

Management of Hypertension in Patients with Type 2 Diabetes Mellitus: Guidelines Based on Current Evidence

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Hypertension and diabetes are becoming increasingly common. Most patients with both disorders have a markedly worsened risk for premature microvascular and macrovascular complications. The appropriate management of the hypertension seen in almost 70% of patients with type 2 diabetes mellitus remains controversial. However, over the past few years, many randomized, controlled trials have provided guidance for more effective therapy. These trials have established the need for a lower goal blood pressure (<130/80 mm Hg) than has previously been recommended. In addition, they have proven the efficacy of drugs from three major classes of antihypertensive agents; however, comparative trials have failed to show definite superiority of any particular class in either lowering blood pressure or reducing cardiovascular morbidity and mortality.

To achieve therapy goals, multiple antihypertensive drugs are usually needed. On the basis of their apparent superiority in slowing diabetic nephropathy, angiotensin-converting enzyme inhibitors should probably be the first choice. Second and third choices should be a long-acting diuretic and a calcium-channel blocker or a β -blocker, respectively. Attention should also be directed toward nonpharmacologic and pharmacologic control of hyperglycemia and dyslipidemia.

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Largely as a consequence of increasing obesity in all industrially developed societies, the incidence of type 2 diabetes mellitus is rapidly rising. This disorder will soon affect more than 300 million people worldwide (1) and more than 20 million people in the United States (2). Of these diabetic patients, more than half will also be hypertensive. Serious cardiovascular events are more than twice as likely in patients with both diabetes and hypertension than in patients with either disease alone (3). Therefore, management of the hypertension so frequently seen in diabetic patients has now become one of the most critical challenges of health care.

Numerous controversies have arisen over the appropriate way to treat hypertension in diabetic patients, leading to considerable confusion among practitioners. These controversies include the potential adverse effects of certain antihypertensive drugs on glucose tolerance and insulin sensitivity (4); the appropriate level of blood pressure at which antihypertensive therapy should be started, as well as the correct goal of such therapy (5); and, most contentiously, the best choices of antihypertensive drugs. Calcium-channel blockers, in particular, have been a source of controversy. Some have claimed that use of calcium-channel blockers induces approximately 60 000 major cardiovascular events annually in diabetic patients with hypertension (6). However, this

concern has been countered by evidence attesting to the safety and effectiveness of this class of drug (7).

Some uncertainty will remain until more definitive data become available. In 2 to 3 years, such data will be provided by massive ongoing trials, such as the Antihypertensive and Lipid Lowering Treatment To Prevent Heart Attack Trial (ALLHAT), the International Verapamil SR/Trandolapril Trial (INVEST), and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), which together involve more than 80 000 patients. However, enough evidence is now available to provide practitioners with sound principles for managing this therapeutic challenge. Specifically, data from four trials involving approximately 10 000 diabetic patients with hypertension have recently been published (8–11), justifying a new look at the evidence. Most of these data are included in a meta-analysis of all 15 randomized, controlled trials of hypertension treatment published since 1995 (12). However, although 10% to 30% of patients included in these trials were diabetic, the meta-analysis did not examine their data separately.

THErapy SHOULD DECREASE BLOOD PRESSURE TO LESS THAN 130/80 MM/HG IN ALL DIABETIC PATIENTS WITH HYPERTENSION

Three randomized, controlled trials have provided conclusive evidence of the impressive benefits of reduc-

ing blood pressure to below 130/80 mm Hg (13–15). In the United Kingdom Prospective Diabetes Study (UKPDS) (13), predetermined blood pressure goals were below 150/85 mm Hg. Therefore, the attained mean blood pressure of 144/82 mm Hg did not establish the level for maximal benefit. However, a subsequent analysis examined the relation between the risk for cardiovascular complications and the levels of systolic blood pressure achieved over a median follow-up of 10.5 years in all 3642 patients with type 2 diabetes mellitus who were screened for but did not enter the UKPDS (8). In these patients, who were treated with various drugs, all diabetic and cardiovascular risks progressively decreased as systolic pressures decreased from greater than 160 mm Hg to less than 120 mm Hg, with no threshold of pressure for a substantive change in risk. This led to the conclusion that “the lower the systolic blood pressure, the lower the risk of complications” (8).

Since these data are observational, they do not provide guidance on the ability of therapy to achieve the maximally beneficial blood pressure level or, in fact, what that level may be. In the Hypertension Optimal Treatment (HOT) trial (14), 1501 diabetic patients with hypertension were randomly assigned to achieve diastolic pressures of less than 90, 85, or 80 mm Hg while taking a dihydropyridine calcium-channel blocker, often with the addition of one or two other drugs. Those assigned to achieve a goal of 80 mm Hg reached a mean level of 81.1 mm Hg, only 4.1 mm Hg lower than those assigned to achieve a goal of 90 mm Hg. Despite this relatively small difference in achieved pressure, significant reductions were seen in all major events (coronary disease, 60%; stroke, 43%; and mortality, 77%). The smaller Appropriate Blood Pressure Control in Diabetes (ABCD) trial (15) included cardiovascular events only as a secondary outcome. However, the 51% reduction in all-cause mortality among patients who received more intensive therapy was statistically significant.

ALL DRUGS REDUCE RISK COMPARED WITH PLACEBO

In three placebo-controlled trials, only a portion of the hypertensive patients had diabetes (9, 16, 17). In two of these trials, diabetic patients achieved even more impressive absolute risk reduction than nondiabetic patients. This finding attests to the inherently higher risk of patients with diabetes and the ability of antihypertensive drugs to reduce these risks. In the Systolic Hyper-

tension in the Elderly Program (SHEP) (16), absolute risk reduction was twice as great for the 583 diabetic patients as for the 4149 nondiabetic patients (51 of 1000 vs. 101 of 1000, respectively). In the Syst-Eur trial (17), the adjusted relative hazards for all cardiovascular events were reduced by 69% in the 492 diabetic patients and 26% in the 4203 nondiabetic patients.

Therapy in SHEP was based on a low-dose diuretic, 12.5 to 25 mg of chlorthalidone per day (16). Coupled with evidence that low-dose diuretics do not increase risk for diabetes (4), the safety of such therapy in diabetic patients seems established. Moreover, diuretics will probably often be needed to achieve goals of therapy because they enhance the efficacy of all other classes of antihypertensives and because volume retention is a common feature of hypertension in diabetic patients.

In the Heart Outcomes Prevention Evaluation (HOPE) (9), the angiotensin-converting enzyme (ACE) inhibitor ramipril was given to half of the high-risk population (approximately 3600 diabetic patients and 5300 hypertensive patients, most of whom were being treated with other antihypertensive agents). The study was not a trial of antihypertensive therapy, and no attempt was made to reach a predetermined level of blood pressure. Blood pressure was lower by only 2/1 mm Hg in patients who received an ACE inhibitor compared with those who received placebo. Nonetheless, the impressive reduction in diabetic and cardiovascular events prompted the investigators to conclude that “ACE inhibition with ramipril is . . . a preventive intervention with multiple mechanisms of benefit, including lowering of blood pressure” (9).

None of these trials used a β -blocker as initial therapy. Because β -blockers may worsen glucose tolerance and insulin sensitivity (4), they might be considered a less appropriate choice for diabetic patients with hypertension. However, in the UKPDS (13), a β -blocker was somewhat more protective than an ACE inhibitor. This suggests that the benefits of this class outweigh its potential harm. In particular, because diabetic patients with hypertension are at high risk for coronary disease, β -blockers are more likely to be beneficial.

PROTECTIVE EFFECTS DIFFER AMONG DRUGS

Almost 5000 diabetic patients with hypertension have been included in randomized, controlled trials that compare one agent with another (10, 11, 18–22) (Table). The Table shows the numbers of events (cor-

Table. Comparative Trials in Diabetic Patients with Hypertension*

Trial (Reference)	Patients	Drugs	Patients Receiving Other Drugs	Decrease in Systolic/ Diastolic Blood Pressure	CHD/CHF	Stroke	Death
	<i>n</i>		%	<i>mm Hg</i>	<i>n/n</i>	<i>n</i>	
UKPDS (18)	400	Captopril	27 (CCB)	15/10	73/12	21	75
	358	Atenolol	36 (CCB)	16/12	48/9	17	59
CAPPP (19)	309	Captopril		16/10	10	24	17
	263	Diuretic/ β -blocker		16/10	25	20	27
ABCD (20)	235	Enalapril	93 (diuretic/ β -blocker)	20/10	9/10	7	14
	235	Nisoldipine	78 (diuretic/ β -blocker)	20/10	27/8	11	18
FACET (21)	189	Fosinopril	31 (amlodipine)	13/8	10	4	4
	191	Amlodipine	26 (fosinopril)	19/8	13	10	5
NORDIL (10)	351	Diltiazem	25 (CCB/ACE inhibitor)	20/19	17/13	21	21
	376	Diuretic/ β -blocker	28 (diuretic/ β -blocker)	23/19	18/7	23	26
INSIGHT (11)	649	Nifedipine GITS	45	30/16	28/9	17	44
	653	Co-amilozide	51	32/15	25/6	19	59
STOP-2 (22)	253	Diuretic/ β -blocker		34/16	26/29	39	67
	235	ACE inhibitor		35/16	17/22	34	56
	231	CCB		34/18	32/24	29	50

* ABCD = Appropriate Blood Pressure Control in Diabetes; ACE = angiotensin-converting enzyme; CAPPP = Captopril Prevention Project; CCB = calcium-channel blocker, CHD = coronary heart disease; CHF = congestive heart failure; FACET = Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial; INSIGHT = International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment; NORDIL = Nordic Diltiazem Study; STOP-2 = Swedish Trial of Old Patients with Hypertension-2; UKPDS = United Kingdom Prospective Diabetes Study.

onary heart disease, congestive heart failure, strokes, and deaths) observed with the different drugs used in seven randomized, controlled trials. A meta-analysis of such trials might be misleading because patients in different trials started with widely divergent risk statuses; achieved various degrees of blood pressure reduction; and had highly variable rates of dropout, admixture of other drugs, and ascertainment of events. For example, in the ABCD trial, which compared an ACE inhibitor (enalapril) with a calcium-channel blocker (nisoldipine), almost 90% of patients also received either a diuretic or a β -blocker. Thus, it would be problematic to definitively classify patients in a meta-analysis as having received an ACE inhibitor or a calcium-channel blocker.

In keeping with reminders that “the quality of the information derived from meta-analysis depends critically on the quality of the studies deemed to be eligible for meta-analysis” (23), it should be noted that previous meta-analyses of some of these trials (24) have been criticized because “all suffer from various flaws in relation to the study design” (25).

The Swedish Trial of Old Patients with Hypertension-2 (STOP-2) is the only completed trial that compared drugs from the three major classes of antihypertensive agents. It included 6614 elderly hypertensive patients, 719 of whom had diabetes. In this trial, patients who received an ACE inhibitor had lower rates of

coronary disease and heart failure; however, rates of stroke and mortality were lower in those who received a dihydropyridine calcium-channel blocker (22).

When all of the events reported in these seven comparative randomized, controlled trials are simply combined and the results are expressed as the number of events per 1000 patients who received one of the three regimens (diuretic with or without β -blocker vs. ACE inhibitor vs. calcium-channel blocker), the overall data provide no clear proof that one class of drug is better than another. However, considerable evidence shows that ACE inhibitors are better than any other class of antihypertensives in protecting against progressive renal damage leading to end-stage renal disease, one of the most common and serious complications seen in diabetic patients with hypertension. The September 2000 consensus report of the National Kidney Foundation states: “Antihypertensive regimens should include an angiotensin-converting enzyme inhibitor in order to provide maximum cardiovascular and renal benefits in this population” (26).

An ACE inhibitor (or an angiotensin II receptor blocker if ACE inhibitors are contraindicated because of cough) seems to be the unequivocal choice for renal protection. Whether this preference extends to all other cardiovascular events remains to be seen. Therefore, the conclusion noted in a recent review of the available evidence about ACE inhibitors seems appropriate:

Based on available data from comparative trials, using ACE inhibitors may be prudent as a first-line agent for the treatment of hypertension in patients with type 2 diabetes. Conclusive evidence on the comparative effects of antihypertensive treatments will come from large prospective randomized trials such as the ALLHAT trial (25).

Various reports from expert committees (26–29) recommend that angiotensin II receptor blockers be used to treat hypertension only in patients who should receive but cannot tolerate an ACE inhibitor, usually because of cough. The value of ACE inhibitor–based therapy in patients with microalbuminuria and type 1 diabetes has been shown to extend to normotensive patients (30). Similar data from randomized, controlled trials in patients with type 2 diabetes suggest that angiotensin II receptor blockers can be considered equal to ACE inhibitors (31–33). Data documenting additive effects of submaximal doses of both an ACE inhibitor and an angiotensin II receptor blocker on blood pressure and albuminuria (34) have prompted clinicians to prescribe such combination therapy. It is not yet known whether these additive effects are greater than those that would be seen with larger doses of either agent alone.

THE NEED FOR MULTIPLE DRUGS

To achieve the desired reduction in blood pressure (<130/80 mm Hg), most diabetic patients with hypertension will require two, three, or four antihypertensive drugs. As noted in the Consensus Report (26),

Data from several major recent trials, including UKPDS and HOT, demonstrate . . . that attainment of these lower goal blood pressures is virtually impossible to achieve with monotherapy. The majority of the time addition of multiple antihypertensive medications including a diuretic, CCB [calcium-channel blocker], or any similar combination is required to achieve these lower blood pressure goals.

The burden, financial and otherwise, of multidrug therapy can be lessened by intensive attention to lifestyle modifications, including weight reduction; physical activity; and moderation of sodium, protein, and alcohol intake. Although these actions alone have not been shown to reduce morbidity or mortality, they may improve control of hyperglycemia and dyslipidemia.

The benefits of intensive therapy may well exceed the miseries and costs of uncontrolled diabetes and hypertension. A randomized, controlled trial in 160 patients with type 2 diabetes showed a 70% reduction in progression of nephropathy, retinopathy, and autonomic neuropathy over a 3.8-year follow-up in those assigned to more intensive compared with standard therapy (35).

CONCLUSION

The following principles seem appropriate for the management of hypertension in diabetic patients. First, the target blood pressure should be below 130/80 mm Hg. Second, all antihypertensive drugs except α -blockers have been shown to be beneficial compared with placebo. Third, more than one drug will usually be required to achieve the target blood pressure. Fourth, the choice of drugs should always include an ACE inhibitor (or an angiotensin II receptor blocker if ACE inhibitors cannot be tolerated) and should usually include a diuretic. If additional therapy is needed, a calcium-channel blocker, β -blocker, or α -blocker may be used. Fifth, attention should be paid to lifestyle changes (weight reduction; regular exercise; and moderation of sodium, protein, and alcohol), as well as control of hyperglycemia, dyslipidemia, and proteinuria. As the population grows older and continues to gain weight, diabetes and hypertension will become even more common. It is to be hoped that an approach similar to that outlined here can limit their serious consequences.

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