The Evidence Base for Tight Blood Pressure Control in the Management of Type 2 Diabetes Mellitus

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Diabetes mellitus is a leading cause of morbidity and death in the United States. Type 2 diabetes mellitus accounts for the majority of affected persons (90% to 95%) and affects older adults, particularly those older than 50 years of age. It affects an estimated 16 million Americans, 11 million of whom have both diabetes and hypertension (1). Most adverse diabetes outcomes are a result of vascular complications. These complications are generally classified as microvascular, such as retinopathy, nephropathy, and neuropathy (although neuropathy may not be entirely a microvascular disease), or macrovascular, such as coronary artery disease, cerebrovascular disease, and peripheral vascular disease.

In order to prevent, or diminish the progression of, microvascular and macrovascular complications, recommended diabetes management necessarily encompasses both metabolic control and cardiovascular risk factor control (2–4). The need for good glycemic control is supported by the Diabetes Control and Complications Trial (5) in type 1 diabetes mellitus and, more recently, the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes mellitus (6). In these studies, tight blood sugar control reduced microvascular complications, such as nephropathy and retinopathy, but had little effect on macrovascular outcomes. Up to 80% of patients with type 2 diabetes mellitus will develop or die of macrovascular disease, underscoring the importance of preventing macrovascular complications.

In an effort to provide internists and other primary care physicians with effective management strategies for diabetes care, the American College of Physicians decided to develop guidelines on the management of hypertension in people with type 2 diabetes mellitus. The target audience for this guideline is all clinicians who provide care to patients with type 2 diabetes. The target patient population is all persons with type 2 diabetes who have hypertension, defined as systolic blood pressure of at least 140 mm Hg or diastolic blood pressure of at least 90 mm Hg. This target patient population includes those who already have some form of microvascular complication and, of particular importance, premenopausal women with diabetes. We will attempt to answer the following questions: 1) What are the benefits of tight blood pressure control in type 2 diabetes? 2) What should the target levels of systolic blood pressure and diastolic blood pressure be for patients with type 2 diabetes? and 3) Are certain antihypertensive agents more effective or beneficial in patients with diabetes?

When analyzing benefit or effectiveness for this review, we included only studies that measured clinical end points. The four major classes of clinical end points were all-cause mortality, cardiovascular mortality, cardiovascular events (myocardial infarction, stroke, or congestive heart failure), and microvascular complications (photocoagulation, nephropathy, neuropathy, or amputation).

The review was divided into two categories. The first included studies that evaluated the effects of blood pressure control if the comparison examined an antihypertensive drug versus placebo or the effects of different target blood pressure levels. The second category evaluated the effect of different classes of drugs. A discussion of this evidence follows.

BLOOD PRESSURE CONTROL
Benefits

Three studies have compared focused treatment of hypertension in subgroups of people with diabetes versus placebo or usual care. They are the Systolic Hypertension in the Elderly Program (SHEP), the Hypertension Detection and Follow-up Program (HDFP), and the Systolic Hypertension in Europe (Syst-Eur) study (7–9).

In SHEP, patients were randomly assigned to intensive treatment versus placebo and usual care by primary providers. The intensive group achieved reductions of 9.8 mm Hg in systolic blood pressure and 2.2 mm Hg in diastolic blood pressure, as well as a significant decline in total cardiovascular events (relative risk [RR], 0.66 [95% CI, 0.46 to 0.94]). The HDFP randomly assigned patients to stepped care (intensive) versus referred care (usual care). The primary data from this trial were analyzed by the Cochrane Database of Systematic Reviews (10), which

Table. **Number Needed To Treat for Benefit for Tight Hypertension Control in the United Kingdom Prospective Diabetes Study***

End Point	NNT_B over a 10-Year Period for Tight Blood Pressure Control†
Any diabetes end point	8.9
Diabetes-related death	16.4
All-cause mortality	23.3
Myocardial infarction	23.3
Stroke	22.7
Microvascular	17.2

* Adapted from Vijan et al. (14). NNT_B = number needed to treat for benefit.
† Number needed to treat for benefit is very sensitive to the starting point from which treatment begins. In the United Kingdom Prospective Diabetes Study, the mean starting blood pressure was 160/94 mm Hg. Thus, it should be noted that the numbers needed to treat for benefit for this study may be smaller than what would be found in current practice, where most patients are expected to have lower initial blood pressure levels.

found an odds ratio for cardiovascular mortality and morbidity of 0.62 (CI, 0.44 to 0.87) in the intensive group.

The Syst-Eur study randomly assigned patients to nitrendipine or placebo. The mean decrease in systolic blood pressure and diastolic blood pressure for diabetic patients in the intervention group was 8.6 and 3.9 mm Hg, respectively, resulting in a 70% reduction in cardiovascular mortality, a 62% reduction in all cardiovascular events, and a 69% reduction in stroke. After adjustment for confounders, there was a 55% reduction in overall mortality.

Target Blood Pressure Levels

Three recent studies, the Hypertension Optimal Treatment (HOT) study, the UKPDS, and the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, specifically compared the effects of randomly assigning participants to different blood pressure targets on cardiovascular outcomes.

In the HOT study, patients were randomly assigned to target diastolic blood pressures of 90, 85, and 80 mm Hg (11). Achieved diastolic blood pressures in each group were 85.2, 83.2, and 81.1 mm Hg, respectively. The group randomly assigned to a target of 80 mm Hg had a significantly lower relative risk for cardiovascular death and major cardiovascular events compared with the group randomly assigned to a target of 90 mm Hg.

The UKPDS (12) randomly assigned patients to a "tight" blood pressure control group with a target of less than 150/85 mm Hg or a "less tight" control group with a target of less than 180/105 mm Hg. The achieved blood pressures were 144/82 mm Hg and 154/87 mm Hg, respectively. (It is important to note that these targets, described as tight and less tight control, do not conform with current standards from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, in which a blood pressure above 140/90 mm Hg is considered uncontrolled.) In the tight control group, there were substantial reductions in risk for any diabetes end point, deaths related to diabetes, and stroke.

In addition, there was also a significant reduction in risk for microvascular disease, with actual improvements in visual acuity.

The ABCD study (13) randomly assigned patients to intensive treatment (target diastolic blood pressure, 75 mm Hg) or moderate control (target diastolic blood pressure, 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. After 5 years of follow-up, there were no differences between the groups in progression of nephropathy, retinopathy, or neuropathy. Total mortality rate was 5.5% in the intensive group and 10.7% in the moderate group, but there were no differences in cardiovascular mortality to explain this.

In summary, in the HOT study, a four-point difference in diastolic blood pressure, from 85 to 81 mm Hg, resulted in a 50% decrease in risk for cardiovascular events in patients with diabetes. If this study is used as the lowest mean value achieved in the trials, a diastolic blood pressure of 80 mm Hg should be the goal for patients with diabetes. It is not clear whether diastolic blood pressure lower than 80 mm Hg is beneficial. Systolic target goals have not been tested in randomized trials, but the UKPDS showed that a 10-point reduction in systolic blood pressure, from 154 mm Hg to 144 mm Hg, led to a substantial decrease in diabetes-related mortality and end points. Thus, while the optimal level of control for systolic blood pressure has not been clearly established, it may be reasonable to target a systolic blood pressure of 130 to 135 mm Hg based on the levels attained in the ABCD trial.

The 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. The **Table** highlights the numbers needed to treat for benefit for tight blood pressure control in the UKPDS (14).

EFFECTIVENESS OF DIFFERENT CLASSES OF ANTIHYPERTENSIVE MEDICATIONS

Three trials have compared calcium-channel blockers and angiotensin-converting enzyme (ACE) inhibitors: the ABCD trial, the Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET), and the Swedish Trial in Old Patients with Hypertension-2 (STOP-2). In a substudy of the ABCD trial (15), patients were randomly assigned to treatment with nisoldipine or enalapril. The achieved blood pressure was the same in each group, but by the end of the study nearly half of the patients were not taking their initially assigned drug. In intention-to-treat analyses, the rate of myocardial infarction was substantially higher (RR, 5.5 [CI, 2.1 to 14.6]) in the nisoldipine group compared with the enalapril group. These effects persisted after adjustment for confounders and for the length of time that the patients were actually exposed to the drugs. The relatively higher mortality rate in the calcium-channel blocker

group was not due to a detrimental or adverse effect of nisoldipine but was most likely a result of the greater efficacy of the ACE inhibitor.

In FACET (16), patients were randomly assigned to fosinopril or amlodipine. Systolic blood pressure control was better in the amlodipine group than in the fosinopril group, while diastolic blood pressure was similar. Despite higher systolic blood pressure, patients randomly assigned to fosinopril had significantly fewer combined cardiovascular events (RR, 0.49 [CI, 0.26 to 0.95]). Individual events were not significantly different between groups, nor was mortality, although all trends favored fosinopril.

In STOP-2, three drug groups were compared: calcium-channel blockers, ACE inhibitors, and β-blockers plus diuretics (17). In a post hoc subgroup analysis, there were no differences in the treatment groups in achieved blood pressure or in the risk for total cardiovascular events or total mortality. Of note, 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]), suggesting an additional benefit from ACE inhibitors beyond their antihypertensive capabilities. There have been other arguments for the use of ACE inhibitors as first-line agents in diabetes. These agents are renoprotective in patients with type 2 diabetes mellitus. The Heart Outcomes and Prevention Evaluation (HOPE) study, which randomly assigned patients with diabetes and one cardiovascular risk factor to ramipril or placebo, showed substantial absolute reduction in overall mortality despite very small changes in blood pressure (18, 19). However, this study was not conducted in hypertensive patients, and it remains to be demonstrated that this is a class effect.

The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) is the largest trial of blood pressure–lowering therapy to date (20). This trial compared the effectiveness of an ACE inhibitor (lisinopril) versus a calcium-channel blocker (amlodipine) versus a thiazide diuretic (chlorthalidone) as first-line therapy for mild to moderate hypertension. The primary outcome was combined fatal coronary heart disease or nonfatal myocardial infarction. Secondary outcomes were all-cause mortality, stroke, combined coronary heart disease (primary outcome, coronary revascularization, or angina with hospitalization), and combined cardiovascular disease (combined coronary heart disease, stroke, treated angina without hospitalization, heart failure, and peripheral arterial disease). The results showed no differences between treatments in primary outcome or all-cause mortality. The amlodipine group had a higher risk for heart failure than the chlorthalidone group. Cholesterol levels, prevalence of hypokalemia, and incidence of new diabetes were higher in the chlorthalidone group than in the other groups after 2 and 4 years of follow-up. However, these differences did not translate into increased cardiovascular events or higher mortality rates. For the diabetic patients, lisinopril appeared to have

no special advantage over chlorthalidone for most cardiovascular and renal outcomes. Moreover, in self-reported black patients, lisinopril was less effective than chlorthalidone in reducing combined cardiovascular end points and stroke and showed a similar trend for heart failure and poorer blood pressure lowering. It should also be noted that on average, 40% of patients required more than one drug; the average number of drugs per patient was two. In addition, one third of patients did not reach the goal blood pressure of 140/90 mm Hg or less.

In addition to STOP-2 and ALLHAT, two trials have compared β-blockers, diuretics, or both with ACE inhibitors: the Captopril Prevention Project (CAPPP) and the UKPDS. The CAPPP trial randomly assigned patients to treatment with captopril or β-blockers with or without diuretics (21). Blood pressure control was similar in both groups, yet the captopril group had significantly lower relative risks for all-cause mortality (RR, 0.54 [CI, 0.31 to 0.96]), for cardiovascular events (RR, 0.59 [CI, 0.38 to 0.91]), and for myocardial infarction (RR, 0.34 [CI, 0.17 to 0.67]). This study has been criticized, however, because of flaws in randomization and post hoc analysis.

In the UKPDS, patients in the intensive control group were randomly assigned to atenolol or captopril (22). Achieved blood pressure was similar in both groups. There were no significant differences in aggregated or individual macrovascular events between the two groups, although patients taking β-blockers required more frequent addition of glucose-lowering agents and gained more weight. The authors concluded that both agents were equally efficacious in reducing the incidence of diabetic complications and that the blood pressure reduction itself may have been more important than the agent used.

In addition to STOP-2 and ALLHAT, two other studies have compared calcium-channel blockers with β-blockers and diuretics: the Nordic Diltiazem (NORDIL) trial and the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT). In the NORDIL trial, diltiazem was compared with β-blockers or diuretics or both (23). Achieved blood pressures were similar in the two groups, and no differences were seen in combined cardiovascular end points or total mortality. In INSIGHT (24), long-acting nifedipine was compared with coamilozide. Again, blood pressure reduction was similar in the two groups and there were no differences in the risk for cardiovascular end points or in total mortality.

Three recent studies of the effects of angiotensin-receptor blockers on the progression and prevention of nephropathy have demonstrated the renoprotective properties of this class of drugs (25–27). These studies did not show, however, any benefit for cardiovascular outcomes, which were secondary outcomes. The Losartan Intervention for Endpoint Reduction (LIFE) study randomly assigned patients with hypertension and signs of left ventricular hypertrophy on electrocardiography to the angiotensin-receptor blocker losartan or the β-blocker atenolol (28). The pri-

mary end point was combined cardiovascular morbidity and mortality, that is, cardiovascular death, stroke, or myocardial infarction. In a prespecified diabetes subgroup of 1195 patients, achieved mean blood pressures were similar (146/79 mm Hg for the losartan group and 148/79 mm Hg for the atenolol group). However, the losartan group had a lower risk for cardiovascular end points (RR, 0.76 [CI, 0.58 to 0.98]) and all-cause mortality (RR, 0.61 [CI, 0.45 to 0.84]).

Taken as a whole, the evidence presented here is most convincing for the use of diuretics, ACE inhibitors, and possibly angiotensin-receptor blockers, while the relative efficacy differences between ACE inhibitors and β-blockers and calcium-channel blockers are unclear. Self-reported black patients with diabetes benefited more from diuretic treatment, while diabetic patients with nephropathy benefited from ACE inhibitor or angiotensin-receptor blocker therapy. Of course, all medication decisions depend on patients' tolerance of the drugs and of different levels of blood pressure. It is not unusual for two or more medications to be needed to attain targeted goals for blood pressure in patients with diabetes. Other classes of drugs, such as α-blockers, may have a role in achieving desired blood pressure targets in patients with type 2 diabetes, but there are little data on their effectiveness in reducing microvascular and macrovascular complications.

To date, there is a lack of evidence to help inform decisions regarding patient-specific target blood pressure levels or medications based on ethnicity, sex, or age. Lifestyle modifications, such as weight loss, exercise, and smoking cessation, are also important recommendations for all persons with diabetes, hypertension, or both.

RECOMMENDATIONS

Recommendation 1: Blood pressure control must be a priority in the management of persons with hypertension and type 2 diabetes.

Up to 80% of patients with type 2 diabetes will develop or die of macrovascular disease. Hypertension is a significant risk factor for cardiovascular disease and also contributes to the development of nephropathy and retinopathy. The clinical trials of blood pressure control in diabetes have shown a consistent and dramatic effect in preventing clinical outcomes, including cardiovascular mortality and morbidity, and possibly even a benefit in preventing microvascular complications.

Recommendation 2: Clinicians should aim for a target blood pressure of no more than 135/80 mm Hg for their patients with diabetes.

In the HOT study, a four-point difference in diastolic blood pressure, from 85 to 81 mm Hg, resulted in a 50% decrease in risk for cardiovascular events in patients with diabetes. When this study is used as the lowest point achieved in the trials, a diastolic blood pressure of 80 mm

Hg should be the goal for patients with diabetes. It is not clear whether diastolic blood pressure lower than 80 mm Hg is beneficial.

Systolic target goals have not been tested in randomized trials, but the UKPDS showed that a 10-point reduction in systolic blood pressure, from 154 mm Hg to 144 mm Hg, led to a substantial decrease in diabetes-related mortality and end points. Thus, while the optimal level of control for systolic blood pressure has not been clearly established, it may be reasonable to target a systolic blood pressure of 130 to 135 mm Hg based on the levels attained in the ABCD trial.

Recommendation 3: Thiazide diuretics or ACE inhibitors can be used as first-line agents for blood pressure control in most patients with diabetes.

In ALLHAT, no difference was shown in cardiovascular events or renal outcomes between diuretic and ACE inhibitor therapy for the diabetes subgroup. However, when the diuretic was compared with the ACE inhibitor, there were significant reductions in rates of stroke and heart failure for self-reported black patients. Thus, thiazide diuretics should always be the first-line therapy for African-American patients. Further analyses from ALLHAT of high-risk renal subgroups, such as self-reported black patients with proteinuria, are expected in the future. Angiotensin-receptor blockers are an acceptable alternative to ACE inhibitors if ACE inhibitors are not tolerated. The results of the LIFE study suggest that angiotensin-receptor blockers could also be considered first-line agents for blood pressure control in patients with type 2 diabetes and signs of left ventricular hypertrophy, but it remains to be seen whether these results are applicable to the entire population of persons with type 2 diabetes and hypertension.

A meta-analysis, done before ALLHAT, of the four trials comparing ACE inhibitors with other agents suggests that ACE inhibitors are a preferred agent for hypertension control in patients with type 2 diabetes (29). These agents may also be favored for other characteristics, such as their renoprotective properties and decreased overall mortality, as seen in the HOPE trial. While the UKPDS found β-blockers and ACE inhibitors to be equally effective, there are other factors to be considered. In the UKPDS, patients receiving β-blockers gained more weight and required the addition of more glucose-lowering agents; however, β-blockers are less costly. In addition, the use of β-blockers may be preferable for patients with type 2 diabetes and known coronary artery disease. The lack of a comparison group with β-blockers in ALLHAT creates uncertainty in the selection of first-line agents.

While calcium-channel blockers compared favorably with placebo, in comparisons with ACE inhibitors they fared poorly. Thus, they are best reserved as second- or third-line agents in patients with diabetes. Calcium-channel blockers should not be used in patients with diabetes who have had a recent coronary event (30).

Recommendation 4: Further studies are warranted on the relative contributions of glucose control and blood pressure control to clinical outcomes such as microvascular and macrovascular complications.

Research relating to the optimal choice of first-line agents for the treatment of hypertension in type 2 diabetes is needed to allow clinicians to make better-informed decisions, particularly in persons with type 2 diabetes and coronary artery disease.

Note: Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

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