blockers with ACE inhibitors in patients with diabetes. Early data on renal outcomes appear to be equivalent (60) and effects on intermediate end points such as blood pressure control seem to be similar, although angiotensin II receptor blockers may be slightly better tolerated (61).

β-Blockers and calcium-channel blockers have proven efficacy compared with placebo, and the evidence suggests that they are similarly efficacious (21, 22, 40, 51, 52). There is evidence, albeit inconsistent, that diuretics, angiotensin-receptor blockers, and ACE inhibitors may be superior to these agents; thus, β-blockers and calcium-channel blockers are probably best used as second- or third-line treatments for hypertension in diabetes (38–41, 51, 52). β-Blockers are safe, effective, and inexpensive and at moderate doses have relatively few side effects. However, in the UKPDS, patients taking β-blockers gained more weight than those taking ACE inhibitors, and β-blocker therapy was more frequently discontinued. In addition, patients taking β-blockers required the addition of new glucose-lowering agents more frequently than those taking ACE inhibitors (47). However, there is little evidence to support the common concern that β-blockers increase risks for hypoglycemia or hypoglycemia unawareness.

Some data suggest that, in the general population, calcium-channel blockers may be more effective in reducing stroke than other agents, but this has not been definitively shown in patients with diabetes (41, 62). Given the lack of clear difference in effectiveness between calcium-channel blockers and β-blockers, cost and side effect profiles should be key considerations in choosing between these agents.

There is also no obvious choice of which class of cal-

cium-channel blocker to use in patients with diabetes. The large-scale studies show no consistent distinction among classes. The NORDIL trial, which used diltiazem, and INSIGHT and STOP-2, which used dihydropyridine agents, had similar overall results. There has been some concern about the use of dihydropyridine agents in patients with type 2 diabetes and albuminuria; however, only limited and inconsistent data suggest that these agents are substantially worse than other classes of drugs (42–45).

Other agents may have a role in achieving desired blood pressure targets in patients with type 2 diabetes. However, there is little information on the effectiveness of these drugs in reducing microvascular and macrovascular outcomes. Recent data suggest that doxazosin, an α-antagonist, yields worse outcomes than thiazide diuretics in control of hypertension in the general population, although this difference may largely be due to differences in blood pressure (62, 63). Nonetheless, in view of the proven efficacy of other agents, α-blockers should be reserved for hypertension that is refractory to other agents in patients with type 2 diabetes.

One of the limitations of the current literature is a lack of strong evidence comparing the effects of blood pressure treatment according to demographic factors, such as ethnicity and age. These factors are important because ethnicity may be a strong predictor of adverse events in patients with diabetes (64–68), and age may change relative or absolute benefits of hypertension treatment, in part because of competing risks for death (69). Also, the effectiveness of different antihypertensive agents in blood pressure lowering may vary by ethnicity and age. For example, in ALLHAT, African-American participants did not respond to ACE inhibitors as well as other participants and had a higher risk for stroke as a result. However, it is not clear how these results relate to the population of African-American persons with diabetes (41).

The dramatic effects of hypertension treatment in diabetes are striking and raise an important question: Where should diabetes treatment priorities lie? Because diabetes is defined by glucose levels, much of the emphasis in diabetes care has been on optimal blood glucose control. However, glucose control is clearly effective only in reducing microvascular end points, and to date only intermediate outcomes have been shown to be reduced. For example, the UKPDS showed that glycemic control reduced progression of retinopathy and photocoagulation, but after 10 years of follow-up, visual acuity, renal function, functional status, and mortality rates were not significantly improved (3). In contrast, control of hypertension is dramatically effective in reducing risk for cardiovascular events and mortality and does so within a 4- to 6-year period (19, 21, 22, 35, 36, 38). Furthermore, hypertension control appears to be more effective than glycemic control in reducing microvascular events (**Table 2**) (36, 70). We do not intend to suggest that glycemic control is an ineffective intervention (70–73), but rather that treatment of hypertension should be prioritized and stressed as the most important intervention for the average population of persons with type 2 diabetes. Blood pressure targets should be 135/80 mm Hg. First-choice agents should probably be thiazide diuretics, angiotensin II receptor blockers, or ACE inhibitors, and second-choice agents should be β-blockers or calcium-channel blockers. Aggressive control of blood pressure in patients with type 2 diabetes has dramatic benefits and should be the first priority in diabetes care.

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