

In Brief

Untreated or poorly controlled hypertension can significantly accelerate the development and progression of both the micro- and macrovascular complications of diabetes. Aggressive blood pressure control improves patient outcomes and reduces health care costs. Unfortunately, nearly two-thirds of people with diabetes do not have blood pressure readings within the target range. Effective antihypertensive regimens maximize nonpharmacological therapies, minimize adverse effects on glucose control, lessen the risk of medication-related side-effects, and provide adequate cardiac and renal protection.

Management of Hypertension in Diabetes

Barry Stults, MD, and Robert E. Jones, MD, FACP, FACE

EPIDEMIOLOGY AND COMPLICATIONS OF HYPERTENSION IN DIABETES

Along with hyperglycemia, dyslipidemia, and cigarette smoking, hypertension is a major contributor to the development and progression of macrovascular and microvascular complications in people with diabetes.¹⁻⁵ Compared to the general population, people with diabetes face a two- to fourfold increased risk of cardiovascular disease (CVD).^{1,6} Concomitant hypertension triples the already high risk of coronary artery disease (CAD), doubles total mortality and stroke risk, and may be responsible for up to 75% of all CVD events in people with diabetes.⁶ Similarly, hypertension significantly accelerates the progression of diabetic nephropathy, retinopathy, and neuropathy.³⁻⁵ Of particular importance, systolic blood pressure is a stronger predictor than diastolic blood pressure for both CVD and renal complications.^{3,6}

In the United States, nearly 75% of adults with diabetes take antihypertensive medication or have a blood pressure $\geq 130/80$ mmHg, the currently accepted treatment threshold for hypertension in people with diabetes.^{3,7-12} In contrast, the prevalence of hypertension (blood pressure $\geq 140/90$ mmHg) in the general U.S. population is only 30%.¹⁰ In people with type 2 diabetes, the prevalence of hypertension is 50% at the time of

diagnosis, increasing to 80% in the presence of microalbuminuria and to $> 90\%$ with macroalbuminuria.³ Although population-based data are limited, between 30 and 43% of adults with type 1 diabetes also have concomitant hypertension; onset of hypertension in these patients frequently correlates with the onset of albuminuria.¹³

HYPERTENSION TREATMENT IN DIABETES: EFFICACY AND GOAL BLOOD PRESSURE

Reducing blood pressure in people with hypertension and diabetes decreases both macrovascular and microvascular complications. Clinical trials using a variety of antihypertensive agents have demonstrated that modest reductions in blood pressure of just 9–11 mmHg systolic and 2–9 mmHg diastolic decrease CVD events by 34–69% and microvascular complications (retinopathy and nephropathy) by 26–46% within just 2–5 years.¹⁴⁻¹⁸

How far should blood pressure be lowered in people with diabetes? Randomized clinical trials have demonstrated substantially improved CVD and microvascular outcomes with a target diastolic blood pressure close to or < 80 mmHg.^{16,17} For the prognostically more important systolic blood pressure, a single randomized clinical trial¹⁸ and prospective observational data from three other clinical trials¹⁹⁻²¹ support improved CVD and

microvascular outcomes with a target systolic blood pressure < 130 mmHg. Based on these data, most international guidelines now recommend a target blood pressure < 130/80 mmHg for people with diabetes.^{3,8-12} For diabetic patients with proteinuria and a total urinary protein-to-creatinine ratio > 500 mg/g, the National Kidney Foundation recommends a target systolic blood pressure < 125 mmHg.³ Limited data suggest possible worsening of both renal and CVD outcomes if systolic blood pressure is lowered to < 110 mmHg.^{3,21}

Most diabetic hypertensive patients with normal renal function require a combination of two to three antihypertensive agents to lower blood pressure to < 130/80 mmHg; patients with concomitant chronic kidney disease may require three or more agents.^{3,10}

Intensive blood pressure control is an essential component of a multifactorial strategy to reduce CVD and microvascular complications in diabetes. The Steno 2 study²² targeted intensive goals for hypertension, hyperglycemia, and dyslipidemia in patients with type 2 diabetes and microalbuminuria. After 8 years, the combined interventions reduced CVD events by 53% and major microvascular complications by 58–63%. An economic modeling study based on clinical trial data²³ has suggested that intensive hypertension control in diabetes is actually cost-saving; it improves health outcomes and reduces total health care costs. In contrast, intensive glycemic and dyslipidemia control are only cost-effective; they improve health outcomes but result in some increase in health care costs.²³

INADEQUATE CONTROL OF HYPERTENSION IN DIABETES

Unfortunately, outside of research settings, control of vascular risk factors is inadequate in people with diabetes. In community-based studies²⁴⁻²⁶ only 28–36% of diabetic hypertensive patients have their blood pressure controlled to < 130/80 mmHg, primarily because of poor control of systolic blood pressure. Similar levels of inadequate blood pressure control have been noted in type 1 diabetic populations.^{13,27} Of great concern, only 4–10% of diabetic patients meet the combined American Diabetes Association goals for blood pressure (< 130/80 mmHg), LDL cholesterol (< 100 mg/dl), and hemoglobin A_{1c} (< 7.0%).²⁴⁻²⁶

Disease, patient, and clinician factors contribute to poor blood pressure control in diabetes. Hypertension, particularly elevated systolic blood pressure, may be intrinsically more difficult to control in the diabetic population. In community settings, patients with diabetes are less likely to have their blood pressure controlled, despite receiving more antihypertensive medications.²⁸ Similar observations have been made in clinical trials where diabetic subjects required 50% more antihypertensive medication to control blood pressure.²⁹ Still, in the recent GEMINI (Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives) clinical trial,³⁰ investigators were able to lower blood pressure to < 130/80 mmHg in 68% of the 1,235 subjects with diabetes, about twice the control rate noted in community studies. Additional factors must contribute to inadequate blood pressure control in people with diabetes.

Patient factors contribute to poor blood pressure control through non-adherence to medications and follow-up visits. Health care costs may reduce adherence by some patients. Inadequate patient knowledge about hypertension and CVD risk is likely to be an additional contributor. In a 2002 survey,³¹ nearly two-thirds of people with diabetes did not consider CVD to be a common complication of diabetes, and more than half did not consider themselves personally at risk for CVD. Only 5% recognized that reducing blood pressure could lower CVD risk.

Clinician inertia—the failure to increase the dose or number of medications at office visits for patients who are not meeting therapeutic goals—is an important contributor to poor control of blood pressure in people with diabetes. In one study at a U.S. academic medical center, only 30% of diabetic hypertensive patients with systolic blood pressure above goal had their antihypertensive regimen increased during the subsequent year.³² In a multicenter study of U.S. academic medical centers,²⁶ only 10% of untreated diabetic patients with a blood pressure ≥ 130/80 mmHg, and only 15% of those with a blood pressure ≥ 140/90 mmHg, were started on antihypertensive medication.

The reasons for clinician inertia have not been defined. Inadequate knowledge may be one contributing

factor. In a 2002 survey of U.S. physicians,³¹ 63% incorrectly ranked glycemic control as the top priority to prevent CVD in diabetic patients. Only 22% correctly identified control of hypertension as the most cost-effective intervention to prevent CVD. Time pressure during short office visits with complicated patients with diabetes may also contribute to clinician inertia.²⁶

DIAGNOSIS OF HYPERTENSION IN DIABETES

Hypertension should be diagnosed accurately, and it should be treated promptly in people with diabetes because they are at high risk for adverse CVD and renal outcomes. The recent Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial³³ compared valsartan and amlodipine-based treatment regimens in high-risk hypertensive patients, many of whom had diabetes. Lowering systolic blood pressure to < 140 mmHg by 6 months of treatment reduced stroke by 45%, CVD events by 25%, and mortality by 21% compared to subjects whose systolic blood pressure remained ≥ 140 mmHg at 6 months.

To avoid a potentially dangerous delay in diagnosis, it is reasonable to confirm a diagnosis of hypertension in people with diabetes if the average blood pressure is ≥ 130/80 mmHg on two successive visits scheduled within 1 month.^{8,9} Blood pressure should be measured carefully with standardized patient preparation, accurate equipment, and appropriate techniques as reviewed in recent clinical practice guidelines.^{9,34} At each visit, if initial blood pressure is ≥ 130/80 mmHg, three readings should be taken, with the first reading discarded and the latter two averaged. Standing blood pressure measurement should also be obtained to screen for significant orthostatic reductions.

Currently, there are insufficient data to determine the role of home- or self-monitoring of blood pressure or 24-hour ambulatory blood pressure monitoring in the diagnosis of hypertension in people with diabetes.⁹ However, diagnostic algorithms extrapolated from studies in nondiabetic populations have been proposed.³⁵

NONPHARMACOLOGICAL TREATMENT OF HYPERTENSION IN DIABETES

There are few data concerning the effects of lifestyle modification on

blood pressure in people with diabetes and hypertension. In the general hypertensive population, comprehensive application of the lifestyle modifications listed in Table 1 is predicted to lower systolic blood pressure by 5 mmHg, a reduction similar to that observed with low-dose, single-drug antihypertensive therapy.⁹

Helpful patient education materials for office use can be obtained online at www.nhlbi.nih.gov/health/public/heart/hbp/hbp_low/index.htm. People with diabetes who are older than 35 years of age should not embark on exercise programs more vigorous than walking without consideration of an exercise test.³⁶ Cycling or swimming programs rather than walking programs should be considered in the presence of significant peripheral neuropathy or major foot deformities.³⁶

Given the modest efficacy of lifestyle modifications and the importance of prompt blood pressure control, diabetic hypertensive patients with blood pressure \geq 140/90 mmHg or with albuminuria or other target organ damage (TOD) should initiate pharmacological therapy concurrently with lifestyle modification at the second office visit. Patients with blood pressures 130–139/80–89 mmHg and no albuminuria or TOD may have a 3-month trial of lifestyle modification alone. Pharmacological therapy should then be initiated if blood pressure is not lowered to $<$ 130/80 mmHg.⁸ Lifestyle modification should be reemphasized at each office visit.

PHARMACOLOGICAL TREATMENT OF HYPERTENSION IN DIABETES

Clinical trials including large numbers of patients with both diabetes and hypertension have demonstrated reductions in CVD events and

microvascular complications, using thiazide diuretics, ACE inhibitors, angiotensin receptor blockers (ARBs), dihydropyridine (DHP) and nondihydropyridine (nonDHP) calcium channel blockers (CCBs), and β -blockers.^{3,10} More recent randomized studies in subjects with diabetes have investigated whether any particular antihypertensive agent more effectively reduces either CVD or renal complications independently of its ability to lower blood pressure.^{3,20,37–39}

Renin-Angiotensin-Aldosterone Axis Blockade

The renin-angiotensin-aldosterone (RAA) axis is a multiorgan endocrine system that regulates electrolytes, blood volume, and blood pressure. The pharmacological targets in this system include inhibitors of the production of angiotensin II (ACE inhibitors), inhibitors of angiotensin II action (ARBs), and the aldosterone receptor antagonists spironolactone and eplerenone.

ACE inhibitors^{16,18} and ARBs⁴⁰ have been shown to reduce CVD events in hypertensive diabetic patients. The MICRO-HOPE (Microalbuminuria Cardiovascular Renal Outcomes–Heart Outcomes Prevention Evaluation substudy) and the PERSUADE (Perindopril Substudy in Coronary Artery Disease and Diabetes)–EUROPA (European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery) trials compared ACE inhibitors with placebo in high-risk subjects with diabetes, many of whom had hypertension.^{41,42} Both studies found a greater reduction in cardiovascular end points with ACE inhibitors than would have been expected through blood pressure lowering alone, although this conclusion has been challenged.⁴³ However, a specific cardioprotective antiatheroscle-

rotic effect for ACE inhibitors and ARBs independent of blood pressure lowering has not been confirmed by data from the diabetic subgroup of the very large Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)³⁹ or by a prospective meta-analysis of 27 randomized trials with 33,395 hypertensive diabetic subjects.³⁸ The meta-analysis found that ACE inhibitors, ARBs, CCBs, and diuretics/ β -blockers (diuretic and β -blocker studies were pooled together for this analysis) had similar efficacy to prevent major CVD events.³⁸ The extent of blood pressure lowering was a more important determinant of CVD prevention than any specific antihypertensive treatment regimen.³⁸

On the other hand, ACE inhibitors and ARBs do have specific renoprotective effects independent of the level of blood pressure or the extent of blood pressure lowering, at least in some subgroups of diabetic patients.^{3,8–10,37,44} In hypertensive diabetic patients with macroalbuminuria and renal insufficiency, ACE inhibitors and ARBs slow progression to end-stage renal disease (ESRD) by \sim 25% compared to other antihypertensive agents; this renoprotective effect may be lost or muted as renal failure progresses and serum creatinine rises to $>$ 3.0 mg/dl.³ An abrupt decline in renal function or a significant increase in serum potassium may occur in patients with renal insufficiency treated with these agents, and frequent monitoring (1–2 weeks) of electrolytes and renal function is recommended after the initiation or upward titration of these drugs. A persistent decline in renal function of $>$ 30% may require discontinuation of therapy.³ A recent study of normo-albuminuric, hypertensive type 2 diabetic patients found that an ACE inhibitor delayed the development of persistent microalbuminuria compared to the CCB verapamil, despite similar levels of blood pressure lowering.⁴⁴ Another recent study demonstrated that ACE inhibitors and ARBs equivalently slow the progressive loss of glomerular filtration rate (GFR) in patients with diabetic nephropathy.⁴⁵ When macroalbuminuria is detected ($>$ 300 mg/day), clinical trials support the use of ARBs in people with type 2 diabetes and ACE inhibitors in patients with type 1 diabetes.³

Whether the independent renoprotective effects of ACE inhibitors and ARBs extend to all patients with diabetes and hypertension or only to

Table 1. Lifestyle Modification to Lower Blood Pressure⁶¹

Modification	Potential Reduction in Systolic/Diastolic Blood Pressure (mmHg)
10-lb weight loss	7/6
American Heart Association Dietary Approaches to Stop Hypertension diet	11.4/5.5
Restriction of alcohol consumption Men: \leq 2 drinks/day Women: \leq 1 drink/day	3.9/2.4
Exercise: 30–60 minutes/day, 4–7 days/week	4.9/3.7
Restriction of dietary sodium to $<$ 2.4 g/day	3.4/1.9

those with albuminuria has not been conclusively determined. In the 12,063 diabetic participants in the ALLHAT hypertension trial,³⁷ there was no difference in the percentage of patients progressing to ESRD or to a decline of $\geq 50\%$ in GFR when comparing an ACE inhibitor or a CCB to a thiazide over 4.9 years. Many of these patients had baseline mild to moderate renal insufficiency, although their albuminuria status was not determined.

Combining ACE inhibitors with ARBs is theoretically attractive. Addition of an ARB to an ACE inhibitor could counteract the incomplete suppression of angiotensin II seen with ACE inhibitors; adding an ACE inhibitor to an ARB would preserve the inhibition of bradykinin degradation by the ACE inhibitor. However, clinical benefits of combination ACE inhibitor and ARB therapy have not yet been fully documented.^{3,46,47} When larger doses of longer-acting ACE inhibitors have been used, for example lisinopril 40 mg/day, there is usually no additive effect from the ARB on blood pressure.^{46,47} Combination therapy may, however, reduce albuminuria by 30–40% compared to monotherapy with either drug.⁴⁷ Pending the results of additional clinical trials, combination therapy with an ACE inhibitor and ARB is not currently recommended.³

High circulating levels of aldosterone increase albuminuria and worsen renal insufficiency in diabetic nephropathy patients treated with ACE inhibitors or ARBs.⁴⁸ Preliminary, short-term randomized clinical trials have been conducted with low-dose (25 mg/day) spironolactone added to maximal ACE inhibitor and/or ARB therapy in type 2 diabetic patients with nephropathy.^{49,50} These studies have demonstrated reductions in blood pressure of up to 10 mmHg systolic and 5 mmHg diastolic along with 33% reductions in albuminuria.^{49,50} However, aldosterone blockade carries a considerable risk of severe hyperkalemia in diabetic patients with renal insufficiency. Treatment of hypertensive diabetic patients with aldosterone antagonists cannot be recommended until long-term cardiovascular and renal benefits have been demonstrated and the safety of these agents has been confirmed.⁵¹

Diuretics

The thiazide diuretics hydrochlorothiazide, chlorthalidone, and indapamide

have been shown to reduce cardiovascular disease events in subjects with diabetes and hypertension.^{10,14,39,52} The ALLHAT trial³⁹ demonstrated that compared to diabetic subjects taking lisinopril or amlodipine, the subjects assigned to chlorthalidone had an equivalent reduction in major cardiovascular end points but also had a significantly lower risk of heart failure. When administered as monotherapy to African-American hypertensive subjects, thiazides lower blood pressure more effectively than ACE inhibitors or ARBs.^{9–12} Thiazide-induced hypokalemia may mitigate some of the cardiovascular benefits seen with thiazides⁵³ and may further impair glucose metabolism; careful monitoring and replacement of potassium is essential.

Thiazides progressively lose their antihypertensive effectiveness as estimated GFR declines below 45 ml/min per 1.73 m², approximately corresponding to a serum creatinine ≥ 1.8 mg/dl in men and ≥ 1.6 mg/dl in women.³ (Using age, race, sex, and serum creatinine, an estimated GFR can be determined at the following website: http://newtech.kidney.org/professionals/kdqi/gfr_calculator.cfm.) Loop diuretics (furosemide, bumetanide, or torsemide) should be substituted for thiazides at this level of renal function. Although their efficacy to reduce CVD events in hypertensive patients has not been studied, loop diuretics effectively lower extracellular volume and blood pressure in patients with hypertension and renal insufficiency. Short-acting loop diuretics such as furosemide or bumetanide require twice-daily administration for treatment of hypertension; the longer-acting loop diuretic torsemide may be administered once daily.³

CCBs

Both the nonDHP (diltiazem and verapamil) and the DHP CCBs (amlodipine, felodipine, and others) reduce CVD events in people with diabetes and hypertension.^{15,17,18,20} With the possible exception of new-onset heart failure, CCBs prevent CVD events as effectively as the other antihypertensive drug classes.³⁸ NonDHP CCBs significantly reduce albuminuria and may slow the progression of proteinuric renal disease.⁵⁴ In contrast, DHP CCBs inconsistently reduce albuminuria and are less effective than ACE inhibitors or ARBs in slowing the progression of diabetic nephropathy.⁵⁴ However, DHP CCBs effectively

lower blood pressure and can be safely combined with an ACE inhibitor or ARB to slow the progression of diabetic nephropathy.⁵⁴

β -Blockers

In the general hypertensive population, β -blockers appear to prevent stroke less effectively than other antihypertensive drug classes. A recent meta-analysis of 13 randomized clinical trials with 105,951 patients comparing β -blockers with other antihypertensive drugs found that β -blockers were 16% less effective for preventing stroke; β -blockers were equally effective compared with other drugs for preventing myocardial infarction.⁵⁵ For diabetic hypertensive people with left ventricular hypertrophy, a large clinical trial found that the ARB losartan reduced CVD events by 25% compared to the β -blocker atenolol.⁴⁰ Even in a study of diabetic hypertensive subjects with stable coronary artery disease, a β -blocker-based regimen did not reduce CVD events any more effectively than a verapamil-based regimen.²⁰ Finally, β -blockers appear to be less effective than other antihypertensive agents for lowering systolic blood pressure.⁵⁶

Blood pressure lowering with carvedilol or metoprolol reduces microalbuminuria by 43 and 30%, respectively, when added to ACE inhibitors or ARBs.⁵⁷ However, carvedilol is nearly 50% more effective than metoprolol for preventing progression from normoalbuminuria to microalbuminuria.⁵⁷ Unlike metoprolol or atenolol, carvedilol does not adversely affect glycemic control or serum lipoprotein levels.³⁰ β -Blockers do not increase the severity of hypoglycemia, and any adverse influence on insulin resistance may be overcome by modifying the glucose-lowering regimen. Because acetylcholine is the neurotransmitter involved in sweating and is not affected by β -blockers, patients taking these drugs can monitor this symptom as a warning sign for hypoglycemia.

Because they are less effective than other agents for lowering blood pressure and preventing stroke, β -blockers should probably be used as third- or fourth-line antihypertensive agents.^{9,10} However, for patients who have concomitant heart failure or a prior myocardial infarction, β -blockers should be used as initial therapy in combination with either ACE inhibitors or ARBs.^{9,10}

α -Blockers

In the ALLHAT trial, diabetic subjects who received doxazosin as their initial antihypertensive agent had an 85% higher incidence of new-onset heart failure compared to subjects assigned chlorthalidone; there was no difference in the incidence of fatal/nonfatal myocardial infarction.⁵⁸ Additionally, α -blockers do not appear to reduce microalbumin excretion in people with diabetes. Based on these observations, α -blockers should not be used as monotherapy to treat hypertension even in men who have concomitant benign prostatic hypertrophy. These drugs should probably be reserved to treat patients in whom blood pressure cannot be successfully lowered with other agents or who are intolerant of other agents.

MANAGEMENT OF HYPERTENSION IN DIABETES

Figure 1 presents an approach to hypertension management in diabetes.^{3,8-12,59} A diagnosis of hypertension is confirmed if carefully measured blood pressure is $\geq 130/80$ mmHg on two office visits over a 1-month period. If average blood pressure is $\geq 140/90$ mmHg or if there is albuminuria or TOD, simultaneous pharmacological and lifestyle modification therapy should be initiated at the second office visit. If initial blood pressure averages 130–139/80–89 mmHg and albuminuria and TOD are absent, an initial trial of lifestyle modification limited to 3 months is reasonable.^{8,9}

For most patients, select a once-daily ACE inhibitor or ARB as initial pharmacological treatment; gradually titrate the dose to the moderate to high doses used in clinical trials.^{3,8-12} Alternatively, if TOD and albuminuria are absent, a low-dose thiazide may be used as initial treatment, particularly in African Americans. If the baseline blood pressure is $\geq 150/90$ mmHg, consider initial combination therapy with an ACE inhibitor or ARB and a thiazide because monotherapy is unlikely to reach the goal blood pressure of $<130/80$ mmHg. Patients who have heart failure or who are post-myocardial infarction should initially be treated with an ACE inhibitor and β -blocker.¹⁰

Patients should be seen monthly with adjustment of the therapeutic regimen at each visit until office-measured blood pressure is $< 130/80$ mmHg on two consecutive visits. If

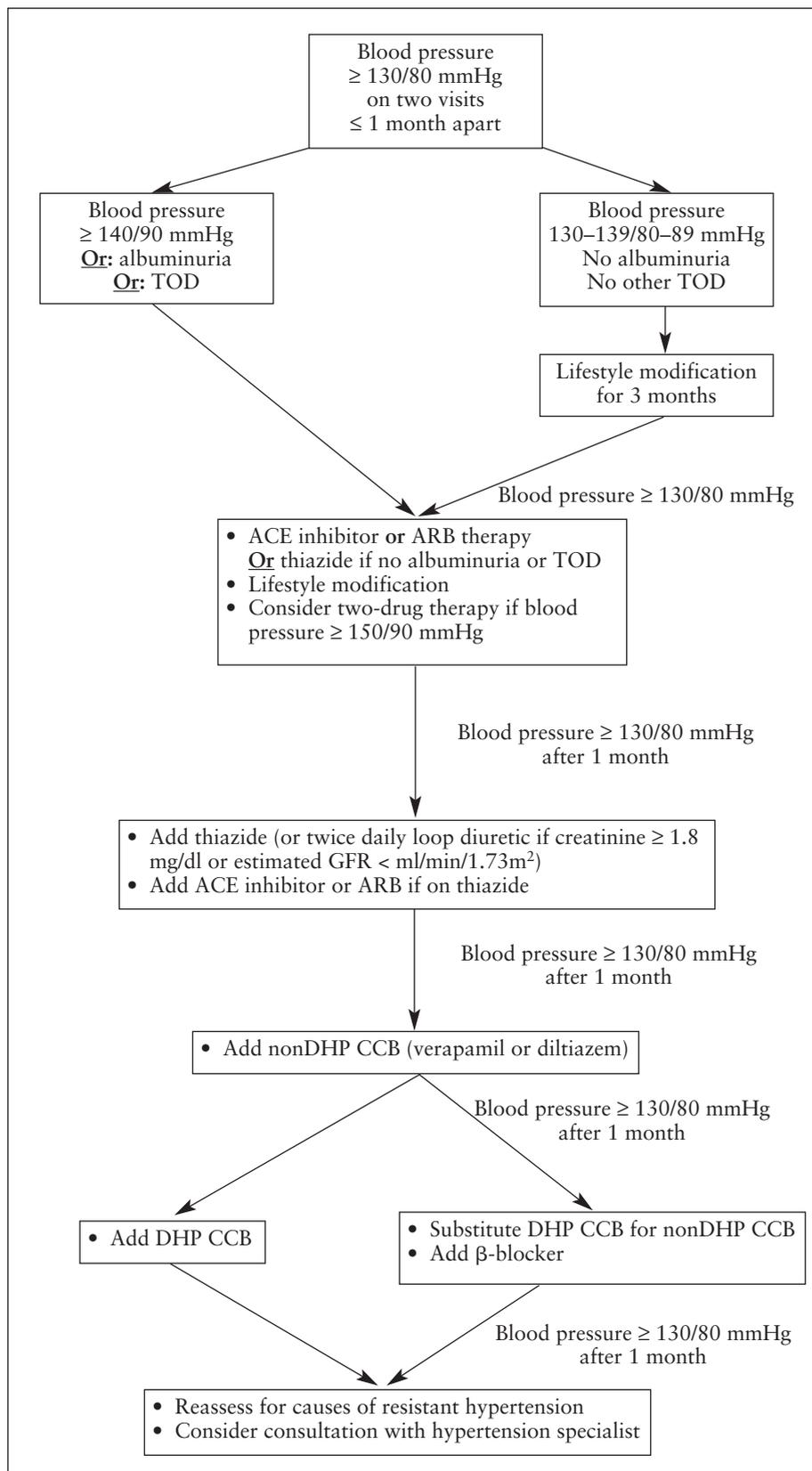


Figure 1. Management of hypertension in diabetes in patients who do not have heart failure and are not post-myocardial infarction.

out-of-office blood pressure measurements are utilized to adjust treatment, note that home- or self-monitored blood pressure is $\sim 5/5$ mmHg lower than office-measured blood pressure; 24-hour ambulatory blood pressure is

10/10 mmHg lower than office-measured blood pressure. The goals for these out-of-office blood pressures are therefore $< 125/75$ mmHg and $< 120/70$ mmHg, respectively, for patients with diabetes.^{34,35}

For most patients, a thiazide diuretic will be second-step therapy; a loop diuretic should be substituted for the thiazide if significant renal insufficiency is present. A once-daily formulation of a nonDHP CCB (verapamil or diltiazem) should generally be third-step therapy.³ If a fourth agent is required, addition of a once-daily DHP CCB may more effectively lower blood pressure than a β -blocker.⁵⁹ If β -blockers are added to the regimen, they should be combined with DHP CCBs rather than nonDHP CCBs to avoid bradyarrhythmia.

Patients with apparently resistant hypertension should be evaluated for adherence, interacting medications (especially alcohol and nonsteroidal anti-inflammatory agents),⁶⁰ and associated conditions such as sleep apnea.¹⁰ A 24-hour ambulatory blood pressure monitor study should be considered to detect whether elevated blood pressure is limited to the office setting ("white coat" hypertension).⁹ Consideration should then be given to consultation with a hypertension specialist.

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Barry Stults, MD, is a professor of medicine, and Robert E. Jones, MD, FACP, FACE, is an adjunct associate professor of medicine at the University of Utah School of Medicine in Salt Lake City.

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