Blood Pressure Management in Patients With Diabetes

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Hypertension is the most common diagnosis in primary care patients. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure defines hypertension as a systolic blood pressure (BP) ≥ 140 mmHg or diastolic BP ≥ 90 mmHg for adults ≥ 18 years of age. These thresholds are reduced to systolic BP ≥ 130 mmHg or diastolic BP ≥ 80 mmHg for individuals with diabetes or renal disease.[1]

More than 74 million adults were estimated to have elevated BP from U.S. population-based surveys in 2006,[2] with equal prevalence among men and women.[2] African Americans have the highest disease burden, with > 40% of adults being affected.[2] Furthermore, the prevalence of hypertension increases with age, approaching 75% in individuals ≥ 80 years of age.[3]

People with diabetes are at greater risk to develop elevated BP. This review offers a summary of recent literature regarding hypertension prevalence and management in adults and children with diabetes and a discussion of the clinical implications and practice recommendations relevant to primary care providers.

Epidemiology of Hypertension Among Those With Diabetes

The estimated prevalence of hypertension in adults with diabetes is 20–60%, which is 1.5–3 times higher than that in age-matched individuals without diabetes.[4,5] The onset of hypertension differs for people with type 1 versus those with type 2 diabetes. Individuals with type 1 diabetes usually develop hypertension because of diabetic nephropathy, with 30% eventually being affected.[6] By contrast, hypertension may be present when type 2 diabetes is diagnosed or may predate the onset of hyperglycemia.[6] Type 2 diabetes is frequently accompanied by advanced age or obesity, both of which increase the risk of hypertension and thereby make it difficult to ascribe elevated BP solely to diabetes.[6]

The presence of hypertension in individuals with diabetes doubles the risk for cardiovascular disease (CVD).[6] With uncontrolled hypertension, there is a consistent positive relationship between elevated systolic BP and increased risk for micro- and macrovascular diseases.[7] Accordingly, > 65% of deaths in patients with diabetes are from CVD.

IN BRIEF

Patients with diabetes who also have hypertension are at increased risk of morbidity and mortality from cardiovascular events. However, blood pressure control is frequently suboptimal in the primary care setting. Large clinical trials support the use of antihypertensive medications in these patients to reduce the risk of cardiovascular disease and death.

Clinical Trial Evidence for BP Control

One important way to decrease CVD risk in individuals with diabetes is by controlling BP. Controlled BP lessens but does not negate the risk of developing diabetes-related macrovascular diseases such as myocardial infarction (MI), stroke, and peripheral vascular disease (PVD). Control of BP has also been strongly related to decreased microvascular complications, including retinopathy, nephropathy, and neuropathy. Several major clinical trials have demonstrated the importance of BP control among patients with diabetes (Table 1).

UKPDS

The U.K. Prospective Diabetes Study (UKPDS) enrolled 5,102 patients with newly diagnosed diabetes. It ran for 20 years (1977–1997) in 23 clinical centers and showed conclusively that the complications of type 2 diabetes could be reduced by improving blood glucose and/or BP control. Patients were randomized to tight BP control (goal < 150/85 mmHg) or to a less stringent regimen (goal < 180/105 mmHg). Patients treated with the ACE inhibitor captopril or the β-blocker atenolol in the tight-control arm had decreased risk of MI, sudden death, stroke, and PVD (relative risk [RR] 0.66 for combined cardiovascular endpoint).[8] There were significant reductions in microvascular events, primarily retinopathy (RR 0.63) for patients in the tight-control arm, but a protective effect was not seen for MI. The significant risk reductions were

Table 1. Clinical Trials of BP Medications in Patients With Diabetes

Study	*n*	Follow-Up Period (years)	BP (mmHg)	Drugs Tested	Impact on Outcomes
UKPDS	5,102	20	Tight goal 150/85 versus less stringent goal < 180/105	Tight: captopril or atenolol	Favors tight control: decreased death from diabetes, stroke, and microvascular disease (retinopathy)
HOT	18,790	3.8	Diastolic goal 80 versus ≤ 90	Calcium channel blocker plus others	≤ 80 group: decreased major cardiovascular events
HOPE, MICRO-HOPE	9,297 (3,577 with diabetes)	3.5 (4.5)	Mean BP for both groups 139/79 at baseline	Ramipril versus placebo	Ramipril group (136/76 mmHg): decreased MI, stroke, cardiovascular death, and all-cause mortality; decreased nephropathy
ALLHAT	42,418, (13,101 with diabetes)	4.9	Mean BP 146/83 at baseline	Amlodipine versus lisinopril versus chlorthalidone	Chlorthalidone group: lower systolic BP than amlodipine or lisinopril; no difference for fatal/nonfatal MI; increased heart failure with amlodipine and lisinopril versus chlorthalidone
ABCD	470	5	Diastolic goal: intensive ≤ 75 versus moderate ≤ 80–89	Nisoldipine versus enalapril	Intensive: decreased death; no difference for retinopathy or neuropathy; increased MI with nisoldipine versus enalapril; renal function stabilized with both drugs
ACCORD BP	4,733	4.7	Systolic goal < 120 versus < 140	Stepped care to reach goals	No difference in nonfatal MI, nonfatal stroke, or cardiovascular death

not sustained 10 years after the trial because participants were not continued on the same antihypertensive regimens during that time period.[9]

HOT trial

The Hypertension Optimal Treatment (HOT) study was a randomized trial, including 18,790 hypertensive patients aged 50–80 years. It helped to establish target diastolic BP goals. First-line therapy employed the calcium channel blocker felodipine, with other drugs added in a stepped-care approach. Overall, the HOT study demonstrated clinical benefits of lowering BP to systolic < 140 mmHg and diastolic < 85 mmHg.[10] In patients with diabetes, there was a 51% reduction in major cardiovascular events among the group with diastolic BP ≤ 80 mmHg compared to the group with diastolic BP ≤ 90 mmHg ($P = 0.005$).

HOPE trial

The Heart Outcomes Prevention Evaluation (HOPE) study investigated the effect of ACE inhibitors on BP and cardiovascular events among those with CVD or a risk factor for CVD. The study randomized 9,297 high-risk patients as follows: 4,645 to treatment with ramipril and 4,652 to placebo. Almost 40% of patients had diabetes. The primary outcome was a composite of MI, stroke, or cardiovascular death.

A total of 651 patients who were assigned to receive ramipril (14.0%) reached the primary end point, compared to 826 patients who received placebo (17.8%) (RR 0.78, 95% confidence interval [CI] 0.70–0.86, $P < 0.001$). Patients treated with ramipril had significant reductions in BP as well as risk reduction of 22% for MI, 33% for stroke, 37% for CVD death, and 24% for all-cause mortality compared to placebo.[11]

A subsequent study, called the Microalbuminuria, Cardiovascular, and Renal Outcomes in the Heart Outcomes Prevention Evaluation (MICRO-HOPE) trial, showed a 22% risk reduction in nephropathy for patients treated with ramipril compared to placebo.[12]

ALLHAT trial

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a randomized, three-armed, double-blind trial. It involved 42,418 participants who were ≥ 55 years of age and was conducted to compare the efficacy of calcium channel blockers, ACE inhibitors, and thiazide diuretics as treatment for patients with hypertension and another CVD risk factor (36% of whom had diabetes).[13]

The primary outcome was combined fatal or nonfatal MI, and there was no significant difference in risk reduction among the drugs tested. Increased risk of heart failure was seen for patients on amlodipine (~ 40% higher) and lisinopril (15% higher) compared to chlorthalidone. Given these findings and the decreased costs associated with chlorthalidone, the investigators concluded that thiazide diuretics should be the preferred agent for treatment of hypertension.

ABCD trial

The Appropriate Blood Pressure Control in Diabetes (ABCD) study focused on the incidence and progression of microvascular disease in people with diabetes. The two study arms randomized 470 patients to intensive BP control (diastolic goal of ≤ 75 mmHg) or moderate control (diastolic goal ≤ 80–89 mmHg). The study also compared the efficacy of the calcium channel blocker nisoldipine to enalapril.

At the conclusion of the study, which lasted ~ 5 years, the mean BP was 132/78 mmHg (intensive) versus 138/86 mmHg (moderate). The incidence of death for participants in the intensive arm was lowered by nearly half compared to that of participants in the moderate BP control arm (51% lower). There was no difference in the progression of retinopathy and neuropathy. Additionally, participants treated with nisoldipine had a significantly higher risk of fatal and nonfatal MI compared to those treated with enalapril.[14,15]

ACCORD BP trial

The purpose of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP trial was to determine the effect on CVD outcomes of lowering systolic BP to < 120 mmHg.[16] The HOT trial had demonstrated clinical benefits from treating systolic BP to < 140 mmHg; however, observational studies have shown an association between lower systolic BP measurements (≤ 120 mmHg) and lower CVD incidence. Patients with high BP and diabetes (n = 4,733) were randomized to intensive BP control (systolic BP < 120 mmHg) or standard BP control (< 140 mmHg).

After ~ 5 years of follow-up, no differences were noted in the primary outcome (nonfatal MI, nonfatal stroke, or cardiovascular death) between the intensive and standard BP control groups.[17] There were numerically fewer cardiovascular events (n = 208) in the intensive group compared to the standard group (n = 237), and patients in the intensive group had fewer strokes than those assigned to the standard group (36 vs. 62 strokes). The intensive blood pressure group, however, had more adverse events, such as abnormally low BP, compared to the standard group (77 vs. 30 events).

From the clinical trials described above, the evidence supporting BP control in individuals with diabetes is strong. However, there is frequently a noticeable gap between clinical trial results and the integration of new evidence into clinical practice. In the outpatient setting, BP monitoring is performed at nearly every visit (> 98% of visits). Yet, the outcome of controlled BP is much lower (about 40%).[3] According to a national survey of Medicare recipients from 1999 to 2006, age- and sex-adjusted rates of BP control were alarmingly low, at 46–56%.[3,18,19] The resultant gap between clinical trial evidence and BP goals achieved is a target for implementation studies that address the barriers to effective hypertension management.

Effectiveness of BP Control: Real-World Practice

There are multiple barriers to reaching BP goals in primary care. These include patient factors (social, economic, physiological, and treatment-related factors), provider factors (clinical inertia, polypharmacy, and time constraints), and system factors.[20] Additionally, the recommended changes to diet and lifestyle are challenging for patients, and the lack of knowledge about health outcomes from poorly controlled hypertension can be a barrier to treatment.[21] Primary care providers may fail to apply treatment guidelines or to know the therapeutic options, may disagree with the guidelines, may not know how to help their patients with self-management, or may fail to recognize the opportunity to intensify medications when BP is uncontrolled.[22–26] System factors—those that affect the delivery of high-quality health care—may include insurance coverage, medication co-payments, access to primary care, self-management programs, and reimbursement schemes.[23,27] Furthermore, the way patients and physicians communicate can affect BP control. Collaborative decision making and proactive com-

munication has been associated with better hypertension control.[28]

Numerous studies have investigated the impact of multicomponent interventions on BP control in a variety of patient populations and settings. Single studies of interventions aimed at both patients and providers have yielded mixed results with respect to improving BP control in patients with diabetes.[29–34] However, systematic reviews and meta-analyses have demonstrated decreases in BP associated with group-based or individual patient education and team-based care involving nurses and pharmacists.[35–37]

Hypertension: Initial Evaluation

Patients with diabetes should have their BP measured and recorded at each office visit with an instrument that has been recently calibrated.[38] Patients should sit for 5 minutes before BP measurement, with feet on the floor and their bare arm supported at the level of the heart. The cuff's bladder should encircle 80% of the patient's arm circumference. If a manual cuff is used, the systolic BP occurs at the first Korotkoff sound, and the diastolic BP occurs at the disappearance of the sound. The average of two measurements taken 2 minutes apart should be recorded. Patients need to be aware of normal BP and their goals because this may improve their awareness of hypertension management.

The diagnosis of hypertension in people with diabetes is made if the mean of two readings on at least two clinic visits is ≥ 130/80 mmHg.[1] The readings should be verified in the contralateral arm. A thorough physical exam for hypertensive patients should also include fundoscopic exam; thyroid exam; cardiac and lung exams; auscultation for bruits in the neck, abdomen, and inguinal areas; palpation of the abdomen for aortic aneurysm; distal pulses; a check for edema in the lower extremities; and a neurological exam.[1] The initial work-up for hypertensive patients also includes an electrocardiogram, urinalysis, and measurement of electrolytes (including glucose, calcium, and potassium), creatinine, hematocrit, and lipids.

Ambulatory BP monitoring and intermittent home BP measurements have been shown to be particularly helpful for patients with white-coat hypertension, questionable adherence to medications, or medication side effects. Banegas et al.[39] demonstrated that 23–60% of participants in a hypertensive cohort had home BP measurements that were actually normal or near normal (BP < 130/80 mmHg). Patients often have higher measured BP values in the clinic setting.[39] In fact, two recent cohort studies demonstrated that ambulatory BP monitoring is better for predicting cardiovascular events than clinic measurements.[40,41] If patients check their BP at home, the home device should be calibrated against the clinic device.

Hypertension Treatment

The BP goal for patients with diabetes is systolic < 130 mmHg and diastolic < 80 mmHg.[38] To achieve these goals, a trial of lifestyle changes may be tried for a period of no longer than 3 months for patients with systolic BP between 130 and 139 mmHg or diastolic BP between 80 and 89 mmHg. If a patient's BP is ≥ 140/90 mmHg, medications and lifestyle changes should be initiated simultaneously.

Blood pressure can be lowered by employing lifestyle changes including weight loss if BMI is ≥ 25 kg/m^2 (average systolic reduction 5–20 mmHg/10 kg reduction), the Dietary Approaches to Stop Hypertension (DASH) eating plan (8–14 mmHg reduction), decreased sodium consumption (2–8 mmHg reduction), increased physical activity (4–9 mmHg reduction), moderate alcohol intake (2–4 mmHg reduction), smoking cessation, and stress reduction.[38] The DASH eating plan consists of fruits, vegetables, grains, and low-fat dairy foods and limitations on saturated fat, total fat, and cholesterol. A goal of 1,500–2,300 mg of sodium intake is also recommended.[1,42]

For patients whose BP is uncontrolled and who have initiated lifestyle changes without success, antihypertensive medications are indicated. Frequently, patients with diabetes who require antihypertensive medications will need at least two medications to reach BP goals.[38] Common medication classes and potential side effects are discussed below and summarized in Table 2.

The BP medication regimen for patients with diabetes should include an ACE inhibitor or angiotensin receptor blocker (ARB), whichever class is better tolerated.[1] These two classes are considered first-line therapy. If needed, both classes of medications can be used for greater BP reduction. ACE inhibitors and ARBs reduce the risk of macrovascular disease and prevent the progression of diabetic nephropathy.[43] Patients with a history of angioedema or bilateral renal artery stenosis should not be prescribed ACE inhibitors, and caution should be used if prescribing an ARB for a patient who has a history of ACE inhibitor–induced angioedema.

Diuretics are another class of antihypertensive medications useful for patients with diabetes. For patients with minimal evidence of chronic kidney disease (estimated glomerular filtration rate [eGFR] ≥ 30 ml/min/1.73m^2), thiazide diuretics are considered second-line therapy after ACE inhibitors and ARBs have been initiated. The

Table 2. Oral BP Medications for Patients With Diabetes and Their Indications*

Class of Medication	Examples	Common Side Effects	Appropriate for Comorbid Conditions	Pediatric Information
ACE inhibitors	Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril	Dry cough, hypotension, hyperkalemia, headache, dizziness, fatigue, nausea, and renal impairment	Chronic kidney disease, heart failure, and cardiovascular disease	Females of childbearing age should use reliable contraception. U.S. Food and Drug Administration (FDA) approval for ACE inhibitors with pediatric labeling is limited to children ≥ 6 years of age and those with a creatinine clearance ≥ 30 ml/min/1.73 m^2.
ARBs	Candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan	Dizziness, headache, myalgias, muscle cramps, hyperkalemia, and renal impairment	Chronic kidney disease and heart failure	Females of childbearing age should use reliable contraception. FDA approval for ARBs with pediatric labeling is limited to children ≥ 6 years of age and to children with a creatinine clearance ≥ 30 ml/min/1.73 m^2.
Diuretics	Thiazide and thiazide-like diuretics include chlorthiazide, chlorthalidone, hydrochlorothiazide, metolazone, indapamide, and polythiazide	Hypokalemia, hyponatremia, hypertriglyceridemia, hypercholesterolemia, and impotence	CVD	FDA approval for hydrochlorothiazide use in pediatric patients. May use in patients from < 6 months old through adulthood.
	Loop diuretics include furosemide, torsemide, and bumetanide			Furosemide is labeled only for treatment of edema in children, but may be useful as add-on therapy in children with resistant hypertension, particularly those with renal disease.
CCBs	Dihydropyridine CCBs include amlodipine, felodipine, isradipine, nicardipine, nifedipine, and nisoldipine	Dizziness, headache, edema, fluctuations in heart rate, flushing, and constipation	CVD	FDA labeling for amlodipine only for pediatric use among patients > 6 years of age
	Non-dihydropyridine CCBs include diltiazem and verapamil			

continued on p. 112

combination of ACE inhibitors or ARBs with thiazides may be more effective than monotherapy with either class of drugs. Patients with a history of gout or hyponatremia should be followed closely because thiazides can exacerbate these conditions.[1] If patients have an eGFR < 30 ml/min/1.73 m^2 (serum creatinine 2.5–3 mg/dl), a loop diuretic is indicated for additional BP management.[38]

As a class, calcium channel blockers (CCBs) are effective in lowering BP in patients with diabetes. With respect to CVD outcomes, CCBs are not effective in lowering the risk of acute MI, stroke, or angina requiring hospitalization compared to ACE inhibitors. Therefore, they are considered later in BP regimens

Table 2. Oral BP Medications for Patients With Diabetes and Their Indications* *continued from p. 111*

Class of Medication	Examples	Common Side Effects	Appropriate for Comorbid Conditions	Pediatric Information
β-blockers	Atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propanolol, timolol; carvedilol†, labetalol†; acebutolol‡, penbutolol‡, and pindolol‡	Bronchospasm, second- or third-degree heart block, bradycardia, nausea, diarrhea, fatigue, dizziness, depression, hallucinations, nightmares, impotence, weight gain, edema, and hypotension	Heart failure and CVD	May impair athletic performance. Labetalol and atenolol should not be used in insulin-dependent diabetic patients. There have been two pediatric studies of β-blockers extended-release metoprolol and bisoprolol in combination with hydrochlorothiazide.

** Does not include other classes of antihypertensives, such as potassium-sparing diuretics, aldosterone-receptor blockers, α-blockers, α agonists, or direct vasodilators*
† These medications also block α receptors.
‡ These medications also have sympathomimetic activity.

for this population.[44] Additionally, CCBs are not effective in preventing the progression of kidney disease.

β-Blockers are another class of antihypertensives that may be utilized. If patients with diabetes have had angina, coronary artery disease, MI, or heart failure, the benefit of β-blockers is clear for secondary prevention.[45] However, β-blockers can exacerbate asthma, reactive airway disease, and second- or third-degree heart block.[1] Of importance in patients with diabetes, β-blockers can cause weight gain, require increased insulin doses, and mask the symptoms of hypoglycemia.[46]

Combinations of medications can have synergistic effects, with reductions in BP greater than if patients are treated with either drug alone.[47] Although many antihypertensive combinations remain more expensive than the individual medications, several are now on discount pharmacy lists at major U.S. retailers. Caution should be used in prescribing non-dihydropyridine CCBs (verapamil or diltiazem) and β-blockers together for patients because the combination can cause bradycardia and heart block.

Patients with uncontrolled hypertension should be seen monthly until the BP is < 130/80 mmHg.[1] Serum potassium and creatinine should be checked at minimum twice a year and within 1–2 weeks after starting thiazide diuretics, ACE inhibitors, or ARBs. Once BP values stabilize, patients can be seen every 3–6 months.[1]

Hypertension in Children and Adolescents

Hypertension in children and adolescents is defined as systolic BP and/or diastolic BP ≥ the 95th percentile for age, sex, and height on three or more readings.[48] National surveys in the United States from 1988 to 2002 have demonstrated increasing numbers of children and adolescents 8–17 years of age with high BP, but the prevalence of hypertension among children with diabetes is unknown.[49–51]

All children > 3 years of age should have their BP measured during well-child exams. For children and adolescents with diabetes, treatment should be initiated with lifestyle changes if BP is in the high-normal range (systolic or diastolic BP > the 90th percentile for age, sex, and height) or BP > 120/80 mmHg on three readings in patients who are overweight or obese.[38,51] For the initial work-up of hypertension in children, an echocardiogram should be obtained to evaluate for left ventricular hypertrophy.[48]

Similar to adults, lifestyle changes include diet and exercise with weight reduction if appropriate. For children whose BP goals are not reached after 3–6 months or those with secondary hypertension, monotherapy with an antihypertensive medication should be started (Table 2). The treatment goal for children and adolescents with diabetes is to bring the BP to < the 90th percentile.[48] Titration of medications should be similar to that described above for adults. The potential teratogenic effects of ACE inhibitors and ARBs needs to be taken into consideration when prescribing these medications to adolescent and young adult women.

Conclusions

Hypertension and diabetes are two common diseases. Increasing age, the presence of obesity, and worsening renal function all contribute to an increased likelihood of hypertension in people with diabetes. With increasing obesity, physical inactivity, and the aging of the population, diabetes

and hypertension are crucial public health concerns for the 21st century. Control of BP among patients with diabetes can affect important CVD outcomes because the relationship between BP and risk of CVD events is continuous, consistent, and independent of other risk factors. Further evidence is needed to support treating patients to BP goals lower than current recommendations.

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