

Controlling Hypertension in Patients with Diabetes

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Hypertension and diabetes mellitus are common diseases in the United States. Patients with diabetes have a much higher rate of hypertension than would be expected in the general population. Regardless of the antihypertensive agent used, a reduction in blood pressure helps to prevent diabetic complications. Barring contraindications, angiotensin-converting enzyme inhibitors are considered first-line therapy in patients with diabetes and hypertension because of their well-established renal protective effects. Calcium channel blockers, low-dose diuretics, beta blockers, and alpha blockers have also been studied in this group. Most diabetic patients with hypertension require combination therapy to achieve optimal blood pressure goals. (*Am Fam Physician* 2002;66:1209-14. Copyright© 2002 American Academy of Family Physicians.)



Nearly one in four adults in the United States has hypertension, and more than 10 million adults have diabetes.¹ Moreover, hypertension is twice as common in persons with diabetes as it is in others.² Obesity may be a common link between the two disorders, but other factors such as insulin resistance³ and autonomic dysfunction⁴ may also be involved. Excess weight with truncal obesity, hypertension, impaired glucose tolerance, insulin resistance, and dyslipidemia are among the components of the metabolic syndrome, which has been associated with an increased risk of coronary heart disease.⁵

In general, only 25 percent of patients with hypertension have adequate control of their blood pressure.⁶ Blood pressure goals are lower, and thus more difficult to achieve, in patients who also have dia-

betes. Elevated blood pressure is known to contribute to diabetic microvascular and macrovascular complications (*Table 1*).^{4,7,8} Fortunately, reductions in blood pressure can decrease the risk of these complications.⁸

To reduce this risk, hypertension must be diagnosed accurately and promptly, and the patient must receive adequate treatment. To confirm the diagnosis of hypertension, blood pressures measured with standard techniques should be elevated on two separate occasions.⁶ Because patients with diabetes and hypertension are at high risk for complications, consensus statements from the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI),⁶ the American Diabetes Association (ADA),⁹ and the National Kidney Foundation (NKF) Hypertension and Diabetes Executive Committees Working Group¹⁰ recommend lower blood pressure goals for patients with diabetes than for the general population.

The most recent guidelines from the ADA and NKF recommend that blood pressure be decreased to less than

See editorial on page 1151.

See page 1128 for definitions of strength-of-evidence levels contained in this article.

TABLE 1

Microvascular and Macrovascular Complications of Hypertension in Patients with Diabetes

Microvascular complications

Renal disease—hypertension contributes to the risk of renal disease in patients with diabetes.

Autonomic neuropathy

Sexual dysfunction—hypertension and antihypertensive therapies may independently contribute to autonomic-associated sexual dysfunction in diabetes.

Orthostatic hypotension—supine hypertension with orthostatic hypotension can occur in persons with diabetes because of autonomic dysfunction. Blood pressure should be measured in the supine, sitting, and standing positions.

Eye disease—hypertension increases the risk of eye disease in patients with diabetes, including glaucoma and diabetic retinopathy with potential blindness.

Macrovascular complications

Cardiac disease—hypertension in patients with diabetes increases the risk of coronary artery disease, congestive heart failure, and cardiomyopathy.

Cerebrovascular disease—hypertension increases the incidence of stroke in patients with diabetes.

Survival rates and recovery from stroke are reduced in patients with diabetes compared with patients without diabetes.

Peripheral vascular disease—hypertension increases the risk of peripheral vascular disease and subsequent foot ulcers and amputations in patients with diabetes.

Information from references 4, 7, and 8.

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130/80 mm Hg, with an optimal target of below 120/80 mm Hg, especially in patients with proteinuria or renal insufficiency.^{9,10} [References 9 and 10—Evidence level C, consensus/expert guidelines] Strategies to attain this goal include lifestyle modifications and pharmacologic therapy.

Lifestyle Modifications

In the Dietary Approaches to Stop Hypertension trial, lifestyle modifications such as exercise and a diet low in salt and high in potassium have clearly been shown to decrease blood pressure.¹¹ [Evidence level A, randomized controlled trial (RCT)] Excessive sodium intake is particularly deleterious in patients with diabetes because it may decrease the antihypertensive effects of medications and their beneficial effects on proteinuria.¹² Weight loss and exercise can help to lower blood pressure and may also improve glycemic control and insulin sensitivity.

Although the benefits of lifestyle modification are clear, few patients are able to achieve blood pressure control with these interventions alone. The JNC VI guidelines recommend that patients with diabetes be started on both antihypertensive medication and lifestyle modifications when hypertension is diagnosed. JNC VI recommends angiotensin-converting enzyme (ACE) inhibitors as preferred agents, with calcium channel blockers (CCBs) and low-dose diuretics as alternatives.⁶ [Evidence level C, consensus/expert guidelines]

Angiotensin II receptor blockers also show promise in the treatment of hypertension in diabetes. In many patients, a combination of two or more of these agents is necessary to reach blood pressure goals. Beta blockers have been shown to reduce cardiovascular risk; however, because of their diabetogenic potential, JNC VI classifies beta blockers as agents that “may have unfavorable effects” in patients with diabetes. Regardless of the agents selected, a reduction in blood pressure helps to prevent diabetic complications.⁸

Pharmacologic Therapy

ACE INHIBITORS

ACE inhibitors have proved beneficial in patients who have had a myocardial infarction or congestive heart failure, or who have diabetic renal disease (early or established).⁶ These agents are considered preferred therapy in patients with hypertension and diabetes, according to guidelines from the ADA, the NKF, the World Health

Organization, and the JNC VI.^{6,9,10,13} [References 6, 9, 10, and 13—Evidence level C, consensus/expert guidelines] Findings from the Heart Outcomes Prevention Evaluation (HOPE) study also support the above recommendations.¹⁴ [Evidence level A, RCT] This trial showed a reduction in cardiovascular events in patients taking a maximum dosage of ACE inhibitors.

Recently, a meta-analysis of trials evaluating the use of antihypertensives in high-risk patients, including those with diabetes, showed that ACE inhibitor therapy resulted in a 20 to 30 percent decrease in the risk of stroke, coronary heart disease, and major cardiovascular events.¹⁵ [Evidence level A, meta-analysis]

A second meta-analysis compared ACE inhibitors with other antihypertensive agents in patients with diabetes.¹⁶ [Evidence level A, meta-analysis] Three of the four studies evaluated showed ACE inhibitors to be of significantly greater benefit when compared with other antihypertensives in the reduction of acute myocardial infarction, cardiovascular events, and all-cause mortality. The one exception was the United Kingdom Prospective Diabetes Study (UKPDS), which compared captopril with atenolol and found the two agents to be similar in terms of reduction in microvascular and macrovascular complications.⁸ [Evidence level A, RCT]

ACE inhibitors may provide additional benefits in patients with diabetes. These patients may have impaired fibrinolysis and endothelial dysfunction, which increase their risk of cardiovascular disease. ACE inhibitors have been shown to improve fibrinolysis and endothelial dysfunction.^{17,18} ACE inhibitors have also been shown to increase insulin sensitivity.⁴

One area of concern is the use of ACE inhibitors in persons with underlying renal disease, which is common in patients with diabetes. A recent post hoc analysis¹⁹ of the HOPE trial demonstrated that in patients with preexisting vascular disease or diabetes combined with an additional cardiovascular risk factor, mild renal insufficiency (i.e., a serum creatinine level of 1.4 to 2.3 mg per dL [124 to 203 μ mol per L]) significantly increased the risk of subsequent cardiovascular events. In this study, ramipril reduced cardiovascular risk without increasing adverse effects. However, in patients with bilateral renal artery stenosis, ACE inhibitors can cause renal insufficiency. To help detect the presence of undiagnosed bilateral renal artery stenosis, physicians should monitor the serum creatinine level at baseline and one week after initiation of ACE inhibitor therapy.

Although lifestyle modifications are beneficial, few patients can achieve adequate blood pressure control with these measures alone.

DIURETICS

Thiazide diuretics have been shown to benefit patients with diabetes and systolic hypertension. The Systolic Hypertension in the Elderly Program trial was initiated to assess the effect of low-dose, diuretic-based antihypertensive treatment on the rates of major cardiovascular events in older patients with isolated systolic hypertension and diabetes.²⁰ [Evidence level A, RCT] The study showed that low-dose chlorthalidone therapy was effective in preventing major cerebrovascular and cardiovascular events in older non-insulin-treated patients with diabetes and isolated systolic hypertension.

Lower dosages of thiazides (e.g., hydrochlorothiazide [Esidrix], 12.5 mg per day) are generally well tolerated and not associated with adverse metabolic effects.⁴ Thiazide diuretics are not as effective in patients with renal insufficiency; in such patients, loop diuretics are preferred. In general, diuretics are effective in the treatment of hypertension. In addition, many less-expensive generic diuretics are available.

CALCIUM CHANNEL BLOCKERS

Controversy exists regarding the use of CCBs, particularly the dihydropyridines (e.g., amlodipine [Norvasc], diltiazem [Cardizem], nifedipine [Procardia]) in treating hypertension in patients with diabetes. Five studies²¹⁻²⁵ have evaluated cardiovascular outcomes in patients with hypertension and diabetes who were treated with dihydropyridine CCBs. Both the Appropriate Blood Pressure Control in Diabetes (ABCD)²¹ trial and the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET)²² demonstrated no significant reduction in cardiovascular events with a dihydropyridine CCB compared with an ACE inhibitor. [Reference 22—Evidence level B, uncontrolled study]

Conversely, the Hypertension Optimal Treatment (HOT) trial,²³ the Systolic Hypertension in Europe trial,²⁴ and the Isolated Systolic Hypertension in China study²⁵ concluded that the use of dihydropyridine CCBs, as monotherapy or in combination with another agent, was

Compared with nonselective beta blockers, cardioselective beta blockers are associated with less blunting of hypoglycemic awareness and less elevation of serum lipid and glucose levels.

associated with a reduction in cardiovascular risk. [References 23 and 24—Evidence level A, RCT] In these trials, the decreased cardiovascular risk appeared to result from achievement of target blood pressure, rather than from intrinsic characteristics of the agent(s) used. In all three trials, many patients required the addition of an ACE inhibitor or other antihypertensive to the dihydropyridine CCB to achieve target blood pressure goals. The combination of an ACE inhibitor and a dihydropyridine CCB has been shown to reduce proteinuria.¹⁰

The nondihydropyridine CCBs (e.g., verapamil [Calan]) demonstrate reductions in cardiovascular risk when used as monotherapy. Combining a nondihydropyridine CCB with an ACE inhibitor in hypertensive patients with diabetes is associated with greater reductions in proteinuria than if either agent was used individually.^{10,26}

ANGIOTENSIN II RECEPTOR BLOCKERS

The Candesartan and Lisinopril Microalbuminuria (CALM) study compared candesartan with lisinopril in patients with type 2 diabetes, hypertension, and microalbuminuria.²⁷ [Evidence level A, RCT] Results of the CALM study showed that candesartan was as effective as lisinopril in blood pressure reduction and minimization of microalbuminuria.

Recently, the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan study was completed.²⁸ [Evidence level A, RCT] The investigators found that losartan therapy produced a renoprotective effect independent of its blood-pressure-lowering effect in patients with type 2 diabetes and nephropathy. In addition, the Irbesartan Microalbuminuria Type 2 Diabetes Mellitus in Hypertensive Patients study recently found irbesartan to be renoprotective in patients with type 2 diabetes who have microalbuminuria.²⁹ [Evidence level A, RCT] The latest study to have been completed, the MicroAlbuminuria Reduction with VALsartan (MARVAL) trial, found that valsartan lowered urine albumin excretion to a greater degree than amlodipine in type 2

diabetic patients with microalbuminuria. This result was also seen in a subset of the study patients who were not hypertensive, which demonstrated valsartan to have a blood-pressure-independent antiproteinuric effect.³⁰ [Evidence level A, RCT]

BETA BLOCKERS

Traditionally, the use of beta blockers in patients with diabetes has been discouraged because of adverse metabolic effects and the masking of hypoglycemic symptoms. Data from the UKPDS 39 study⁸ showed no difference in hypoglycemic episodes in patients treated with atenolol compared with captopril, but the mean weight gain in the atenolol group was greater. This study also demonstrated similar risk reduction in microvascular and macrovascular diseases in the groups treated with captopril and atenolol.

Cardioselective beta blockers are preferred over the nonselective type because the former are associated with less blunting of hypoglycemic awareness and less elevation of lipid and glucose levels. Another alternative in the hypertensive patient with diabetes is the α_1 beta blocker carvedilol, which has been shown to cause fewer alterations in lipid and glucose levels compared with traditional beta blockers.³¹ Beta-blocker therapy can be advantageous in many patients with diabetes because of its proven ability to decrease cardiovascular morbidity and mortality in persons with atherosclerotic heart disease.⁶

ALPHA BLOCKERS

Alpha-adrenergic blockers are not considered first-line agents in the treatment of hypertension in patients with diabetes. These agents may be combined with other agents to treat poorly controlled blood pressure.

COMBINATION THERAPY

Most patients with concomitant hypertension and diabetes require more than one agent to attain adequate blood pressure control. In the HOT trial,²³ 68 percent of patients were maintained on combination antihypertensive therapy. The combination of ACE inhibitors and CCBs (dihydropyridine or nondihydropyridine) is associated with a reduction in cardiovascular events and proteinuria.^{10,22-25} The combination of a dihydropyridine and a nondihydropyridine CCB has been shown to have a synergistic blood-pressure-lowering potential.³² [Evidence level B, lower-quality RCT]

Caution should be used with the combination of nondi-

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hydropyridine CCBs and beta blockers because of the potential for additive negative cardiac inotropic effects. Combinations of beta blockers and ACE inhibitors have shown few additive effects on blood pressure when used in patients with a pulse rate of less than 84 beats per minute.³³ The final phase of the CALM study²⁷ examined combination treatment with candesartan and lisinopril. Study participants showed good tolerance for the two agents together and a more effective reduction in blood pressure.

Figure 1, a treatment algorithm for patients with hypertension and diabetes, is based on a recent consensus statement from the NKF.¹⁰ [Evidence level C, consensus /expert guidelines]

The authors indicate that they do not have any conflicts of interest. Sources of funding: none reported.

REFERENCES

1. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988-1994. *Diabetes Care* 1998;21:518-24.
2. Epstein M, Sowers JR. Diabetes mellitus and hypertension. *Hypertension* 1992;19:403-18.
3. National High Blood Pressure Education Program Working Group report on hypertension in diabetes. *Hypertension* 1994;23:145-58.
4. Fineberg SE. The treatment of hypertension and dyslipidemia in diabetes mellitus. *Prim Care* 1999;26:951-64.
5. Vega GL. Results of expert meetings: obesity and cardiovascular disease. Obesity, the metabolic syndrome, and cardiovascular disease. *Am Heart J* 2001;142:1108-16.
6. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997;157:2413-46.
7. Bakris G, Sowers J, Epstein M, Williams M. Hypertension in patients with diabetes. Why is aggressive treatment essential? *Postgrad Med* 2000;107:53-6,61-4.
8. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 1998;317:713-20.
9. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 2002;25:213-29.
10. Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, et al., for the National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Preserving renal function in adults with hypertension and diabetes: a consensus approach. *Am J Kidney Dis* 2000;36:646-61.
11. Moore TJ, Conlin PR, Ard J, Svetkey LP. DASH (Dietary Approaches to Stop Hypertension) diet is effective treatment for stage 1 isolated systolic hypertension. *Hypertension* 2001;38:155-8.
12. Bakris GL, Smith A. Effects of sodium intake on albumin excretion in patients with diabetic nephropathy treated with long-acting calcium antagonists. *Ann Intern Med* 1996;125:201-4.
13. World Health Organization–International Society of Hypertension

FIGURE 1.

- Blood Pressure Lowering Treatment Trialists' Collaboration. Protocol for prospective collaborative overviews of major randomized trials of blood-pressure-lowering treatments. *J Hypertens* 1998; 16:127-37.
14. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253-9.
 15. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet* 2000;356:1955-64.
 16. Pahor M, Psaty BM, Alderman MH, Applegate WB, Williamson JD, Furberg CD. Therapeutic benefits of ACE inhibitors and other antihypertensive drugs in patients with type 2 diabetes. *Diabetes Care* 2000;23:888-92.
 17. Vaughan DE, Rouleau JL, Ridker PM, Arnold JM, Menapace FJ, Pfeffer MA. Effects of ramipril on plasma fibrinolytic balance in patients with acute anterior myocardial infarction. HEART Study Investigators. *Circulation* 1997;96:442-7.
 18. Di Pasquale P, Valdes L, Albano V, Bucca V, Scalzo S, Pieri D, et al. Early captopril treatment reduces plasma endothelin concentrations in the acute and subacute phases of myocardial infarction: a pilot study. *J Cardiovasc Pharmacol* 1997;29:202-8.
 19. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Ann Intern Med* 2001; 134:629-36.
 20. Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H, et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA* 1996;276:1886-92.
 21. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998;338:645-52.
 22. Tatti P, Pahor M, Byington RP, Di Mauro P, Guarisco R, Strollo G, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998;21:597-603.
 23. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;351:1755-62.
 24. Tuomilehto J, Rastenyte D, Birkenhager WH, Thijs L, Antikainen R, Bulpitt CJ, et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. *N Engl J Med* 1999;340:677-84.
 25. Wang JG, Staessen JA, Gong L, Liu L, for the Systolic Hypertension in China (Syst-China) Collaborative Group. Chinese trial on isolated systolic hypertension in the elderly. *Arch Intern Med* 2000;160:211-20.
 26. Bakris GL, Weir MR, DeQuattro V, McMahon FG. Effects of an ACE inhibitor/calcium antagonist combination on proteinuria in diabetic nephropathy. *Kidney Int* 1998;54:1283-9.
 27. Mogensen CE, Neldam S, Tikkanen I, Oren S, Viskoper R, Watts RW, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ* 2000;321:1440-4.
 28. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861-9.
 29. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;345:870-8.
 30. Viberti G, Wheeldon NM. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. *Circulation* 2002;106:672-8.
 31. Giugliano D, Acampora R, Marfella R, De Rosa N, Ziccardi P, Ragone R, et al. Metabolic and cardiovascular effects of carvedilol and atenolol in non-insulin-dependent diabetes mellitus and hypertension. A randomized, controlled trial. *Ann Intern Med* 1997;126:955-9.
 32. Saseen JJ, Carter BL, Brown TE, Elliott WJ, Black HR. Comparison of nifedipine alone and with diltiazem or verapamil in hypertension. *Hypertension* 1996;28:109-14.
 33. Belz GG, Breithaupt K, Erb K, Kleinbloesem CH, Wolf GK. Influence of the angiotensin converting enzyme inhibitor cilazapril, the beta-blocker propranolol and their combination on haemodynamics in hypertension. *J Hypertens* 1989;7:817-24.