REVIEW ARTICLE

A Practical Approach to Achieving Recommended Blood Pressure Goals in Diabetic Patients

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Approximately 11 million Americans have both hypertension and diabetes mellitus. This double diagnosis places such patients at high risk for renal damage, especially end-stage renal disease. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends a blood pressure goal of less than 130/85 mm Hg to reduce or slow the onset of renal disease and cardiovascular events in patients with hypertension and diabetes mellitus. Recent data, however, now suggest that an even lower diastolic blood pressure goal (ie, <80 mm Hg) may be necessary. Studies have shown that use of angiotensin-converting enzyme inhibitors can prevent the progression of microalbuminuria to overt proteinuria, reduce proteinuria in patients with overt diabetic nephropathy, slow the deterioration of the glomerular filtration rate, delay progression to end-stage renal disease, and lower blood pressure. Thus, all diabetic patients with blood pressure greater than 130/80 mm Hg should begin angiotensin-converting enzyme inhibitor treatment and be titrated to moderate or high doses until the blood pressure goal is achieved. However, monotherapy still may not control blood pressure to the recommended target. Studies have shown that use of multiple antihypertensive agents is necessary and successful in helping patients reach their target blood pressure, and this may offer more renoprotection than one agent used singly. A case study that applies these concepts in outpatient practice is included.

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Hypertension and diabetes mellitus damage not only the cardiovascular system but also the kidneys. Diabetes mellitus, for instance, contributes to a reduced filtration rate, which leads to increased glomerular blood flow and glomerular capillary pressure, which in turn leads to proteinuria and glomerular damage. Hypertension can be either a cause or a consequence of chronic renal disease. Uncontrolled elevated blood pressure (BP) is believed to cause renal damage via ischemia in the renal tubule, provoking a reduction in renal mass and increased glomerular capillary pressure.[1,2]

More than 11 million Americans have both diabetes mellitus and hypertension—comorbid conditions that strongly predispose the individual to renal and cardiovascular damage.[3] In patients with diabetes mellitus, hypertension can contribute as much as 75% of all diabetes mellitus–related complications, including nephropathy and end-stage renal disease (ESRD).[4]

Blood pressure has been shown to directly affect renal function. The declining rate of renal function in patients with diabetic nephropathy seems to be a continuous function of arterial pressure of 125/75 mm Hg or less (**Figure 1**).[5] Therefore, individuals with diabetes mellitus and BP values greater than 125/75 mm Hg have a greater likelihood of progressing to ESRD. To that end, intensive BP control, using lifestyle modification and pharmacotherapy, is important in managing the diabetic patient with hypertension. The purpose of this article is to discuss the importance of BP control in patients with diabetes mellitus, with emphasis on using multidrug therapy in this patient population. To illustrate this

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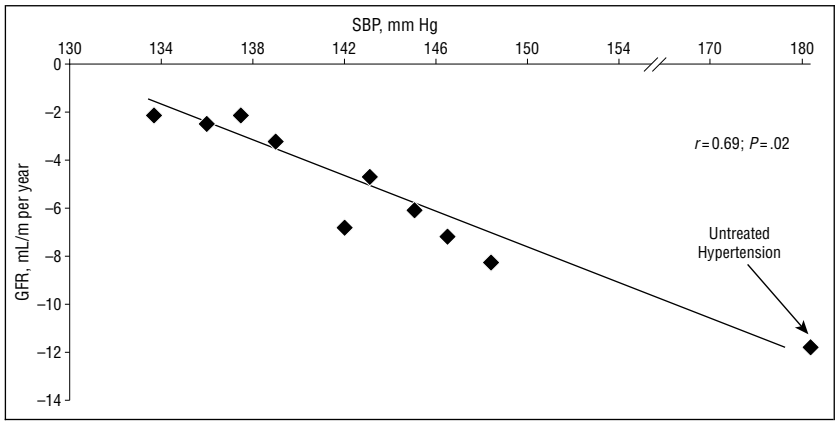

Figure 1. Rates of decline in glomerular filtration rate (GFR) vs the systolic blood pressure (SBP) in studies extending for 3 years or more in patients with type 2 diabetes mellitus nephropathy. Adapted from Bakris.[5]

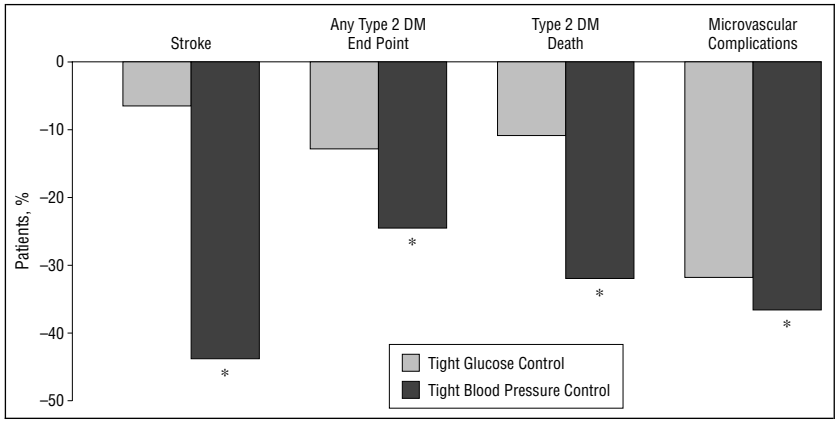

Figure 2. Comparative effects of tight glucose control vs tight blood pressure control in the United Kingdom Prospective Diabetes Study.[9] Asterisk indicates $P<.05$ compared with glucose control; DM, diabetes mellitus. Reproduced with permission from Bakris et al.[3]

strategy, a patient management case is presented.

IMPORTANCE OF BP CONTROL VS GLUCOSE CONTROL

Aggressive management of high BP is more important in reducing cardiovascular events and slowing renal disease progression than is intensive control of blood glucose levels.[5-9] The United Kingdom Prospective Diabetes Study[9] was a 9-year, randomized controlled trial that evaluated the effect of tight BP control and glucose level control in more than 4000 people with type 2 diabetes mellitus. This study[9] found that diastolic BP control (goal, <85 mm Hg) had a greater impact on reducing cardiovascular events than did tight glucose level control (ie, hemoglobin A_{1c} goal, <7%) (**Figure 2**). This reduction in cardiovascular risk included a decrease in the number of strokes and any diabetes mellitus–associated end point, including deaths.

These data demonstrate the link between hypertension and renal damage and the connection between BP control and renoprotection. The Multiple Risk Factor Intervention Trial[10] identified significant associations between BP and the rate of renal dysfunction, thereby creating a presumption for a causal role for hypertension. In that study, a strong, graded relationship was demonstrated between both systolic and diastolic BP and ESRD, independent of associations between the disease and age, race, income, use of hypoglycemic medication, history of myocardial infarction, serum cholesterol concentration, and cigarette smoking. Compared with men who have optimal BP (ie, <120/80 mm Hg), the relative risk of ESRD for those with a BP greater than 210/120 mm Hg was 22.1 ($P<.001$). In short, the higher the BP, the higher the risk for renal disease.[10]

The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI)[11] suggests that antihypertensive drug therapy should be initiated, along with lifestyle modifications and, particularly, weight loss, to reduce BP to less than 130/85 mm Hg. The JNC VI also states that use of angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (CCBs), and low-dose diuretics is preferred because of fewer adverse effects on glucose metabolism, lipid profiles, and renal function.[12,13]

CONTROLLING PROTEINURIA CAN CURB RENAL DAMAGE

Increased urinary protein or albumin excretion (microalbuminuria) is a fundamental sign of and an independent predictor for the outcome of renal and cardiovascular disease. The prevalence of microalbuminuria in hypertensive individuals without diabetes mellitus can be as low as 7%, depending on age, race, and ethnicity. The prevalence of microalbuminuria in patients with type 2 diabetes mellitus is estimated to be as high as 40%.[14]

The Modification of Diet in Renal Disease Study[15] found that strict BP control slowed the decline in glomerular filtration rate (GFR) in a subgroup of patients with proteinuria, an independent risk factor for the progression of renal disease. Therefore, the presence of proteinuria may identify patients with renal disease or diabetes mellitus who would benefit from stricter control of BP (than the current JNC VI recommendations of <130/85 mm Hg). Based on the Modification of Diet in Renal Disease Study, patients with urinary protein levels of 0.25 to 1.0 g/d should have a target BP of 130/80 mm Hg. For patients with urinary protein levels greater than 1 g/d, a BP as low as 125/75 mm Hg may be advisable.[15] Moderate protein restriction (0.8 g per kilogram of body weight per day) is recommended in proteinuric patients to assist in reducing the degree of proteinuria, which in turn reduces the rate of progression of renal disease.[14]

RENAL BENEFITS OF VARIOUS ANTIHYPERTENSIVE AGENTS

Some antihypertensive agents confer more renoprotection than do others. The JNC VI[11] states that low-dose diuretics have a favorable impact on type 2 diabetes mellitus. Diuretics are often preferred in patients with concomitant diabetes mellitus because of fewer adverse effects on glucose homeostasis and renal function than β-adrenergic blocking agents, another class that is recommended as first-line therapy in hypertension.[11] However, thiazide diuretics are not effective with advanced renal insufficiency (serum creatinine level ≥2.5 mg/dL [≥221 μmol/L]), and loop diuretics are needed (often at relatively large doses). Combining a loop diuretic with a long-acting thiazide diuretic, such as metolazone or hydrochlorothiazide (high dose), is effective in patients resistant to a loop diuretic alone.

Treatment with ACE inhibitors can also benefit the hypertensive patient with concomitant diabetes mellitus. A meta-analysis[16] of 41 studies showed that although all the available antihypertensive drug classes lowered BP to a greater extent than did placebo, ACE inhibitors lowered urinary protein excretion more than the other classes. A meta-analysis[17] of 100 studies of patients with type 1 and type 2 diabetes mellitus concluded that appropriate lowering of BP by any means slowed the rate of loss of renal function. However, only ACE inhibitors seemed to preserve GFR and decrease proteinuria independent of the BP effects.[17]

The salutary effects of ACE inhibitors may be related to their ability to dilate efferent arterioles, thereby reducing intraglomerular pressure. The beneficial effects may also result from restoration of glomerular permselectivity in proteinuric nephropathies.[18,19] This may explain why use of ACE inhibitors delays the progression of renal disease in normotensive diabetic patients with microalbuminuria.[20]

Clinically, studies have shown that ACE inhibitors slow the deterioration in GFR and delay progression to ESRD. In a clinical trial using the drug captopril,[21] a 50% risk reduction in the combined end points of death, dialysis, and transplantation was noted among patients with type 1 diabetes mellitus nephropathy who received an ACE inhibitor compared with other agents used to lower arterial pressure. Similarly, the Ramipril Efficacy in Nephropathy study[22] showed that in patients with chronic nephropathies and a urinary protein level of 3 g/d or less, use of the ACE inhibitor ramipril safely reduced the rate of GFR decline and halved the combined risk of doubling of the serum creatinine level or ESRD. Furthermore, the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study[23] showed that use of benazepril hydrochloride significantly improved renal survival compared with use of placebo ($P<.001$) in patients with various underlying renal diseases.

Adrenergic receptor binders have been shown in short-term clinical studies to lower urinary protein levels in patients with renal disease. A 6-month study[24] of valsartan therapy showed a sustained reduction in BP and urinary protein levels, even in patients with advanced renal failure. A 12-week study[25] using losartan potassium showed that for comparable BP reductions, a greater reduction in urinary albumin levels was seen with losartan vs felodipine (a CCB) use in hypertensive patients with or without type 2 diabetes mellitus. Long-term studies are needed to confirm whether these antiproteinuric effects of losartan can be deemed renoprotective.[25]

BP CONTROL MAY REQUIRE MULTIPLE DRUGS

Although use of an ACE inhibitor is key in antihypertensive therapy of a diabetic patient, other drugs may also have renal benefits. In fact, some combinations are more beneficial together than they would be if used alone. Because not all patients attain BP control with monotherapy, use of an additional antihypertensive agent may be necessary.

One reason BP is so difficult to control is because only half of all hypertensive patients respond to monotherapy.[26] Hypertension is a multifactorial disease in which many systems interact and lead to an increase in BP. Therefore, use of 2 or more complementary agents may improve response rates because more than 1 physiologic pathway is interrupted.

Studies have underscored the need for combination therapy. In the Hypertension Optimal Treatment Study,[7] 74% of study participants needed to take 2 or more antihypertensive agents to lower their diastolic BP to 80 mm Hg or less. The cardioprotective effect of low-dose combination therapy exceeded that of higher-dose monotherapy.[7] Likewise, in the United Kingdom Prospective Diabetes Study,[9] 29% of patients in the tight BP control group required treatment with 3 or more medications to achieve a BP of 144/82 mm Hg and to reduce the complications and death related to diabetes mellitus. Clinical trials[6,27-30] that have randomized patients to lower levels of BP require an average range of 2.8 to 4.2 different antihypertensive agents to achieve the desired goal BP (**Figure 3**).

Which drugs work best in a combination that can benefit the kidneys and the rest of the cardiovascular system? A 3-year comparison[31] between captopril and nifedipine-based therapy on the progression of renal insufficiency showed no difference between the agents on BP reduction or progression of renal insufficiency in the first 2 years. In the last year, however, 5 times more people went on to receive dialysis in the nifedipine group. In general, this study[31] demonstrated that better BP control lowered the rate of decline in renal function in both treatment groups as opposed to any independent renoprotective pathway. Thus, administering an ACE inhibitor with a CCB can be potentially useful. In another study[32] of proteinuria, when an ACE inhibitor was combined with a long-acting dihydropyridine CCB, amlodipine, the results were more favorable than when the CCB was used as monotherapy. Benazepril monotherapy produced, as expected, significantly reduced urinary albumin excretion (UAE). Yet,

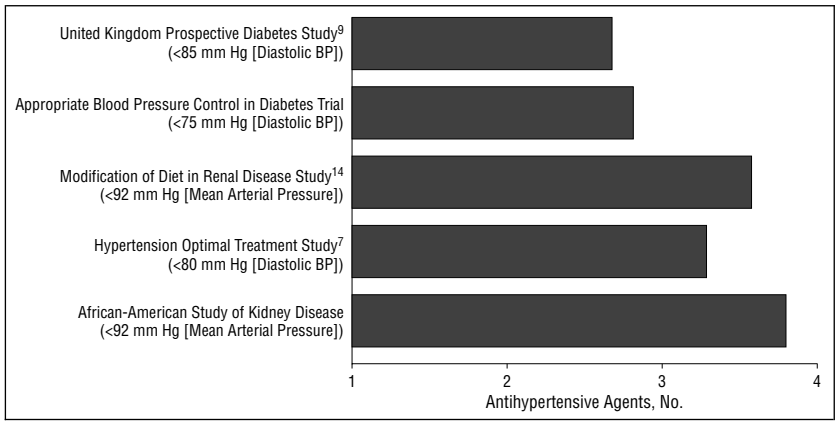

Figure 3. Recently completed cardiovascular and renal trials in which patients received 2 or more antihypertensive agents for intensive blood pressure control.[6,27-29] BP indicates blood pressure. Reproduced with permission from Bakris et al.[3]

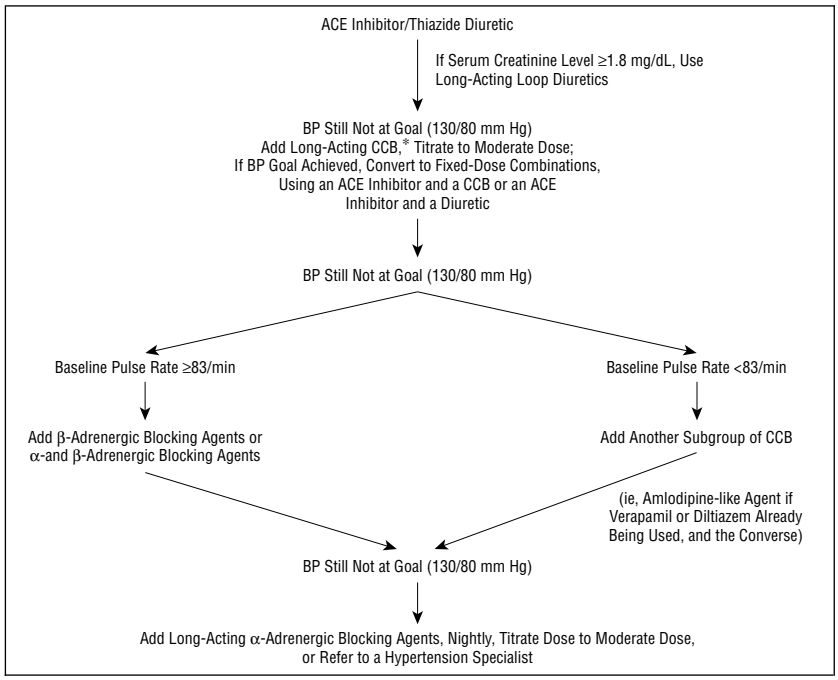

Figure 4. Clinical approach to managing hypertension in a diabetic patient. Everyone with diabetes mellitus, renal insufficiency, or both should be instructed on lifestyle modifications as per the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[11] Everyone, however, should initiate therapy if blood pressure (BP) is greater than 130/85 mm Hg. If BP is less than 15/10 mm Hg above goal (ie, 130/80 mm Hg), then angiotensin-converting enzyme (ACE) inhibitors can be used alone. Asterisk indicates that calcium channel blockers (CCBs) (eg, verapamil and diltiazem) have been shown to reduce cardiovascular mortality rates and progression of diabetic nephropathy independent of ACE inhibitor use.[27,39] To convert serum creatinine levels to micromoles per liter, multiply milligrams per deciliter by 88.4. Modified with permission from Bakris et al.[3]

combination therapy tended to produce a greater reduction in UAE and also increased creatinine clearance ($P<.02$), an effect not seen with benazepril used alone. At study termination (6 months), the ACE and CCB therapy showed a greater decrease (−24.6%; $P<.02$) than did monotherapy (−19.7%; $P<.04$); however, BP was also lower in the combination group. This study supports the results of an earlier study[33] that suggest that the combination of an ACE inhibitor, lisinopril, and a CCB, verapamil, provides greater reduction in UAE than does use of either agent alone. That combination resulted in the slowest decline in renal function over time, an effect that correlated with reductions in albumin excretion. Moreover, this benefit on proteinuria occurred without additional BP reduction. An additional study[34] demonstrates that the combination of an ACE inhibitor and a nondihydropyridine CCB reduces proteinuria better than either agent used alone; this effect occurred independent of its BP-lowering activity. A recent trial[35] compared the effects of felodipine added to ramipril therapy in hypertensive patients with type 2 diabetes mellitus and impaired renal function. This ACE inhibitor–CCB combination improved UAE and led to further improvement in BP control and renal function than did ACE inhibitor monotherapy.[35]

Additional drugs can also be added to ACE inhibitor therapy to achieve target BP. For example, very low doses of a diuretic (eg, hydrochlorothiazide, 6.25 mg/d) can potentiate the effect of the other agent without producing adverse metabolic effects.[36] β-Adrenergic blocking agents have additive BP-lowering abilities if the patient's baseline pulse rate is 84/min or greater.[37] At pulse rates less than 84/min, little effect on BP has been observed when β-adrenergic blocking agents are combined with ACE inhibitors.

A PLAN TO ACHIEVE TARGET BPs

Based on data that evaluated the success of reaching BP goals in an outpatient setting, BPs greater than 15/10 mm Hg above the target BP require the use of 2 different antihypertensive agents.[38] These data, together with the results of clinical trials, have led to the development of a treatment algorithm for hypertensive patients with diabetes mellitus, renal insufficiency, or both (**Figure 4**).[3,39]

Diuretic and ACE inhibitor combinations seem to be ideal as initial therapy based on both drug classes' records of reducing cardiovascular events and renal disease progression (Figure 4).[3] If the patient's BP is not at goal (ie, 130/80 mm Hg), then a CCB should be added because these agents have shown additive BP-lowering abilities with either ACE inhibitors or diuretics. If goal BP is achieved, then the patient should be converted to a fixed-dose combination product (ie, an ACE inhibitor and a CCB or an ACE

inhibitor and a diuretic). If BP does not remain at goal and the baseline pulse rate is 83/min or greater, then an adrenergic blocking agent should be added; otherwise, another subgroup CCB (other than the one added earlier) should be added. For example, the combination of a nondihydropyridine and a dihydropyridine CCB has additive, even synergistic, BP-reducing capabilities.[40,41] Thereafter, if BP remains uncontrolled, then a long-acting α-adrenergic blocking agent should be added at bedtime, and referral to a hypertension specialist should be considered.[3]

PATIENT MANAGEMENT CASE

The application of these principles is described in the following patient management case. The patient is a 57-year-old black woman who recently moved to the city and has a 5-year history of diabetes mellitus and a 10-year history of hypertension. She stated that she was feeling well and had no somatic complaints. She was seen at the office because she needed to establish a relationship with a physician who would continue managing her diabetes mellitus and hypertension. Her review of systems was unremarkable. The patient's family history was positive for cardiovascular disease; her parents both died of myocardial infarction. Her mother also had diabetes mellitus and hypertension. She was uncertain whether her father was hypertensive.

Regarding her social history, she works as a receptionist in a business office and denies smoking cigarettes or drinking alcohol. She is married and has 3 children. Physical examination showed that she is moderately obese, 170 cm in height, and 89.6 kg (body mass index [calculated as weight in kilograms divided by the square of height in meters], 31.2; body mass index >25.0 is considered an indication of obesity). She had a sitting BP of 164/100 mm Hg with no orthostatic change. Her pulse rate was 88/min and regular.

The patient's current medications included hydrochlorothiazide, 25 mg once daily; metformin, 500 mg twice daily; and glyburide, 2.5 mg once daily. When queried why she was not taking an ACE inhibitor, she stated that her former physician considered ACE inhibitors to be ineffective in black persons. A head, eyes, ears, nose, and throat examination revealed grade 2 hypertensive retinopathy but was otherwise unremarkable. Her lungs were clear, and the remainder of her physical examination was unremarkable other than 1+ pedal edema. Laboratory analysis findings were unremarkable except for a hemoglobin A_{1c} level of 8.3%; fasting blood sugar level, 192 mg/dL (10.6 mmol/L); low-density lipoprotein cholesterol, 153 mg/dL (4.0 mmol/L); high-density lipoprotein cholesterol, 36 mg/dL (0.93 mmol/L); triglyceride level, 350 mg/dL (4.0 mmol/L); elevated total cholesterol, 300 mg/dL (7.8 mmol/L); and urinalysis showing 1+ proteinuria. Her serum creatinine level was 1.4 mg/dL (124 μmol/L).

This patient has several risk factors—age, dyslipidemia, diabetes mellitus, and family history of cardiovascular disease—that highlight her need to achieve goal BP and lipid management. First, glucose control should be improved, with stronger emphasis on dietary restraint and weight loss, particularly because her body mass index is 31.2. Also, an increase in the dose of her oral hypoglycemic agent may be beneficial. Second, lipid management should be obtained with dietary modifications and lipid-lowering therapy. Concomitantly, the patient's BP management must be changed.

Using the previously recommended scheme for treating elevated BP (Figure 4), the following approach is suggested for this patient. This patient needs to take an ACE inhibitor to protect her kidneys because ACE inhibitors have renal benefits in patients with diabetes mellitus, including impeding the increase in UAE, slowing the transition from microalbuminuria to overt albuminuria, and delaying the progression of albuminuria to overt nephropathy in diabetic patients.[17,21,42] She can continue taking the thiazide diuretic for 2 reasons: (1) her serum creatinine level is less than 1.8 mg/dL (159 μmol/L) (she would be given a loop diuretic if it were not) and (2) thiazide diuretics are often preferred in patients with concomitant diabetes mellitus because of their favorable adverse event profile and benign effect on glucose homeostasis and renal function. The physician prescribed the following medications: benazepril, 10 mg once daily; hydrochlorothiazide, 25 mg once daily; metformin, 500 mg 3 times daily; glyburide, 2.5 mg once daily; and a once-daily statin.

After 4 weeks, the patient returned to the physician's office. Her fasting blood glucose level had decreased slightly. However, her BP was still elevated at 155/105 mm Hg. The physician increased her benazepril dose to 20 mg once daily.

Eight weeks after her initial visit, her BP, at 150/98 mm Hg, remained far from her goal of 130/80 mm Hg. At this point, the physician opted to include a long-acting CCB in her antihypertensive regimen because, as discussed, such a combination may control BP and renal complications better than ACE inhibitor monotherapy. The physician gave her amlodipine, 5 mg once daily.

Six weeks later, this patient returned to her physician. Her BP was now 135/88 mm Hg. With her goal in sight, the physician decided to use a fixed combination of an ACE inhibitor and a CCB (ie, amlodipine and benazepril, 5:20). Fixed-dose combination agents serve the purpose of providing 2 different antihypertensive agents in a single dosage form, and, thus, compliance is enhanced.

What if this patient still had not approximated her BP goal? Using Figure 4, the decision would be made according to her baseline pulse rate: if 83/min or more, an α- or β-adrenergic blocking agent could be added. If her pulse rate was less than 83/min, another CCB subgroup could be added, such as verapamil or diltiazem.

This case study has several lessons. First, all patients with diabetes mellitus and hypertension should be taking an ACE inhibitor (except those with advanced renal failure: serum creatinine level >4.0-5.0 mg/dL

[>354-442 µmol/L]) for renoprotection and BP control. Second, physicians should take their time in achieving BP control. A patient may need to be seen monthly for 4 to 6 months before actually achieving the desired BP goal. Immediate- or short-acting CCBs or other types of agents (ie, hydralazine) will not produce long-standing benefits in these patients. Such agents have never been shown to reduce cardiovascular mortality rates, and, although they reduce the BP numbers, they markedly increase sympathetic nerve activity. Finally, hypertension is a multifactorial disease. Using more than 1 agent can attack BP from different vantage points. Administering a single agent, and maximizing the dosage, can expose the patient to adverse events that may result in total noncompliance.

COMMENT

Good BP control is important in protecting the human kidney from damage. The latest position paper from the American Diabetes Association suggests that urinalysis be performed annually in adults: if the findings are positive for protein, a quantitative measure can be helpful in the development of a treatment plan to decrease proteinuria; if the results are negative for protein, then a test for the presence of microalbumin is necessary. Such screening should begin at the time of diagnosis for type 2 diabetes mellitus; for patients with type 1 diabetes mellitus, screening should begin at puberty and then at 5 years' disease duration.[12] Other important strategies to protect against severe renal insufficiency include the following:

- Control for blood glucose levels in diabetic patients: intensive insulin therapy reduced the risk of albuminuria and microalbuminuria by 54% and 39%, respectively, in clinical trials for patients with type 1 diabetes mellitus[43]
- Encourage smoking cessation: cigarette smoking is associated with the development and progression of microalbuminuria[44]
- Control for hyperlipidemia: limited data confirm that correction of lipid abnormalities is important in slowing the progression of renal insufficiency[45]
- Restrict protein intake to help reduce proteinuria

Elevated systolic and diastolic BP markedly accelerate the progression of diabetic nephropathy. Aggressive antihypertensive management can greatly reverse a decline in GFR. Appropriate therapy with antihypertensive medications can significantly increase the median life expectancy in patients with type 1 diabetes mellitus, with a reduction in mortality from 94% to 45% and a reduction in the need for dialysis and transplantation from 73% to 31% sixteen years after the development of overt nephropathy.[12] A meta-analysis of clinical studies of nondiabetic renal disease progression has shown that ACE inhibitors can reduce the presence and degree of renal failure, thus encouraging use of these agents as soon as urinary protein is detected.[46] They also reduce BP to the recommended diastolic range of 80 to 90 mm Hg while diminishing UAE. All diabetic patients with a BP of 130/80 mm Hg or greater should receive either a once-daily ACE inhibitor or a once-daily angiotensin receptor blocker and be titrated to moderate or high doses until the BP goal is achieved. Moreover, 2 recent trials support the concept that angiotensin receptor blockers may be the drugs of first choice to prevent nephropathy in patients with type 2 diabetes mellitus[47,48]; thus, they should be considered first-line agents in this clinical setting.

Adding another drug to ACE inhibitor or angiotensin receptor blocker therapy may result in more renoprotection than the ACE inhibitor or angiotensin receptor blocker therapy used alone. More studies are emerging that show such a trend when ACE inhibitors are administered in conjunction with CCBs. Future trials should concentrate on whether the effects of such combinations offer novel pathways that curb renal damage independent of their BP-lowering effects. In that way, we can determine the proper therapies and dosages that can provide renoprotection before renal damage is extensive.

CONCLUSIONS

The goal BP in a patient with diabetes mellitus is less than 130/80 mm Hg. Lower BP levels (ie, <125/75 mm Hg) are recommended in patients with diabetes mellitus who have urinary protein levels greater than 1 g/d. All patients with diabetes mellitus or renal insufficiency should be taking an ACE inhibitor as part of their antihypertensive regimen, unless specifically contraindicated. An alternative to ACE inhibitor therapy may be angiotensin receptor blockade; however, data from clinical trials are not yet available to offer such a recommendation. The addition of either a diuretic or a CCB should be second-line therapy in these patients to help achieve the BP goal. Also, clinicians should understand that, in most cases, 2 or even 3 different antihypertensive medications will be needed to help achieve these goals and that failure to do so will minimize the benefit of antihypertensive treatment on renal or cardiovascular event reduction.

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