Step Care Therapy for Hypertension in Diabetic Patients

JOSEPH L. BLACKSHEAR, MD, AND GARY L. SCHWARTZ, MD

For diabetic patients, a goal blood pressure lower than 130/80-85 mm Hg is strongly supported by clinical trial results. We review the agents, sequence, and dosing used in clinical trials and propose a treatment algorithm. Multiaagent antihypertensive therapy is required to attain goal blood pressure in most patients. Step sequences to obtain this goal are suggested. In general, we favor initial therapy with an angiotensin-converting enzyme inhibitor, followed by the addition of a diuretic. The presence of comorbid conditions may dictate variation from this scheme. The effect of antihypertensive agents on established cardiovascular diseases, proteinuria, renal function, and metabolic factors is discussed. Tailored recommendations for specific clinical scenarios are described.

A large clinical trial base with hard cardiovascular end points supports a blood pressure goal lower than 130/80-85 mm Hg in diabetic patients with hypertension. Attempts of the recently published United Kingdom Prospective Diabetes Study (UKPDS) to attain “tight” blood pressure control, a goal of 150/85 mm Hg, necessitated the use of at least 2 medications in 60% of the patients and at least 3 medications in approximately 30%. In the Hypertension Optimal Treatment (HOT) study, 5 titration steps were used in an attempt to attain randomized goal diastolic blood pressures of ≤90, ≤85, and ≤80 mm Hg. After 6 months, 48%, 59%, and 66% of patients, respectively, were taking at least 2 medications (8.4% were diabetic patients). This suggests that achievement of a blood pressure goal lower than 130/80-85 mm Hg requires combination therapy in most diabetic patients with hypertension. Long-standing concern about the possible adverse metabolic effects of some antihypertensive medications on glycemic control in diabetic patients inhibits implementation of multidrug therapy. The evidence base now suggests that achieving the blood pressure goal is more important than the effects of certain drugs on glycemic control or controversies surrounding which agent should be prescribed first.

Buried in the methods sections of recent trials are the agents, doses, and sequences that successfully reduced cardiac events. Our objective is to summarize these data and to suggest step sequences. Although most of these trials studied patients with type 2 diabetes mellitus, inferences can be generalized to diabetic patients regardless of type of disease. We consider the implications of the recently published Heart Outcomes Prevention Evaluation (HOPE), in which the angiotensin-converting enzyme (ACE) inhibitor ramipril, when used in diabetic and nondiabetic patients with cardiovascular risk factors but without either heart failure or known left ventricular systolic dysfunction, significantly reduced death, myocardial infarction, stroke, coronary revascularization, and diabetic complications.

PLACEBO, TREATMENT INTENSITY, AND COMPARATIVE STUDIES

Placebo-controlled studies include the Systolic Hypertension in the Elderly Program (SHEP) and the Systolic Hypertension in Europe (Syst-Eur) studies, in which substantial benefits to diabetic subgroups were noted (Table 1). Intensity-of-therapy studies include UKPD5 and HOT, in which treatment intensity improved outcome (Table 1). In HOT, after an average follow-up of 3.8 years, 42% of patients received an ACE inhibitor, 28% a β-blocker, and 22% a diuretic. Importantly, although the achieved blood pressures in the diabetic patients targeted to ≤90 and ≤80 mm Hg differed by only 4 mm Hg, the relative difference in cardiovascular events was 50%. The Appropriate Blood Pressure Control in Diabetes (ABCD) trial result was...
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>No. of patients</th>
<th>Goal blood pressure (mm Hg)</th>
<th>Step therapy (mg)†</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syst-Eur†</td>
<td>PC</td>
<td>544</td>
<td>Decrease SBP 20 or SBP ≤150</td>
<td>1. Nitrendipine, 10-40 qd 2. Enalapril, 5-20 qd, or captopril, 12.5-25 qd-bid 3. Hydrochlorothiazide, 12.5-25 qd-bid</td>
<td>70% decrease in all major events</td>
</tr>
<tr>
<td>Syst-China‡</td>
<td>PC</td>
<td>583</td>
<td>Decrease SBP 20</td>
<td>1. Chlorthalidone, 12.5-25 qd 2. Atenolol, 25-50 qd 3. Reserpine, 0.05-0.10 qd</td>
<td>34% decrease in major CV events</td>
</tr>
<tr>
<td>HOT‡</td>
<td>INT</td>
<td>1501</td>
<td>DBP ≤90 vs DBP ≤85 vs DBP ≤80‡</td>
<td>1. Felodipine, 5 qd 2. ACE inhibitor or β-blocker 3. Felodipine, 10 qd 4. Double drug in step 2 5. Diuretic</td>
<td>2.06 higher RR of major CV events in ≤90 vs ≤80 mm Hg group</td>
</tr>
<tr>
<td>ABCD‡‡</td>
<td>INT</td>
<td>470</td>
<td>DBP &lt;75 vs DBP 80-89‡</td>
<td>1. Enalapril, 5-40 qd, vs nisoldipine, 10-60 qd† 2. Metoprolol or hydrochlorothiazide 3. Physician’s choice</td>
<td>&lt;75 mm Hg for group; decrease in all-cause mortality from 10.7% to 5.5%</td>
</tr>
</tbody>
</table>

*ABCD = Appropriate Blood Pressure Control in Diabetes; ACE = angiotensin-converting enzyme; bid = twice daily; CV = cardiovascular; DBP = diastolic blood pressure; HOT = Hypertension Optimal Treatment; INT = Intensity of Therapy; PC = placebo controlled; qd = every day; RR = relative risk; SBP = systolic blood pressure; SHEP = Systolic Hypertension in the Elderly Program; SR = sustained release; Syst-China = Systolic Hypertension in China Trial; Syst-Eur = Systolic Hypertension in Europe Trial; tid = 3 times daily; UKPDS = United Kingdom Prospective Diabetes Study.

†Agents added sequentially if goal blood pressure was not achieved.
‡Allocated by randomization.

consistent with the results of UKPDS and HOT, as it also demonstrated the benefit of more intense blood pressure control in diabetic patients.

In contrast to the consistency of benefit in placebo-controlled and intensity-of-therapy trials, the regimen-comparative trials in diabetic patients are less consistent, are reported less completely, and often have confounding influences. Statistical comparisons of varying drug regimens were undertaken in UKPDS, the Swedish Trial in Old Patients with Hypertension-2 (Stop-Hypertension-2), the Captopril Prevention Project (CAPPP), the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET), the Nordic Diltiazem (NORDIL) study, and the Intervention as a Goal in Hypertension Treatment (INSIGHT) study (Table 2). Several criticisms have been raised regarding some of these studies. In ABCD more patients assigned to enalapril required additional treatment with diuretics and β-blockers to achieve control compared with those assigned to nisoldipine. Additionally, more patients assigned to the ACE inhibitor group quit the study because of inadequate blood pressure control. Thus, although the data are valid by intention to treat, there are possible confounding influences of unique actions of the adjunctive therapies used. In CAPPP the results for the group assigned to conventional therapy were not analyzed separately for β-blockers and diuretics, and neither β-blockers nor diuretics were randomly assigned, both of which potentially influenced the results of this study. In FACET neither diuretics nor β-blockers were allowed. The group initially assigned to fosinopril had a 51% relative reduction in any major vascular event (P=.03). Although randomized, FACET has been criticized for being underpowered and unblinded. In INSIGHT only total mortality was presented, and cardiovascular events in the diabetic subgroup have not yet been reported.

**STEP CARE RECOMMENDATIONS**

The available trial data suggest that reduction of blood pressure to target levels is substantially more important than which agent is used first. This strategy appears to be
true regardless of whether minor wrong-way metabolic changes are caused by medication. Several publications have recently reviewed the issue of which agent to use first.\(^2\)\(^-\)\(^6\)\(^,\)\(^25\) The consensus of these reviews is that \(\beta\)-blockers, diuretics, ACE inhibitors, or calcium antagonists can be used first and that combination therapy will frequently be needed to attain a blood pressure goal lower than 130/80-85 mm Hg. Kjeldsen et al\(^{25}\) declined to recommend ACE inhibitors as first-line therapy because patients with uncontrolled hypertension, defined as blood pressure greater than 160/90 mm Hg, were not randomized in HOPE and because the benefits seen in HOPE were not solely attributable to blood pressure reduction. However, the mean entry blood pressure in HOPE\(^{29}\) was 139/79 mm Hg, suggesting

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Goal blood pressure (mm Hg)</th>
<th>Step therapy (mg)†</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>STOP-HTN 2(^{19})‡</td>
<td>719</td>
<td>≤160/95</td>
<td>1A. (\beta)-Blocker or diuretic&lt;br&gt;2A. Diuretic or (\beta)-blocker&lt;br&gt;1B. Felodipine or isradipime, 2.5 qd&lt;br&gt;2B. (\beta)-Blocker&lt;br&gt;1C. Enalapril or lisinopril, 10 qd&lt;br&gt;2C. Hydrochlorothiazide, 12.5-25 qd</td>
<td>No difference in CV mortality; data on stroke, MI not presented</td>
</tr>
<tr>
<td>ABCD(^{15,16})</td>
<td>470</td>
<td>≤75 or 80-89 DBP</td>
<td>1. Enalapril, 5-40 qd, vs nisoldipine, 10-60 qd&lt;br&gt;2. Metoprolol or hydrochlorothiazide&lt;br&gt;3. Physician’s choice</td>
<td>Increase of 5.5 (95% CI, 2.1-14.4) in rate of fatal and nonfatal MI with nisoldipine</td>
</tr>
<tr>
<td>CAPPP(^{20})§</td>
<td>572</td>
<td>≤90 DBP</td>
<td>1. Captopril, 50-100 qd-bid&lt;br&gt;2. Hydrochlorothiazide, 25 qd, or benfluromethaside, 2.5 qd&lt;br&gt;3. Calcium antagonists</td>
<td>41% decrease in fatal/nonfatal MI and other CV death with captopril</td>
</tr>
<tr>
<td>FACET(^{31})</td>
<td>380</td>
<td>≤140/90</td>
<td>1. Fosinopril, 20 qd, vs amlodipine, 10 qd&lt;br&gt;2. Amlodipine, 10 qd, or fosinopril, 20 qd</td>
<td>51% decrease in any major vascular event with fosinopril</td>
</tr>
<tr>
<td>NORDIL(^{22,3})⁄⁄</td>
<td>727</td>
<td>≤98 DBP</td>
<td>1. Diltiazem, 180-360 qd&lt;br&gt;2. ACE inhibitor&lt;br&gt;3. (\beta)-Blocker or diuretic&lt;br&gt;4. Other&lt;br&gt;1. Thiazide or (\beta)-blocker&lt;br&gt;2. (\beta)-Blocker or thiazide&lt;br&gt;3. ACE inhibitor or (\alpha)-blocker&lt;br&gt;4. Other (no calcium antagonist blocker)</td>
<td>No difference in CV end points</td>
</tr>
<tr>
<td>INSIGHT(^{33})</td>
<td>1302</td>
<td>Decrease of 20/10</td>
<td>1. Nifedipine-GITS, 30 qd, vs hydrochlorothiazide, 25 qd, vs amlorilide, 2.5 qd&lt;br&gt;2. Double dose in step 1&lt;br&gt;3. Atenolol, 25 qd, or enalapril, 5 qd&lt;br&gt;4. Double dose in step 3&lt;br&gt;5. Other</td>
<td>No difference</td>
</tr>
</tbody>
</table>

\(^{*}\)CAPPP = Captopril Prevention Project; CI = confidence interval; FACET = Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial; GITS = gastrointestinal transport system; INSIGHT = Intervention as a Goal in Hypertension Treatment; MI = myocardial infarction; NORDIL = Nordic Diltiazem; STOP-HTN-2 = Swedish Trial in Old Patients with Hypertension-2. Other abbreviations are explained in the first footnote to Table 1.

\(^{†}\)Agents added sequentially if goal blood pressure not attained.

\(^{‡}\)Random allocation to groups A through C (1 = first drug used; 2 = second drug used, if needed).

\(^{§}\)Random allocation to standard treatment (\(\beta\)-blocker, diuretic, or both) vs 1 through 3.

\(^{⁄⁄}\)Randomization was steps 1 through 4 in left column vs 1 through 4 in right column.
Table 3. Step Therapy for Hypertension in Diabetic Patients With Comorbid Conditions*

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>New type 2 DM without CVRF/TOD (ISH)</td>
<td>ACE inhibitor or diuretic</td>
<td>Diuretic or ACE inhibitor</td>
<td>β-Blocker or CA</td>
</tr>
<tr>
<td>New type 2 DM with CVRF/TOD† (ISH)</td>
<td>ACE inhibitor</td>
<td>ACE inhibitor and β-blocker CA</td>
<td>CA or β-blocker</td>
</tr>
<tr>
<td>CAD with ischemia</td>
<td>ACE inhibitor and β-blocker</td>
<td>CA</td>
<td>β-Blocker or CA</td>
</tr>
<tr>
<td>CVRF/TOD† (ISH)</td>
<td>Diuretic</td>
<td>Diuretic</td>
<td>CA or β-blocker Other agents</td>
</tr>
<tr>
<td>CAD without ischemia</td>
<td>ACE inhibitor and β-blocker</td>
<td>Diuretic</td>
<td>β-Blocker Other agents</td>
</tr>
<tr>
<td>Prior MI and normal LV function</td>
<td>ACE inhibitor and β-blocker</td>
<td>Diuretic</td>
<td>CA</td>
</tr>
<tr>
<td>CHF or decreased LV function</td>
<td>ACE inhibitor and β-blocker</td>
<td>Loop diuretic ± spironolactone</td>
<td>D-CA</td>
</tr>
<tr>
<td>Proteinuria and normal renal function</td>
<td>ACE inhibitor</td>
<td>ND-CA</td>
<td>Diuretic β-Blocker</td>
</tr>
<tr>
<td>Proteinuria and decreased renal function</td>
<td>ACE§/ inhibitor</td>
<td>Diuretic</td>
<td>ND-CA β-Blocker</td>
</tr>
</tbody>
</table>

*Goal blood pressure <130/80-85 mm Hg. CA = calcium antagonist; CAD = coronary artery disease; CHF = congestive heart failure; CVRF/TOD = cardiovascular risk factors/target organ damage; D-CA = dihydropyridine CA; DM = diabetes mellitus; ISH = isolated systolic hypertension; LV = left ventricular; ND-CA = non-dihydropyridine CA. Other abbreviations are explained in the first footnote to Table 1.

†In patients with diabetes and known CAD, there is a strong impetus to use ACE inhibitors to reduce the likelihood of subsequent CV events. Many of these patients also have a clear indication for β-blockers. Ideally, both are prescribed; if this strategy results in excessively low blood pressure, then either agent or a low-dose combination may be used.

‡Preferred if CAD and ischemia are not controlled.

§Observe potassium and creatinine, discontinue ACE inhibitor if creatinine level doubles from baseline.

¶Use loop diuretic if creatinine level >2 mg/dL or creatinine clearance <30 mg/min; caution must be exercised in attempting use of ND-CA and β-blocker because excessive bradycardia may result.

that most diabetic enrollees had entry blood pressures higher than the current goal blood pressure for diabetic patients. The resultant decrease in morbidity, mortality, and diabetic complications associated with ramipril in HOPE has been mentioned previously. Thus, the ACE inhibitor advantage in reducing cardiovascular adverse events in diabetic patients in ABCD, FACET, and CAPP, along with well-established benefit regarding progression of nephropathy and microalbuminuria, suggests that ACE inhibitors should be used when possible in such patients. Patients may have a condition that dictates use of a different agent first, such as venous insufficiency and peripheral edema (diuretic preferred) or angina, prior myocardial infarction, or tachyarrhythmias (β-blocker preferred) (Table 3). Our general treatment recommendations are listed in the algorithm in Figure 1. We emphasize that low- or medium-dose combination therapy may often be preferred because of the unique attributes of the agents and because of improved patient tolerance. We do not favor maximizing the dose of an agent at each step before another agent is added.

The very elderly diabetic cohort (age ≥75 years) is at increased risk of adverse effects of therapeutics, and lower doses and more intense scrutiny for common adverse effects, such as hepatotoxicity, renal insufficiency, hyponatremia or prerenal azotemia, and excessive bradycardia, are warranted. Orthostatic hypotension may be more problematic in elderly diabetic patients with neuropathy. Nonsteroidal anti-inflammatory agents may attenuate the effects of diuretics and ACE inhibitors, worsen renal function, or aggravate hyperkalemia, and alternatives to these commonly prescribed therapies should be sought for elderly patients.

Step 1—ACE Inhibitors

ACE inhibitors reduce the risk of deterioration of renal function in patients with type 1 diabetes mellitus and nephropathy, reduce proteinuria, improve survival in patients with recent myocardial infarction and reduced left ventricular function, or congestive heart failure with reduced left ventricular function, and decrease diabetic complications independent of an effect on blood pressure. Data also suggest improvement in glycemic control, mediated by improvements in insulin sensitivity. ACE inhibitors have neutral effects on lipid parameters. Angiotensin receptor blockers (ARBs) also reduce diabetic proteinuria, but whether the other cardiovascular protective benefits attributable to ACE inhibitors can also be associated with ARBs is unclear. Thus, we favor use of an ARB only if there is cough intolerance to ACE inhibitors.
Figure 1. General algorithm for management of hypertension in diabetic patients.

*In many patients with congestive heart failure (CHF) due to left ventricular systolic dysfunction, diuretics will already have been prescribed to treat symptoms of fluid overload. Angiotensin-converting enzyme (ACE) inhibitors and β-blockers should then be added for further improvement of symptoms and survival. As noted in the footnote to Table 3, combined β-blocker and ACE inhibitor therapy is likely indicated in patients with known coronary artery disease (CAD), diabetes, and a clear indication for β-blocker use.

AR = angiotensin receptor blocker; BP = blood pressure; MI = myocardial infarction.
†If management of proteinuria is a priority, diltiazem or verapamil may be substituted for the ACE inhibitor and diuretic.

Agents used in the previously cited trials include enalapril, captopril, fosinopril, lisinopril, and ramipril. Caution should be exercised when using these drugs in diabetic patients with baseline potassium values greater than 5.0 mEq/L or those with renal insufficiency. After initiation of therapy, plasma potassium levels up to 5.5 mEq/L may be
observed without intervention; however, greater increases should prompt the addition of a non–potassium-sparing diuretic and serial assessments of potassium. Persistent elevations greater than 5.5 mEq/L should be considered potentially hazardous. Although cough occurs less frequently with ARBs compared to ACE inhibitors, angioedema may complicate therapy with either class of agents. Evidence favoring ACE inhibitors is especially compelling in patients with type 1 diabetes mellitus and nephropathy.

Step 2—Diuretics or β-Blockers Depending on Patient Factors

Comorbidities frequently affect the use of a second agent. In the absence of a need for β-blocker therapy (angina, prior myocardial infarction, congestive heart failure due to systolic dysfunction), we prefer low-dose diuretic therapy. Diuretics are synergistic with ACE inhibitors in reducing blood pressure, probably by increasing renin levels and thus increasing the efficacy of converting enzyme inhibition. In addition, diabetic patients with hypertension appear to have increased exchangeable total body sodium, and their blood pressure may be more susceptible to plasma volume interventions than nondiabetics. ACE inhibition alone is often insufficient to attain goal blood pressures. In the study by Lewis et al., 75% of patients who took captopril required the addition of diuretics by the end of the study to achieve blood pressure control. Thiazides and loop diuretics also reduce the risk of hyperkalemia in diabetic patients treated with ACE inhibitors. Low-dose chlorthalidone as used in SHEP, hydrochlorothiazide, and furosemide as used as the second agent in UKPDS are reasonable choices. When glycemic control is a problem, indapamide or furosemide may be preferred. Spironolactone at low doses may be added to either thiazide or loop diuretic (and background ACE inhibitor) in diabetic patients with congestive heart failure if baseline plasma potassium is 5.0 mEq/L or lower and plasma creatinine is 2.5 mg/dL or lower; however, we advocate post-treatment monitoring of plasma potassium levels to screen for hyperkalemia. A loop diuretic will be required for efficacy if the plasma creatinine level is greater than 2.0 mg/dL or creatinine clearance is lower than 30 mL/min.

In SHEP, diabetic patients treated with chlorthalidone at 12.5–25.0 mg/d had an increase in fasting blood glucose from baseline to 1 year (161±63 to 182±60 mg/dL) vs placebo-treated patients (160±60 to 165±60 mg/dL). Indapamide at doses of 1.25 to 2.5 mg/d has antihypertensive effects equivalent to 12.5 to 25.0 mg of hydrochlorothiazide or chlorthalidone, and based on numerous small studies, it probably has less effect on glycemic control in diabetic patients than does hydrochlorothiazide or chlorthalidone. Furosemide, used as the second step agent in UKPDS at doses of 20 mg/d to 40 mg twice daily, appeared to have little effect on glycemic control. Potassium-sparing diuretics have been used with caution in diabetic patients because of their reduced defenses against hyperkalemia. However, as a group, potassium-sparing diuretics do not worsen glycemic control in diabetic patients. In the Randomized Aldactone Evaluation Study (RALES) of severe congestive heart failure, more than 200 diabetic patients received spironolactone, 12.5 to 50.0 mg/d, in addition to ACE inhibitors and a loop diuretic. No significant increase in the incidence of serious hyperkalemia was observed with use of exclusion criteria at entry of a creatinine level greater than 2.5 mg/dL or serum potassium level greater than 5 mEq/L (B. Pitt, MD, written communication, September 2001). Doses of spironolactone at 25 to 50 mg/d are within the definition of efficacy based on the sixth report of the Joint National Committee, and in the RALES pilot study, a dose of spironolactone at 25 mg/d significantly reduced blood pressure. In the INSIGHT study, the combination of hydrochlorothiazide at 25 mg and amiloride at 2.5 mg was used. In that trial there was more hyperkalemia associated with the combination diuretic therapy than with the nifedipine gastrointestinal transport system. However, the diabetic subset was not reported separately. No hyperkalemia was reported in the primary study. Diuretics as a group may increase low-density lipoprotein cholesterol and triglyceride levels.

Step 3—β-Blockers

As noted previously, evidence supports use of ACE inhibitors in diabetic patients with hypertension to reduce the risk of cardiovascular events, the leading cause of death among such patients. The extensive literature on secondary prevention of mortality with β-blockers in patients with prior myocardial infarction, the importance of β-blockers in relieving angina and reducing mortality in diabetic patients with known coronary disease, and the improved survival in those with congestive heart failure and left ventricular systolic dysfunction also make β-blocker therapy highly desirable in diabetic patients with these coronary diagnoses. For these reasons, optimal therapy includes both agents, unless the combination results in excessive lowering of blood pressure (Table 3). In addition, despite the apparent adverse metabolic consequences of atenolol vs captopril therapy in UKPDS (discussed subsequently), comparisons of these 2 agents head-to-head in UKPDS showed a slight but not significant favorable trend for atenolol.

β-Blockers increase the risk of the development of diabetes in a hypertensive population, worsen glycemic control in diabetic patients with hypertension, and may
increase triglyceride and low-density lipoprotein cholesterol levels and reduce high-density lipoprotein cholesterol levels. β-Blockers may also impair awareness of hypoglycemia and delay recovery from hypoglycemia. It is likely that selective β<sub>1</sub>-blocking agents cause less metabolic derangement compared to nonselective agents. In UKPDS<sup>18</sup> glycemic control after 4 years was adversely affected by atenolol vs captopril, with average hemoglobin A<sub>1c</sub> values of 7.5%±1.4% in the atenolol group and 7.0%±1.4% in the captopril group. The atenolol-assigned patients also frequently required the addition of a second oral hypoglycemic medication compared with the captopril group. Carvedilol, a nonselective β-blocker with α-antagonist properties (which theoretically improve carbohydrate metabolism) at a dose of 25 mg/d was compared to atenolol at 50 mg/d. Atenolol-treated patients had a 0.3% increment in glycosylated hemoglobin over 3 months vs a 0.1% decrement for carvedilol-treated patients. Other measures of glycemic control changed directionally in a similar fashion. The least adverse effect on glycemic control appears to be a subclass effect of all combined β- and α-antagonists.<sup>45,46</sup> In general we favor selective β<sub>1</sub>-blockers, or, if metabolic control of diabetes is particularly problematic, carvedilol because it produces less aggravation of hyperglycemia and hyperlipidemia.

**Step 4—Calcium Blockers**

Amlodipine, nisoldipine, nifedipine and gastrointestinal transport system (all 3 dihydropyridine-type calcium blockers), and diltiazem (nondihydropyridine) have all recently been used in large-scale clinical trials. In a placebo-controlled study (Syst-Eur),<sup>12</sup> the dihydropyridine calcium antagonist nifedipine showed a benefit in patients with type 2 diabetes mellitus. In ABCD<sup>35</sup> nisoldipine was associated with an increase in myocardial infarction compared with enalapril.

Nondihydropyridine calcium antagonists, including verapamil, appear to reduce microalbuminuria in proportion with their blood pressure reduction.<sup>47</sup> They appear to have no effect on glycemic control or lipid levels. The nondihydropyridine calcium antagonists verapamil and diltiazem, which also lower heart rate, when used in combination with ACE inhibitors may provide additional protection to the kidneys in diabetic patients with nephropathy.<sup>48</sup>

**Other Agents and Combinations**

In a small minority of diabetic patients with hypertension, more than 4 agents may be necessary. A second diuretic, central α-antagonist, angiotensin II receptor blocker, or direct vasodilator may be used. Numerous single-pill antihypertensive drug combination preparations are available.<sup>1</sup>

**CONCLUSIONS**

A large body of clinical trial data has shown the importance of reduced blood pressure to target levels in diabetic patients for the prevention of cardiovascular morbidity and mortality. These trials have generally used step care approaches to attain goal blood pressure, a goal that was a higher level than the currently recommended goal of lower than 130/80-85 mm Hg. Attainment of the new goal blood pressure clearly requires combination therapy in most patients. Unique metabolic benefits of agents such as ACE inhibitors should be exploited when possible, and the choice of drug should be tailored to important comorbid conditions. Minor adverse metabolic consequences of agents such as diuretics and β-blockers may be tolerated or circumvented, and they should not preclude use of such agents because the reduction of blood pressure is clearly worth the cost in improved outcomes. Several comparative clinical trials are now under way in which more than 30,000 diabetic patients with hypertension have been randomized.<sup>25</sup> These should offer further guidance about initial and subsequent step therapies.

**REFERENCES**


Questions About Step Care Therapy for Hypertension in Diabetic Patients

1. Which one of the following is true regarding goal blood pressure in diabetic patients with hypertension?
   a. Systolic <160 mm Hg
   b. <145/90 mm Hg
   c. <130/80-85 mm Hg
   d. Diastolic <90 mm Hg
   e. Diastolic <85 mm Hg

2. Which one of the following is the primary consideration in managing diabetic hypertension?
   a. Effect of therapy on glycemic control
   b. Effect of therapy on lipid metabolism
   c. Effect of therapy on heart rate
   d. Attainment of goal blood pressure
   e. Limiting therapy to a single antihypertensive agent

3. Which one of the following conditions in a diabetic patient does not mandate use of a β-blocker as a preferred component of an antihypertensive regimen?
   a. Congestive heart failure due to left ventricular systolic dysfunction
   b. Prior myocardial infarction
   c. Exertional angina
   d. Microalbuminuria
   e. Silent myocardial ischemia

4. Which one of the following statements about management of diabetic hypertension is false?
   a. Most patients require at least 2 agents to attain goal blood pressure
   b. ACE inhibitors likely provide unique cardiovascular protective benefits to diabetic patients beyond their ability to lower blood pressure
   c. The choice of antihypertensive agent(s) is more important than the intensity of treatment
   d. Diuretics are particularly useful because increased total body sodium is documented in diabetic patients with hypertension
   e. Selective β₁-blockers appear to have less adverse metabolic effects on diabetic patients compared with nonselective β-blockers

5. Which one of the following cautionary statements regarding diabetic hypertension is false?
   a. Use of combined nondihydropyridine calcium antagonist and β-blockers may slow heart rate excessively
   b. Plasma creatinine should be reassessed when ACE inhibitor therapy is initiated in diabetic patients in whom renal function is reduced at baseline
   c. Hyperkalemia is a potential problem related to β-blockers and calcium antagonists
   d. Hyperkalemia is a potential problem with ACE inhibitors, and this tendency can be offset by using combination therapy with a thiazide (normal renal function) or loop diuretic (compromised renal function)
   e. Cough may limit the use of ACE inhibitor therapy

Correct answers:
1. c, 2. d, 3. d, 4. c, 5. c