

Treatment of Hypertension in Adults With Diabetes

AMERICAN DIABETES ASSOCIATION

Hypertension (defined as a blood pressure $\geq 140/90$ mmHg) is an extremely common comorbid condition in diabetes, affecting ~20–60% of patients with diabetes, depending on obesity, ethnicity, and age. In type 2 diabetes, hypertension is often present as part of the metabolic syndrome of insulin resistance also including central obesity and dyslipidemia. In type 1 diabetes, hypertension may reflect the onset of diabetic nephropathy. Hypertension substantially increases the risk of both macrovascular and microvascular complications, including stroke, coronary artery disease, and peripheral vascular disease, retinopathy, nephropathy, and possibly neuropathy. In recent years, adequate data from well-designed randomized clinical trials have demonstrated the effectiveness of aggressive treatment of hypertension in reducing both types of diabetes complications.

Scope

These recommendations are intended to apply to nonpregnant adults with type 1 or type 2 diabetes.

Target audience

These recommendations are intended for the use of health care professionals who care for patients with diabetes and hypertension, including specialist and primary care physicians, nurses and nurse practitioners, physicians' assistants, educators, dietitians, and others.

The recommendations in this paper are based on the evidence reviewed in the following publication: The treatment of hypertension in adult patients with diabetes (Technical Review). *Diabetes Care* 25:134–147, 2002.

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Abbreviations: ACE, angiotensin-converting enzyme; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARB, angiotensin receptor blocker; DCCB, dihydropyridine calcium channel blocker; HOT, Hypertension Optimal Treatment; JNC VI, Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; UKPDS, U.K. Prospective Diabetes Study.

Method

These recommendations are based on the American Diabetes Association Technical Review "Treatment of Diabetes in Adult Patients with Hypertension" (1). A technical review is a systematic review of the medical literature that has been peer-reviewed by the American Diabetes Association's Professional Practice Committee.

Evidence review: hypertension as a risk factor for complications of diabetes

Diabetes increases the risk of coronary events twofold in men and fourfold in women. Part of this increase is due to the frequency of associated cardiovascular risk factors such as hypertension, dyslipidemia, and clotting abnormalities. In observational studies, people with both diabetes and hypertension have approximately twice the risk of cardiovascular disease as nondiabetic people with hypertension. Hypertensive diabetic patients are also at increased risk for diabetes-specific complications including retinopathy and nephropathy. In the U.K. Prospective Diabetes Study (UKPDS) epidemiological study, each 10-mmHg decrease in mean systolic blood pressure was associated with reductions in risk of 12% for any complication related to diabetes, 15% for deaths related to diabetes, 11% for myocardial infarction, and 13% for microvascular complications. No threshold of risk was observed for any end point.

Evidence for target levels of blood pressure in patients with diabetes

The UKPDS and the Hypertension Optimal Treatment (HOT) trial both demonstrated improved outcomes, especially in preventing stroke, in patients assigned to lower blood pressure targets. Optimal outcomes in the HOT study were achieved in the group with a target diastolic blood pressure of 80 mmHg (achieved 82.6 mmHg). Randomized clinical trials demonstrate the benefit of targeting a diastolic blood pressure of ≤ 80 mmHg. Epidemiological analyses show that blood pressures $\geq 120/70$ mmHg are associated with increased cardiovascular event rates and mortality in persons with diabetes. Therefore, a target blood pressure goal of $< 130/80$ mmHg is reasonable if it can be safely achieved. There is no threshold value for blood pressure, and risk continues to decrease well into the normal range. Achieving lower levels, however, would increase the cost of care as well as drug side effects and is often difficult in practice. Whether even more aggressive treatment would further reduce the risk is an unanswered question, but may be answered by clinical trials now in progress.

Evidence for non-drug management of hypertension

Dietary management with moderate sodium restriction has been effective in reducing blood pressure in individuals with essential hypertension. Several controlled studies have looked at the relationship between weight loss and blood pressure reduction. Weight reduction can reduce blood pressure independent of sodium intake and also can improve blood glucose and lipid levels. The loss of one kilogram in body weight has resulted in decreases in mean arterial blood pressure of ~ 1 mmHg. The role of very low calorie diets and pharmacologic agents that induce weight loss in the management of hypertension in diabetic patients has not

been adequately studied. Some appetite suppressants may induce increases in blood pressure levels, so these must be used with care. Given the present evidence, weight reduction should be considered an effective measure in the initial management of mild-to-moderate hypertension, and these results could probably be extrapolated to the diabetic hypertensive population.

Sodium restriction has not been tested in the diabetic population in controlled clinical trials. However, results from controlled trials in essential hypertension have shown a reduction in systolic blood pressure of ~5 mmHg and diastolic blood pressure of 2–3 mmHg with moderate sodium restriction (from a daily intake of 200 mmol [4,600 mg] to 100 mmol [2,300 mg] of sodium per day). A dose response effect has been observed with sodium restriction. Even when pharmacologic agents are used, there is often a better response when there is concomitant salt restriction due to the aforementioned volume component of the hypertension that is almost always present. The efficacy of these measures in diabetic individuals is not known.

Moderately intense physical activity, such as 30–45 min of brisk walking most days of the week, has been shown to lower blood pressure and is recommended in the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI). The American Diabetes Association Consensus Development Conference on the Diagnosis of Coronary Heart Disease in People with Diabetes has recommended that diabetic patients who are 35 years of age or older and are planning to begin a vigorous exercise program should have exercise stress testing or other appropriate noninvasive testing. Stress testing is not generally necessary for asymptomatic patients beginning moderate exercise such as walking. Smoking cessation and moderation of alcohol intake are also recommended by JNC VI and are clearly appropriate for all patients with diabetes.

Evidence for drug therapy of hypertension

There are a number of trials demonstrating the superiority of drug therapy versus placebo in reducing outcomes including cardiovascular events and microvascular complications of retinopathy and pro-

gression of nephropathy. These studies used different drug classes, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), diuretics, and β -blockers, as the initial step in therapy. All of these agents were superior to placebo; however, it must be noted that many patients required three or more drugs to achieve the specified target levels of blood pressure control. Overall there is strong evidence that pharmacologic therapy of hypertension in patients with diabetes is effective in producing substantial decreases in cardiovascular and microvascular diseases.

There are limited data from trials comparing different classes of drugs in patients with diabetes and hypertension. The UKPDS-Hypertension in Diabetes Study showed no significant difference in outcomes for treatment based on an ACE inhibitor compared with a β -blocker. There were slightly more withdrawals due to side effects and there was more weight gain in the β -blocker group. In postmyocardial infarction patients, β -blockers have been shown to reduce mortality.

There are numerous studies documenting the effectiveness of ACE inhibitors and ARBs in retarding the development and progression of diabetic nephropathy. ACE inhibitors have a favorable effect on cardiovascular outcomes, as demonstrated in the MICROHOPE study. This cardiovascular effect may be mediated by mechanisms other than blood pressure reduction. It is possible that other drug classes may behave similarly.

Some studies have shown an excess of selected cardiac events in patients treated with dihydropyridine calcium channel blockers (DCCBs) compared with ACE inhibitors. Ongoing trials including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study should help to resolve this issue. DCCBs in combination with ACE inhibitors, β -blockers, and diuretics, as in the HOT study and the Systolic Hypertension in Europe (Syst-Eur) Trial, did not appear to be associated with increased cardiovascular morbidity. However, ACE inhibitors and β -blockers appear to be superior to DCCBs in reducing myocardial infarction and heart failure. Therefore, DCCBs appear to be appropriate agents in addition to, but instead of, ACE inhibitors and β -blockers. Non-DCCBs (i.e., verapamil and dil-

tiazem) may reduce coronary events. In short-term studies, non-DCCBs have reduced albumin excretion.

There are no long-term studies of the effect of α -blockers, loop diuretics, or centrally acting adrenergic blockers on long-term complications of diabetes. The α -blocker arm of the ALLHAT study was stopped by the data and safety monitoring committee because of an increase in cases of new-onset heart failure in patients assigned to the α -blocker. While this could merely represent unmasking of heart failure in patients previously treated with an ACE inhibitor or a diuretic, it seems reasonable to use these as second-line agents when preferred classes have been ineffective or when other specific indications, such as benign prostatic hypertrophy (BPH), are present.

Summary

There is a strong epidemiological connection between hypertension in diabetes and adverse outcomes of diabetes. Clinical trials demonstrate the efficacy of drug therapy versus placebo in reducing these outcomes and in setting an aggressive blood pressure–lowering target of <130/80 mmHg. It is very clear that many people will require three or more drugs to achieve the recommended target. Achievement of the target blood pressure goal with a regimen that does not produce burdensome side effects and is at reasonable cost to the patient is probably more important than the specific drug strategy.

Because many studies demonstrate the benefits of ACE inhibitors on multiple adverse outcomes in patients with diabetes, including both macrovascular and microvascular complications, in patients with either mild or more severe hypertension and in both type 1 and type 2 diabetes, the established practice of choosing an ACE inhibitor as the first-line agent in most patients with diabetes is reasonable. In patients with microalbuminemia or clinical nephropathy, both ACE inhibitors (type 1 and type 2 patients) and ARBs (type 2 patients) are considered first-line therapy for the prevention of and progression of nephropathy. However, other strategies including diuretic and β -blocker–based therapy are also supported by evidence. Because of lingering concerns about the lower effectiveness of DCCBs (compared with ACE inhibitors, ARBs, β -blockers, or diuretics) in decreasing coronary events and heart failure and in

Table 1—Indications for initial treatment and goals for adult hypertensive diabetic patients

	Systolic	Diastolic
Goal (mmHg)	<130	<80
Behavioral therapy alone (maximum 3 months) then add pharmacologic treatment	130–139	80–89
Behavioral therapy + pharmacologic treatment	≥140	≥90

reducing progression of renal disease in diabetes, these agents should be used as second-line drugs for patients who cannot tolerate the other preferred classes or who require additional agents to achieve the target blood pressure. Other classes, including α -blockers, may be used under specific indications (such as symptoms of BPH for α -blockers) or other agents have failed to control the blood pressure or have unacceptable side effects. Blood pressure, orthostatic changes, renal function, and serum potassium should be monitored at appropriate intervals.

Treatment decisions should be individualized based on the clinical characteristics of the patient, including comorbidities as well as tolerability, personal preferences, and cost.

Recommendations

Refer to Table 1 for recommendations on initial treatment and goals for adult hypertensive diabetic patients.

Screening and diagnosis

Expert opinion:

- Blood pressure should be measured at every routine diabetes visit. Patients found to have systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg should have blood pressure confirmed on a separate day.
- Orthostatic measurement of blood pressure should be performed to assess for the presence of autonomic neuropathy.

Treatment

A-Level evidence:

- Patients with diabetes should be treated to a diastolic blood pressure < 80 mmHg.
- Patients with a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg should be given lifestyle/behavioral therapy alone for a maximum of 3 months and then, if targets are not achieved, should also be treated pharmacologically.
- Patients with hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) should receive drug therapy in addition to lifestyle/behavioral therapy.
- Initial drug therapy may be with any drug class currently indicated for the treatment of hypertension. However, some drug classes (ACE inhibitors, β -blockers, and diuretics) have been repeatedly shown to be particularly beneficial in reducing CVD events during the treatment of uncomplicated hypertension and are therefore preferred agents for initial therapy. If ACE inhibitors are not tolerated, ARBs may be used. Additional drugs may be chosen from these classes or another drug class. (A)
- If ACE inhibitors or ARBs are used, monitor renal function and serum potassium levels. (E)
- While there are no adequate head-to-head comparisons of ACE inhibitors and ARBs, there is clinical trial support for each of the following statements:
 - In patients with type 1 diabetes, with or without hypertension, with any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. (A)
 - In patients with type 2 diabetes, hypertension and microalbuminuria, ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. (A)
 - In those with type 2 diabetes, hypertension, macroalbuminuria (> 300 mg/day), nephropathy, or renal insufficiency, an ARB should be strongly considered. If one class is not tolerated, the other should be substituted.
- In patients over age 55 years, with hy-

pertension or without hypertension but with another cardiovascular risk factor (history of cardiovascular disease, dyslipidemia, microalbuminuria, smoking), an ACE inhibitor (if not contraindicated) should be considered to reduce the risk of cardiovascular events.

- In patients with a recent myocardial infarction, β -blockers, in addition, should be considered to reduce mortality.

B-Level evidence:

- Patients with diabetes should be treated to a systolic blood pressure < 130 mmHg.

C-Level evidence:

- In patients with microalbuminuria or overt nephropathy, in whom ACE inhibitors or ARBs are not well tolerated, a non-DCCB or β -blocker should be considered.

Expert consensus

- If ACE inhibitors or ARBs are used, monitor renal function and serum potassium levels.
- In elderly hypertensive patients, blood pressure should be lowered gradually to avoid complications.
- Patients not achieving target blood pressure on three drugs, including a diuretic, and patients with a significant renal disease should be referred to a specialist experienced in the care of patients with hypertension.

Bibliography

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