Position Paper

ASH Position Paper: Treatment of Hypertension in Patients With Diabetes—An Update

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This report updates concepts on hypertension management in patients with diabetes. It focuses on clinical outcomes literature published within the last 3 years and incorporates these observations into modifications of established guidelines. While the fundamentals of treatment and goal blood pressures remain unchanged, approaches to specific patient-related issues has changed. This update focuses on questions such as what to do when a patient has an elevated potassium level when therapy is initiated and whether combinations of agents that block the renin-angiotensin system still be used. In addition, there are updates from trials, just published and in press, that focus on related management issues influencing cardiovascular outcomes in persons with diabetes. Last, an updated algorithm is provided that incorporates many of the new findings and is suggested as a starting point to achieve blood pressure goals. J Clin Hypertens (Greenwich). *2008;10:707–713.* ©*2008 Le Jacq*

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This review provides the reader with an update on treatment of hypertension in patients with diabetes as reviewed by the American Society of Hypertension. Hypertension, which affects more than 70 million Americans, is the most prevalent risk factor for development of cardiovascular and kidney disease.[1,2] The prevalence of hypertension is estimated at about 30% of the adult population in developed countries and is predicted to increase by almost 60% in the next 2 decades.[3,4] Diabetes is a major risk factor for cardiovascular disease and the most common cause of kidney failure in the Western world.[1,5] Moreover, cardiovascular mortality and morbidity is increased substantially in the presence of diabetes.[6]

More than 75% of adults with diabetes have blood pressure (BP) levels ≥130/80 mm Hg or are using antihypertensive medication.[1] In the natural history of type 1 diabetes, development of an elevated BP (ie, >130/80 mm Hg) is a major predictor of nephropathy and future declines in kidney function.[1,7] In contrast, hypertension is already evident in most patients with type 2 diabetes at the time of diagnosis. The implications of hypertension on cardiovascular risk, however, are similar in both types of diabetes.[1,8] Mortality is increased 7.2-fold when hypertension is present in patients with diabetes.[1]

Since the publication of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), several important observations regarding BP management and glycemic control in patients with diabetes are now apparent. First, post hoc analyses of 2 different cardiovascular

outcome trials note that even though diuretics worsen glycemic control, cardiovascular event rates were not higher.[9,10] Specifically, a post hoc analysis of the Systolic Hypertension in the Elderly Program (SHEP) notes that worsening of glycemic control with diuretics did not result in a reduced long-term benefit of thiazide-type diuretic (chlorthalidone)–induced lowering of systolic pressures on cardiovascular risk.[10] In addition, an analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) subgroup with diabetes failed to show a higher cardiovascular event rate in the diuretic group even though they had the greatest worsening of glycemic control.[9] Note, however, that these trials do not answer the question fully, as these were post hoc analyses and patients were followed only over a limited period of time. Thus, the true implications of new-onset diabetes on mortality are not known. Further, the impact of drug-induced increases in diabetes incidence on microvascular diseases such as retinopathy and nephropathy, although not systemically studied, are likely substantial.

Many post hoc analyses, however, uniformly demonstrate that diuretics and β-blockers not only worsen glycemic status among those with diabetes but also increase development of new-onset diabetes in those with impaired fasting glucose.[11–13] Hence, they increase number of medications taken and need for more frequent physician visits. Both thiazide diuretics, through hypokalemia and other mechanisms related to increased visceral adiposity,[14] and vasoconstricting β-blockers worsen insulin sensitivity[15]; exceptions to this statement include the newer vasodilating β-blockers, such as carvedilol and nebivolol. These vasodilating agents have neutral effects on glycemic control and increase insulin sensitivity.[16–18] Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCBs) have beneficial or neutral effects on insulin sensitivity and glycemic control.[11,15,19] Note also that renin-angiotensin system (RAS) blockers administered concomitantly with thiazide diuretics do not prevent worsening of glycemic control in obese persons with impaired fasting glucose.[20] These data, taken together with the findings of the most recent meta-analysis by the blood pressure trialists[21] indicate that since it is BP lowering and not the class of antihypertensive agent used that reduces cardiovascular events, one should use antihypertensive agents that do not worsen preexisting metabolic conditions.

Second, a substantial amount of epidemiologic and post hoc analyses' clinical trial data supports the notion that presence of proteinuria (ie, >300 mg/d in patients with diabetes) is associated with higher cardiovascular event rates.[22,23] Moreover, all studies among patients with diabetes indicate that proteinuria reduction of >30% within the first 6 to 12 months of BP-lowering therapy reduces cardiovascular events and development of heart failure as well as slows kidney disease progression.[24,25] Taken together, these data support the notion that treatment of BP in persons with diabetes must focus not only on achievement of BP goal but also on reducing proteinuria if present. Thus, as suggested by the most recent diabetes guidelines, all patients with diabetes should be evaluated for albuminuria at least once annually.[1] Antihypertensive agents found to maximally reduce proteinuria when BP is reduced include blockers of the RAS either alone or combined along with nondihydropyridine CCBs.[1,26]

Last, there has been an improvement in achievement of BP goals over the past decade. All current guidelines recommend a BP goal of <130/80 mm Hg in patients with diabetes to maximally reduce cardiovascular events and progression of nephropathy.[27–29] An analysis of the National Health and Nutrition Examination Survey (NHANES) 1999–2003 data demonstrates that the recommended BP goal of <140/90 mm Hg is achieved in only about one-third of persons with diabetes; 25% are at a goal of <130/80 mm Hg.[30] More recent analysis of NHANES 2003–2004 notes that 84% of those with hypertension and diabetes were treated, and the number in whom the BP goal of <130/80 mm Hg was achieved increased to 35%.[31]

In cardiovascular outcome trials among patients with hypertension, the proportion of participants in whom BP goals are achieved is roughly double that in clinical practice. An assessment of the subgroup with diabetes in these outcome trials over the past decade indicates that an average of 2.9 appropriately dosed antihypertensive medications are required to achieve BP goals. Among persons with diabetes and preexisting kidney disease, stage 3 or higher, this average increases to about 3.5 medications.[32] Thus, a key tenet in the approach to achieve BP goal in patients with diabetes is to select agents for maximal efficacy and tolerability to achieve BP goal that have the fewest adverse effects and, if possible, the lowest cost.

STRATEGIES FOR CONTROLLING BP

The basic paradigm to achieve BP goals in persons with diabetes has not changed appreciably from that suggested in JNC 7, but there are some important considerations that have emerged. Specifically,

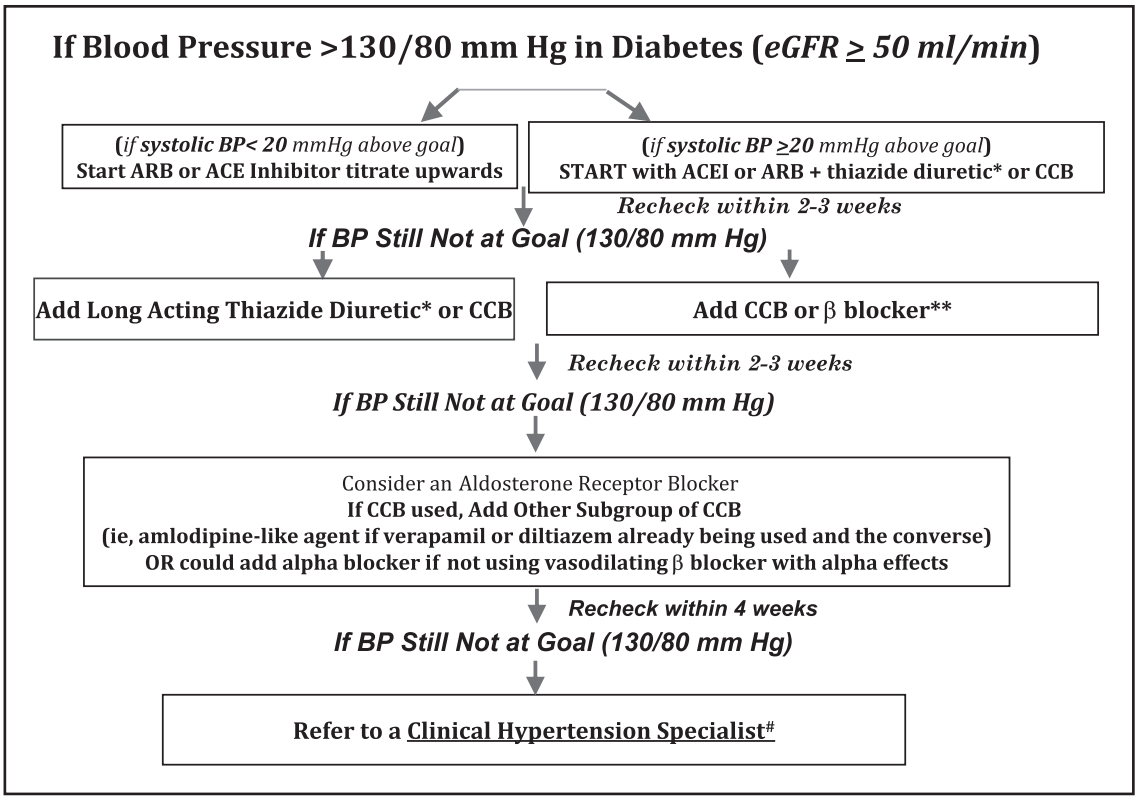

Figure. A Suggested Approach to Achieve BP Goal in Patients with Diabetes.
^Represents kidney function (estimated glomerular filtration rate-eGFR) that generally responds well to thiazide diuretics.
**Chlorthalidone is the suggested thiazide like diuretic since this is the diuretic used in clinical trials and forms the bases for the cardiovascular outcome data.*
***Vasodilating beta blockers have a better tolerability profile and less metabolic consequences as compared to older agents such as atenolol.*
#Specialists can be found at http://www.ash-us.org/specialist_program/directory.htm#
Adapted from Ruilope et al.[50]

blockers of the RAS are still recommended as initial agents for BP management along with a second agent, usually a CCB or thiazide-like diuretic, if BP is >20/10 mm Hg above the goal pressure of <130/80 mm Hg. Since no difference in cardiovascular outcomes has been noted between antihypertensive agents if BP is appropriately lowered, this approach mitigates against worsening of metabolic control and is in concert with both JNC 7 and recent European guidelines.[27,28] It places RAS-blocking agents as appropriate agents for those with the compelling indication of diabetes.

Lifestyle changes should have a central role in helping to manage hypertension in all patients with BP values >130/80 mm Hg (Figure). These include weight loss, increase in physical exercise, reduction of alcohol intake, smoking cessation and, perhaps most important, low sodium intake to levels <2.4 g/d. Low salt intake should be encouraged through appropriate dietary counseling and encouragement by the physician and staff (Table I). In addition, the American Diabetes Association guidelines should also be followed to optimize glycemic control.[33] This is important especially for morbidity reduction (ie, reduction of neuropathy and blindness). While mortality reduction is associated with good glycemic control, the level to which glucose needs reduction appears to be higher than previously thought. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial tested whether a lower level of glucose, defined as a hemoglobin A_{1c} value <6.5%, would result in a lower cardiovascular event rate was stopped early by the data safety monitoring board secondary to a higher cardiovascular event rate in the lower glucose control group.[34] Similarly, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation (ADVANCE) trial did not show any improvement in cardiovascular outcome with aggressive treatment of glycated hemoglobin to <6.5%.[35] This study did show a 20% reduction in new-onset nephropathy with aggressive

Table I. Lifestyle Modifications to Prevent and Manage Hypertension[a]	
Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m2).
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat.
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most days of the week).
Moderate alcohol use	Limit consumption to no more than 2 drinks (e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men and to no more than 1 drink per day in women and lighter weight persons.
[a]Adopted from JNC 7[27].	

Table II. Approach Needed to Maximally Reduce Cardio-Renal Risk[a]
• Lifestyle modifications-as per Table 1 • Achieve BP <130/80 mmHg • Achieve LDL <70 mg/dl • Achieve glycemic control (<7% HbA1c)[a] • Antiplatelet therapy-low dose aspirin 75–162 mg/day • In those with *albuminuria* or *proteinuria*- reduce by >30% after starting treatment within 6 months.
[a]Based on ADA guidelines, AACE guidelines indicates <6.5% HbA1c.

glycemic treatment, however. Thus, the guideline put forth by the American Diabetes Association of a hemoglobin A_{1c} value of <7% appears to be the one that would provide the greatest cardiovascular risk reduction along with BP reduction.

In addition to the lifestyle measures, all patients with diabetes and a BP >130/80 mm Hg should be started on a once-daily RAS blocker and dose-maximized within the first month of treatment if BP is not <130/80 mm Hg. If BP is >20/10 mm Hg above goal, then combination therapy with an RAS blocker and either a thiazide-like diuretic, if kidney function is appropriate, or a CCB should be initiated. Whether choosing an ACE inhibitor or an ARB, dosage should be titrated to the highest tolerated level necessary for BP to reach goal. If an ACE inhibitor is started and the adverse effect of cough appears, treatment should be changed to an appropriate dose of an ARB. If within a month after monotherapy titration the BP goal is not achieved, then either a low-dose thiazide diuretic (12.5 mg of chlorthalidone or hydrochlorothiazide) or a CCB should be added. In the case of a patient with an estimated glomerular filtration rate (eGFR) <50 mL/min, the thiazide diuretic should be replaced by a loop diuretic in adequate doses (once-daily torsemide or twice-daily furosemide or bumetinide). Note that chlorthalidone can be used in such patients down to an eGFR of 40 mL/min.

It should be noted that this algorithm (Figure) serves as a general guide, as there is no substitute or guide for good clinical judgment for any given patient. Therefore, if potassium levels are elevated (>5 mEq/L), either due to long-standing diabetes and consequent type IV renal tubular acidosis or chronic kidney disease (usually an eGFR <40 mL/min), before initiating RAS-blocking therapy, a review of all high potassium–containing foods and substances as well as over-the-counter agents that cause hyperkalemia, such as NSAIDs, must be discussed with the patient. Observational data support that reductions of up to 0.6 mEq/L in serum potassium can be achieved just by following these lifestyle interventions. Under circumstances when potassium levels are elevated, use of loop diuretics twice or thrice daily may be appropriate to enable the use of RAS-blocking agents. While there are no cardiovascular outcome data from clinical trials in patients with relatively high potassium levels, post hoc analyses of heart failure and kidney disease progression studies report cardiovascular risk reduction in those with eGFR values of <50 mL/min with serum potassium levels up to 5.6 mEq/L on RAS-blocking therapy.[24,36]

Minimization of the number of antihypertensive pills improves patient adherence and the effectiveness of lowering BP.[37,38] Thus, conversion of the full combination treatment to a fixed-dose combination of an RAS blocker/diuretic or an RAS blocker/CCB should be given strong consideration. It should also be noted that based on the data from the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET), use of an ACE inhibitor/ARB combination is not supported either for BP reduction or reduction in cardiovascular outcomes.[39]

This combination does have advantages for further proteinuria reduction in persons with advanced diabetic nephropathy[40] but this has not been shown to translate into a cardiovascular risk reduction in those with diabetic nephropathy.

If after 2 to 4 weeks of adding a diuretic or CCB, BP is still not at goal, titration of the thiazide to 25 mg/d and of the CCB to the maximum tolerated dose is recommended. This combination of medications will ensure that target BP is achieved in the majority of cases (Figure). However, in at least of 20% of the remaining cases, a fourth and possibly a fifth agent will be needed. Under these circumstances, a β-blocker is useful. Moreover, a vasodilating β-blocker is generally better tolerated and metabolically neutral compared with vasoconstricting agents.[41] β-Blockers are especially useful in patients with elevated pulse rates and should be considered for BP control if the pulse rate is elevated on at least 2 separate antihypertensive medications.[42] Alternatively, combination of a non-dihydropyridine CCB (verapamil or diltiazem) in moderate doses with a dihydropyridine CCB has additive effects on BP reduction[43] and will help achieve goal BP.

There is potentially a role for α-blockers for BP control as a fourth- or fifth-line agents; however, these agents are major culprits of orthostatic hypotension, especially in patients with diabetes, and should be avoided if an α/β-blocker is already being used or if the patient has diabetic neuropathy with a substantial decrease in BP or symptoms on standing.

Last, the role of aldosterone blockade as a fourth-line strategy is very important in patients with diabetes and obesity. Individuals with obstructive sleep apnea and central obesity have demonstrated major benefits of BP reduction with the use of aldosterone antagonism.[44,45] In a study of 76 patients with uncontrolled BP on an average of 4 medications, including an ACE inhibitor or ARB and a thiazide diuretic, addition of spironolactone (12.5–25 mg/d) resulted in an average 25-mm Hg reduction in systolic BP and an average 12-mm Hg reduction in diastolic BP after 6 months of follow-up.[46] Reductions in BP were similar in African American and Caucasian individuals. Moreover, the BP-lowering response was not predicted by baseline plasma aldosterone, 24-hour urinary aldosterone, plasma renin activity, or plasma aldosterone/renin ratio. These BP-lowering effects of aldosterone receptor blockade were confirmed in a report of 1411 participants in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) unselected for plasma aldosterone and plasma renin activity. They received spironolactone mainly as a fourth-line antihypertensive agent for uncontrolled BP and were receiving an average of 3 drugs.[47] Use of spironolactone was again associated with a BP drop of 21.9/9.5 mm Hg that was largely unaffected by factors like age, sex, smoking, and diabetic status. Recent data in obese patients demonstrates that the adipocyte releases substances that increase aldosterone, and this may be the reason for this observation.[48] Given the benefits aldosterone blockade in these individuals and those with sleep apnea, one is reminded of hyperkalemia as a limiting factor in their use.[44,47] The reader is referred to the earlier discussion on this topic.

CONCLUSIONS

The high cardiovascular risk in these patients requires an integrated therapeutic intervention that apart from effective antihypertensive therapy should include optimal achievement of goals for glycemic and lipid control, as well as inhibition of platelet aggregation (Table II). The treatment goals for glycemic control are set to a hemoglobin A_{1c} level of <7% and plasma preprandial glucose concentrations (average of several measurements) of 70 to 130 mg/dL.[33] All patients with diabetes should be treated with a statin and, if needed, complimentary lipid-lowering drugs to reduce low-density lipoprotein cholesterol to <70 mg/dL, triglycerides to <150 mg/dL, and to raise high-density lipoprotein cholesterol to >40 mg/dL in men and >45 mg/dL in women.[49] Further, in patients with diabetes and hypertension, antiplatelet therapy should generally consist of aspirin in dosages of 75 to 162 mg/d.[1]

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The American Society of Hypertension will publish a series of Position Papers in their official journals throughout the coming months; this article is the second in the series. The first in the series addressed the topic of Home and Ambulatory Blood Pressure Monitoring and appeared in *The Journal of the American Society of Hypertension*; it will be reprinted for the readership of *The Journal of Clinical Hypertension* in an upcoming issue. The citation for the first Position Paper follows:

Pickering TG and White WB, on behalf of the American Society of Hypertension Writing Group. When and how to use self (home) and ambulatory blood pressure monitoring. *JASH*. 2008;2(3):119–124.