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# Hypertension Management in the Diabetes Patient

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*Approximately 11 million of the 17 million US citizens with type 2 diabetes mellitus also have hypertension. The development of diabetic nephropathy in patients with type 1 diabetes is frequently associated with hypertension, and both may present several years after the onset of diabetes. In type 2 diabetes, hypertension may precede the development of diabetes by several years. Differences that exist between type 1 and type 2 diabetes and the development of hypertension may indicate differences in the concomitant disease processes, yet the inevitable development of both diseases con-*

*tributes to significant increases in risk of cardiovascular disease. The pharmacist must be familiar with blood pressure treatment goals in the hypertensive-diabetic patient and appropriate pharmacotherapeutic management. This article outlines treatment goals in the patient with diabetes and concurrent hypertension, reviews trials assessing pharmacologic treatments, and provides a summary of monitoring parameters to guide the pharmacist in the management of this population.*

KEY WORDS: Diabetes, hypertension, ACE inhibitors, ARBs, comorbidities.

## INTRODUCTION

It is estimated that 11 million of the 17 million US citizens with type 2 diabetes mellitus also have hypertension.<sup>1</sup> In patients with type 1 diabetes, the development of diabetic nephropathy is frequently associated with hypertension, both of which may present several years after the onset of diabetes. In type 2 diabetes, hypertension may precede the development of diabetes by several years. The temporal differences that exist between type 1 and type 2 diabetes and the development of hypertension may indicate significant differences in the concomitant disease processes, yet the inevitable development of both diseases contributes to significant increases in risk of cardiovascular disease. Furthermore, the microvascular and macrovascular complications of diabetes are exacerbated when hypertension is present as comorbidity. As a result of the prevalence of the diabetes-hypertension combination, the pharmacist must be familiar with blood pressure treatment goals and appropriate pharmacotherapeutic interventions in the patient with hypertension and diabetes. This article briefly outlines treatment goals in the patient with diabetes and concurrent hypertension, reviews key trials assessing pharmacologic treatment options, and provides a summary of monitoring parameters to guide the pharmacist in the management of this challenging population.

## PATHOPHYSIOLOGY

A detailed review of the pathophysiologic features of hypertension and diabetes is outside the scope of this article. However, several findings are important to demonstrate the additive or perhaps “synergistic” nature of the relationship between the two disease processes. The pathophysiologic relationship between diabetes and hypertension in type 1 patients with nephropathy may be based on a genetic predisposition. Researchers have identified an alteration in the so-

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dium/lithium countertransport in patients with type 1 diabetes. Similarly, essential hypertension may predispose an individual to the development of type 2 diabetes. Obesity has also been shown to play a role in the development of hypertension in the patient with type 2 diabetes. Hyperinsulinemia has been proposed as the common derangement leading to the development of the metabolic syndrome (obesity, hypertension, abnormal lipid levels, and elevated insulin levels). Hyperinsulinemia has also been shown to increase total body sodium and plasma volume through an antinatriuretic effect. Diabetes and hypertension individually may lead to vascular damage, with an increased risk if both diseases are present concomitantly. Total body sodium is increased, as is the vascular response to vasoconstrictors.<sup>2,3</sup>

The renin-angiotensin-aldosterone system (RAAS) is often at low or normal levels in patients with diabetes. This may represent a derangement in the RAAS in the face of increased total body sodium. This pathologic component may explain the clinical benefit of the angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin-receptor blockers (ARBs) on progression of diabetes-induced nephropathy even when blood pressure remains unchanged following initiation of treatment. It is speculated that the reduction in angiotensin II activity that is seen when either class is administered results in a reduction in the intraglomerular pressure, thereby reducing proteinuria as well as diminished growth factor stimulation by angiotensin II.<sup>4</sup> The Heart Outcomes and Prevention Evaluation trial evaluated the effect of ramipril in 3577 patients with diabetes and at least 1 additional cardiovascular risk factor present. With administration of ramipril, modest blood pressure declines were seen (2.4 mmHg/1 mmHg), yet the ramipril group had a 0.75 (95% confidence interval [CI] 0.64 to 0.88) relative risk when compared to the conventional treatment group.<sup>5</sup> Although the above outlined mechanisms provide a useful explanation for the interrelationship between diabetes and hypertension, several inconsistencies also exist, such as the finding that insulin may have a vasodilatory effect. The astute clinician must be aware of the interrelatedness of the diseases and develop an appreciation for the importance of aggressive therapy in this population.

#### GOALS OF ANTIHYPERTENSIVE THERAPY

The recently released "Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" (JNC VII)

provides the reader with a current systematic review of the significant trials in hypertension. Based on evaluation of the clinical evidence, a blood pressure goal of < 140/90 mmHg is established for the treatment of hypertension. However, for those patients with diabetes or renal disease, the treatment goal is aggressively decreased to < 130/80 mmHg.<sup>6</sup> Similar treatment goals are outlined in the American Diabetes Association's 2003 Annual Review of Treatment Recommendations.<sup>7</sup> Support for this level of reduction is based on the findings of several large, randomized trials that included patients with diabetes. In the Systolic Hypertension in the Elderly Program trial, elderly patients with diabetes and isolated systolic hypertension (systolic blood pressure > 160 mmHg; diastolic blood pressure < 90 mmHg) treated aggressively with chlorthalidone were shown to have a cardiovascular event (including non-fatal or fatal myocardial infarction, major coronary heart disease, stroke, transient ischemic attacks, aortic aneurysm, and endarterectomy) relative risk of 0.66 (95% CI 0.46 to 0.94) when compared with the placebo-controlled group. Blood pressure reductions of 9.8/2.2 mmHg were seen in the group with diabetes.<sup>8</sup>

The Hypertension Optimal Treatment randomized trial assessed target diastolic blood pressure at three levels (< 90 mmHg, < 85 mmHg, and < 80 mmHg) in 18,790 patients. Results seen in the 1501 patients with diabetes in the trial were reported separately. Reduced event rates were seen with more aggressive reductions in blood pressure in all end points. Major cardiovascular events (51% reduction) and cardiovascular mortality (67% reduction) were significantly reduced (51% and 67%, respectively) when the < 80 mmHg group was compared with the < 90 mmHg treatment arm. To achieve the desired blood pressures, all patients were initially placed on felodipine 5 mg orally daily. Therapy with an ACE inhibitor or a  $\beta$ -blocker was initiated as step 2, with dosage titration in steps 3 and 4. A diuretic was added as step 5. In addition, patients were randomized to 75 mg of aspirin daily. This treatment demonstrated a reduction in the incidence of myocardial infarction of 2.5 per 1000 patient-years.<sup>9</sup>

The United Kingdom Prospective Diabetes Study 38 (UKPDS 38) also stratified patients with diabetes into levels of blood pressure control with a "tight" control group (target blood pressure of < 150/85 mmHg) and a "less tight" control group (target blood pressure of < 180/105 mmHg). Average blood pressures in the groups at the conclusion of the study period were 144/82 mmHg (tight) and 154/87 mmHg (less tight). Significant reductions were seen in the tight control group in the following end points: diabetes-related end points, deaths related to diabetes, stroke, and microvascular

end points. Blood pressures in the 2 groups averaged 144/82 mmHg in the tight control group and 154/87 mmHg in the less tight control group.<sup>10</sup> Therefore, statistically significant reductions were seen in the risk of the above end points with only a 5-mmHg difference in average diastolic blood pressure between the 2 groups.

The Appropriate Blood Pressure Control in Diabetes (ABCD) trial targeted 2 levels of reduction in diastolic blood pressure: a diastolic goal of 75 mmHg and a diastolic goal of 80 to 89 mmHg. The trial was conducted in 470 patients with type 2 diabetes. At the conclusion of the 5-year study, progression of renal disease was not different in the 2 groups, nor was the incidence of myocardial infarction, congestive heart failure, or stroke. However, total mortality was 5.5% in the aggressively treated group and 10.7% in the less aggressively treated group.<sup>11,12</sup>

From the cited studies, it is clear that aggressive reductions in both the systolic and diastolic blood pressure will result in a risk reduction for common pathologic end points among patients with hypertension and diabetes. In a recent article, Vijan and Hayward analyzed the UKPDS trial to calculate the number needed to treat based on the various end points of the study. Tight blood pressure control in 8.9 patients for 10 years would prevent 1 patient from reaching any diabetes end point. Treatment of 16.4 patients for 10 years would prevent 1 diabetes-related death. In addition, 1 myocardial infarction would be prevented by treating 23.3 patients for 10 years with tight blood pressure control.<sup>13</sup> It is important for the pharmacist to note that aggressive control of blood pressure brings with it a more significant improvement in cardiovascular outcomes than is seen with aggressive control of blood glucose.

### CLINICAL TRIALS IN PATIENTS WITH HYPERTENSION AND DIABETES

Several clinical trials have been published within the past 5 years comparing various antihypertensive agents in patients with diabetes. Reviews of reported trials reveal that ACE inhibitors and ARBs were most often included as a treatment option. Several studies also included the dihydropyridine calcium-channel blockers,  $\beta$ -blockers, or diuretics. Several published trials will be reviewed to further differentiate the antihypertensive agents and to identify appropriate pharmacologic interventions based on clinical trials.

The Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT) enrolled more than 33,000 patients aged 55 years or older with hypertension and at least one other coronary heart disease risk factor. Among those enrolled, 36% were pa-

tients with diabetes. Patients were assigned initially to 1 of 4 treatment arms—lisinopril, amlodipine, doxazosin, or chlorthalidone. The doxazosin arm was stopped early after a preliminary evaluation of the data indicated an increased risk of heart failure in those patients treated with doxazosin when compared with the chlorthalidone-treated group. Results seen with lisinopril and amlodipine were similar to those seen with chlorthalidone among most patient subgroups. In patients with diabetes, lisinopril or amlodipine offered few significant benefits over chlorthalidone. The risk of heart failure was lowest in the chlorthalidone-treated group. An elevated risk for combined cardiovascular disease was seen in the lisinopril group when compared with the chlorthalidone-treated group, relative risk 1.08 (CI 1.00 to 1.17). These beneficial effects were seen with chlorthalidone despite an increased risk of hyperlipidemia, hypokalemia, and onset of diabetes in those treated with chlorthalidone.<sup>14</sup>

The ABCD trial evaluated aggressive control of blood pressure in 950 patients with type 2 diabetes and compared treatment with nisoldipine versus enalapril.<sup>11</sup> The primary end points of the study related to progression of renal disease. The risk of myocardial infarction, a secondary end point, was significantly higher in the nisoldipine-treated group with a relative risk of 5.5 (CI 2.1 to 14.6), whereas blood pressure was equal in the 2 groups.<sup>11,15</sup> The perceived increased risk of myocardial infarction in the nisoldipine group may be due to a decreased risk of myocardial infarction in the enalapril-treated group. A subset study of the 470 patients with existing hypertension was separated from the entire study population and results reported in a later publication. Renal function, as measured by creatinine clearance, was stabilized in both the intensive and the moderate control groups regardless of therapy with either nisoldipine or enalapril. In those patients with overt albuminuria, creatinine clearance declined steadily regardless of intensive or moderate therapy.<sup>12</sup>

The Fosinopril versus Amlodipine Cardiovascular Events Trial was conducted in 380 patients with type 2 diabetes and hypertension (systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg) to compare the effect of the 2 agents on serum lipids and diabetes control. Cardiovascular events in the 2 groups were compared as secondary end points. Amlodipine was found to control systolic blood pressure to a greater extent than fosinopril with similar reductions in diastolic blood pressure seen between the 2 agents. However, the combined cardiovascular events end point had a relative risk in the fosinopril group of 0.49 (CI 0.26 to 0.95) when compared with the amlodipine

group. In addition, although not statistically significant, other adverse end points were seen less often in the fosinopril group. Because this trial was not powered to robustly compare the vascular event risk for the 2 agents, the authors suggest further trials are needed to delineate these differences.<sup>16</sup> That comparison, on a class basis, was completed in the ALLHAT.<sup>14</sup>

ACE-inhibitor therapy (enalapril or lisinopril) was again compared with calcium-channel blocker therapy (felodipine or isradipine) in the Swedish Trial in Old Patients with Hypertension-2 that included 6600 patients aged 70 to 84 years with blood pressures  $\geq 180$  mmHg systolic and  $\geq 105$  mmHg diastolic. In addition,  $\beta$ -blocker therapy (atenolol, metoprolol, or pindolol) with diuretics was also compared. Efficacy in reducing blood pressure was equal in all groups as was the risk for cardiovascular events or total mortality. The end point of myocardial infarction was seen more commonly in patients receiving the calcium-channel blocker than the ACE inhibitor.<sup>17</sup>

The UKPDS compared intensive therapy (goal blood pressure  $< 150/< 85$  mmHg) with either captopril or atenolol with a less intensively controlled group (goal blood pressure  $< 180/< 105$  mmHg) that was treated but avoided the use of ACE inhibitors or  $\beta$ -blockers. Overall, intensive control resulted in a reduction in risk for diabetes and cardiovascular end points as mentioned above.<sup>10</sup> UKPDS 39 reported the results of the captopril versus enalapril analysis. Both agents were found to have a similar effect on blood pressure, and both resulted in a similar reduction in the risk of macrovascular end points. The study concluded that it was the blood pressure end point and not the pharmacologic intervention that is critical in reducing complications in the patients with hypertension and diabetes.<sup>18</sup> The findings of UKPDS are in contrast to the results of the Captopril Prevention Project, which compared captopril to  $\beta$ -blockers with the potential addition of diuretics. In that trial, equivalent results were seen in blood pressure reduction. However, among patients with diabetes, significant risk reductions were seen in the captopril-treated group for all-cause mortality, cardiovascular events, and myocardial infarction.<sup>19</sup>

Two recent trials have evaluated angiotensin II receptor blockade in patients with diabetes. The Irbesartan Diabetic Nephropathy Trial (IDNT) compared irbesartan with amlodipine and placebo in 1715 patients with type 2 diabetes and nephropathy. Target blood pressure was  $< 135/85$  mmHg. The primary end point of the trial was a composite of a doubling of serum creatinine, development of end-stage renal disease, or death from any cause. A secondary cardiovascular composite end point was also reported.

Irbesartan resulted in a risk reduction of 20% when compared with placebo (unadjusted relative risk 0.80 [0.66-0.97,  $P = .02$ ]) and a 23% reduction when compared with amlodipine in the composite endpoint (unadjusted relative risk 0.77 [0.63-0.93,  $P = .006$ ]), whereas blood pressure in the 2 treatment arms was essentially the same. Blood pressure in the placebo arm was significantly higher. The risk of the secondary cardiovascular outcome was similar in all 3 groups, with no significant difference seen between the groups. The authors concluded that irbesartan was effective in reducing the progression of nephropathy in patients with type 2 diabetes and that the effect was not dependent on blood pressure reduction.<sup>20</sup> The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial evaluated the effect of losartan versus atenolol on cardiovascular morbidity and mortality in patients diagnosed with hypertension and left ventricular hypertrophy. A subset of the trial population, 1195 patients with diabetes, was analyzed separately after a mean follow-up of 4.7 years. The risk of the primary end point (a composite of cardiovascular mortality, stroke, and myocardial infarction) was reduced in the losartan group (relative risk 0.76 [95% CI 0.58-0.98;  $P = .031$ ]) when compared with the atenolol group. Death from cardiovascular disease and all-cause mortality was also reduced in the losartan-treated patients. Hospitalization due to heart failure was also less likely in the losartan-treated patients. As in the IDNT, blood pressure reductions were similar in the 2 treatment arms. The authors concluded that losartan's beneficial effect might have resulted from antagonism of the detrimental effects of angiotensin II, which was not seen in the atenolol arm. Furthermore, the greater efficacy of losartan in reversing left ventricular hypertrophy may play a role in the beneficial effects seen with losartan.<sup>21</sup>

## RECOMMENDATIONS FOR THE PHARMACIST

### Focus on Blood Pressure Goals

The determination of the most appropriate therapy for the patient with diabetes and hypertension must first focus on control of blood pressure. As has been outlined above, the current goal of  $< 130/80$  mmHg for the patient with diabetes and hypertension is well supported in the literature. Far too often, the clinician, physician, or pharmacist fails to recognize that achievement of the outcomes documented in the clinical trials discussed above depends on aggressive adherence to the stated goals. Reaching a plateau in therapy that is between the initial elevated blood pressure

and the goals presented in clinical trials and systematic reviews will generally ensure that projected outcomes are only partially achieved. Furthermore, the pharmacist must recognize the significance of his or her contact with the patients, to remind them of the importance of compliance with the antihypertensive regimen, to reiterate the consequences of poor control, to determine if untoward effects may be limiting adherence, and to act as a liaison with the prescriber. It has been recently shown that the pharmacist can have a profound effect on the achievement of outcomes in the management of hypertension.<sup>22,23</sup>

### Identify Appropriate Nonpharmacologic Interventions

The JNC VII guidelines are clear with regard to initiation of therapy, for the patient with hypertension and diabetes. Those patients with diabetes classified in the prehypertension category should be treated with lifestyle modifications and medications in contrast to those without diabetes, in which case lifestyle modifications alone are appropriate initial interventions. It is important that the pharmacist not overlook the significant benefit that lifestyle modifications may provide in the management of hypertension. Rigorous adherence to lifestyle modification may result in a blood pressure lowering of up to 20 mmHg in systolic blood pressure, replacing the need to increase dosages or to add a second or third agent to a regimen.<sup>6</sup>

### Pharmacologic Regimens Must Reflect the Clinical Evidence

JNC VII states that thiazide diuretics,  $\beta$ -blockers, ACE inhibitors, ARBs, and the calcium-channel blockers have all been shown to be effective in reducing cardiovascular death and stroke in patients with hypertension and diabetes.<sup>6</sup> Clearly, the ACE inhibitors have been shown to be beneficial, with improvement in both cardiovascular outcomes and renal outcomes documented. The ALLHAT also demonstrated a role for diuretics in the management of the black patient with diabetes and hypertension.<sup>14</sup> The LIFE trial has demonstrated that direct antagonism of the angiotensin II receptor may improve cardiac outcomes.<sup>21</sup> And, as was seen in several studies, the beneficial effect of either the ACE inhibitors or the ARBs may be independent of blood pressure reduction.<sup>5,20,21</sup> Furthermore, ACE inhibition has been shown to reduce the risk of cardiovascular complications when compared with either calcium-channel blockers or  $\beta$ -blockers.<sup>9,10,15,16,18</sup> Clearly, the calcium-channel blockers should be re-

served for second- or third-line agents. Nephropathy or microalbuminuria should be treated with an ACE inhibitor in patients with type 1 diabetes, and either an ACE inhibitor or an ARB can be used in the management of patients with type 2 diabetes to reduce progression of nephropathy. Therefore, the pharmacist can play a critical role in the management of the patient with hypertension and diabetes by ensuring that either an ACE inhibitor or an ARB is prescribed, unless a contraindication exists.

### SUMMARY

Hypertension and diabetes are common disease states that are frequently found concomitantly in patients. Their pathologic effects are profound individually and additively when seen as comorbidities. Because of the additive morbidity and mortality, the clinician must be aware of current management guidelines and the importance of aggressive therapy and monitoring. The unique benefits seen with antagonism of the RAAS, beyond simply a reduction in blood pressure, suggest that blood pressure may be only a surrogate marker for other pathologic processes. It is imperative that all clinicians managing this unique population be aware of the continually emerging clinical trial data and treatment goals. Significant reductions in cardiovascular and diabetes-related outcomes have been seen with aggressive interventions. This level of care must be considered for all patients with hypertension and diabetes.

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