High Blood Pressure and Diabetes Mellitus

Are All Antihypertensive Drugs Created Equal?

Ehud Grossman, MD; Franz H. Messerli, MD; Uri Goldbourt, PhD

Objective: To analyze the available data to assess the benefits of antihypertensive therapy in hypertensive patients with diabetes mellitus.

Methods: A MEDLINE search of English-language articles published until June 1999 was undertaken with the use of the terms diabetes mellitus, hypertension or blood pressure, and therapy. Pertinent articles cited in the identified reports were also reviewed. Included were only prospective randomized studies of more than 12 months’ duration that evaluated the effect of drug treatment on morbidity and mortality in diabetic hypertensive patients. We estimated the risk associated with combination of diabetes mellitus and hypertension and the effect of treatment on morbidity and mortality.

Results: The coexistence of diabetes mellitus doubled the risk of cardiovascular events, cardiovascular mortality, and total mortality in hypertensive patients (approximate relative risk of 1.73-2.77 for cardiovascular events, 2.25-3.66 for cardiovascular mortality, and 1.73-2.18 for total mortality). Intensive blood pressure control to levels lower than 130/85 mm Hg was beneficial in diabetic hypertensive patients. All 4 drug classes—diuretics, β-blockers, angiotensin-converting enzyme inhibitors, and calcium antagonists—were effective in reducing cardiovascular events in diabetic hypertensive patients. In elderly diabetic patients with isolated systolic hypertension, calcium antagonists reduced the rate of cardiac end points by 63%, stroke by 73%, and total mortality by 55%. In more than 60% of diabetic hypertensive patients, combination therapy was required to control blood pressure.

Conclusions: Intensive control of blood pressure reduced cardiovascular morbidity and mortality in diabetic patients regardless of whether low-dose diuretics, β-blockers, angiotensin-converting enzyme inhibitors, or calcium antagonists were used as a first-line treatment. A combination of more than 1 drug is frequently required to control blood pressure and may be more beneficial than monotherapy.

Arch Intern Med. 2000;160:2447-2452
METHODS

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We included only prospective randomized studies of more than 12 months’ duration that compared the effects of active treatment with placebo, or 2 active treatments with placebo, and evaluated the effects of drug treatment on morbidity and mortality in diabetic hypertensive patients. For each trial, we retrieved the following data: patients’ baseline characteristics, follow-up period, decrease in BP, percentage of patients continuing to receive monotherapy, and the incidence of morbidity and mortality. The following categories were used to classify outcome: coronary heart disease included fatal and nonfatal myocardial infarction and sudden cardiac death; cerebrovascular events included fatal and nonfatal stroke and transient ischemic attacks; and cardiovascular mortality included coronary heart disease and cerebrovascular mortality. In some studies, information could not be fully assessed or was not reported.

We also tried to estimate the risk associated with the combination of diabetes mellitus and hypertension. The target levels of BP were also determined for diabetic hypertensive patients.

RESULTS

RISK OF HYPERTENSION AND DIABETES MELLITUS

Results derived from the placebo groups in prospective studies in the elderly showed that the risk of stroke, cardiovascular, and all-cause mortality are doubled in diabetic hypertensive patients when compared with non-diabetic patients (Table 1).15,17-19 In the Hypertension Optimal Treatment (HOT) study, 501 hypertensive diabetic patients aged 50 to 80 years, allocated to a target diastolic BP of 90 mm Hg or less, had a 2.5-fold increase in the rate of stroke compared with 5763 nondiabetic patients (Table 1).20 Similarly, Tuomilehto et al21 showed that diabetes increased the risk of death from stroke remarkably, particularly in women. In the Framingham study, the combination of diabetes and hypertension increased the risk of poor cognitive performance.22 Aromaa et al14 followed up for 6 years a group of 139 diabetic and 8725 nondiabetic Finnish men, aged 40 to 64 years, initially free of coronary vascular disease. The age-adjusted risk of death was 1.93 in hypertensive nondiabetic patients and 2.99 in hypertensive diabetic patients relative to normotensive nondiabetic subjects, and for cardiovascular death it was 2.62 and 4.69, respectively. Elevated BP has been identified as a major risk factor in progression of diabetic nephropathy.23 The risk of retinopathy, left ventricular hypertrophy, and cardiovascular morbidity and mortality is also doubled in hypertensive patients when diabetes is present.24-29

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GOAL BP LEVELS IN DIABETIC PATIENTS

Guidelines recommended lowering BP to less than 130/85 mm Hg in diabetic patients.9,30 This recommendation was mainly based on the evidence from trials of the effect of lowering BP on renal function in diabetic patients with or without renal disease.6,8,31-33 However, only recently it has become evident that lowering BP to these and even lower levels indeed reduced significantly the risk of cardiovascular morbidity and mortality. In the HOT study,20 there was evidence that, in hypertensive patients with diabetes, lowering BP to the lowest target level (diastolic BP, ≤80 mm Hg) resulted in 51% reduction in major cardiovascular events compared with the target group of 90 mm Hg or less. Comparing the rate of events in diabetic vs nondiabetic hypertensive patients in the groups with a target diastolic BP of 80 mm Hg or less and 90 mm Hg or less showed a remarkable benefit in terms of cardiovascular and total mortality in the group with the low target BP (Table 2), even though the BP differences were considerably smaller than anticipated. These findings were supported by the recent findings from the UKPDS.3 This latter study showed that tight control of BP in hypertensive patients with type 2 diabetes (average of 144/82 mm Hg in the tight control group vs 154/87 mm Hg in the less tight control group) was associated with a reduction of 37% in microvascular end points and 44% in the risk of stroke events.

PROSPECTIVE STUDIES AMONG DIABETIC HYPERTENSIVE PATIENTS

We identified 8 studies that reported outcome in diabetic hypertensive patients (Table 3). Three studies compared the effects of 2 active treatments in diabetic hypertensive patients13,14,34 and 1 study reported the effects of intensive BP lowering in diabetic hypertensive patients.20 Four additional prospective, randomized, double-blind studies compared the effects of active treatment with placebo on morbidity and mortality in diabetic hypertensive patients.5,15-19 Systolic Hypertension in the Elderly Program compared a diuretic (chlorthalidone) with placebo,17 Syst-Eur and Systolic Hypertension in China (Syst-China) compared a dihydropyridine calcium antagonist (nitrendipine) with placebo,15,18,19 and UKPDS5,16 compared tight BP control with either captopril or atenolol vs less tight control of BP.

In 2 studies that compared calcium antagonists with ACE inhibitors, a significantly higher incidence of cardiovascular events was observed in patients assigned to captopril than those assigned to conventional treatment.34 In the HOT study,
lowering BP to a diastolic target level of 80 mm Hg or less with calcium antagonist–based therapy lowered cardiovascular events by 51%.20

In all 4 prospective, randomized, double-blind studies that compared the effects of active treatment with placebo,5,15-19 antihypertensive treatment reduced cardiac end points, stroke, and total mortality (Table 5). A comparison between the study results is of questionable validity because the studies differed in the inclusion criteria, initial BP, age, and time of follow-up. However, it seems that all 4 drugs effectively reduced cardiovascular events and mortality. The profile of adverse effects of all drugs was comparable (Table 6).

The coexistence of hypertension and diabetes almost doubles the risk of cardiovascular events.15,17,37,39 Data from the Hypertension Detection and Follow-up Program showed that 5-year mortality rates were 1.5 to 1.8 times higher for hypertensive patients with evidence of diabetes than for those without.37 Intensive lowering of BP in diabetic hypertensive patients is associated with significantly reduced risks of cardiovascular events and total mortality.5,20 In these patients, intensive BP control is more beneficial than tight glucose control.5,36 Thus, even drugs that partially impair glucose control can reduce cardiovascular morbidity and mortality if they lower BP effectively. The ACE inhibitors were considered the drugs of choice in diabetes-hypertension since they have beneficial effects on renal function above and beyond those simply due to BP control.10,12,37,39

An ACE inhibitor, lisinopril, also has been shown to slow the progression of renal disease in normotensive insulin-dependent diabetic patients, even if they have no albuminuria.12 In a meta-analysis of 100 studies providing data on renal function, proteinuria, or both, before and after treatment with an antihypertensive agent, Kasiske et al40 showed that ACE inhibitors decreased proteinuria independent of changes in BP, treatment duration, and the type of diabetes or stage of nephropathy. Indeed, 2 studies published recently showed that ACE inhibitors are superior to calcium antagonists in reducing cardiovascular events in diabetic hypertensive patients.13,14 However, both studies have some weaknesses that make the conclusions doubtful. In the Appropriate Blood Pressure Control in Diabetes study,14 significantly more patients assigned to enalapril maleate required additional therapy with diuretics and β-blockers than those assigned to the calcium antagonist. Moreover, significantly more patients in the enalapril group discontinued the study because of uncontrolled BP. The Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial13 was small, uncontrolled, and open labeled and has been extensively criticized.31

Unlike these studies, the results from the HOT study20 showed that, in diabetic-hypertensive patients, lowering BP with calcium antagonist–based therapy lowered the risk of cardiovascular events. This study did not compare the results of calcium antagonist–based therapy with results of a placebo or another treatment but showed that calcium antagonist–based antihypertensive treatment was effective in diabetic hypertensive patients. The Captopril Prevention Project was designed to show the superiority of captopril over conventional therapy with β-blockers and diuretics in diabetic hypertensive patients. The Captopril Prevention Project did not show the superiority of captopril over conventional therapy with β-blockers and diuretics in diabetic hypertensive patients. However, the results for the group assigned to conventional therapy were not analyzed separately for β-blockers and diuretics, and it is known that, at least in elderly hypertensive patients, diuretics are superior to β-blockers.52 Moreover, patients assigned to captopril re-

### Table 1. Risk of Cardiovascular Morbidity and Mortality in Elderly Diabetic Hypertensive Patients

<table>
<thead>
<tr>
<th>Risk</th>
<th>Nondiabetic</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac end points</td>
<td>1.30</td>
<td>1.74</td>
</tr>
<tr>
<td>All cardiovascular events</td>
<td>2.07</td>
<td>2.25</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.02</td>
<td>2.54</td>
</tr>
<tr>
<td>Total mortality</td>
<td>1.73</td>
<td>2.18</td>
</tr>
<tr>
<td>No. of patients</td>
<td>2057</td>
<td>240</td>
</tr>
</tbody>
</table>

### Table 2. Effect of Intensive Blood Pressure Lowering on the Risk of Diabetic Hypertensive Patients (HOT Study20)

<table>
<thead>
<tr>
<th>Risk</th>
<th>Nondiabetic</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>2.00</td>
<td>2.25</td>
</tr>
<tr>
<td>No. of patients</td>
<td>5763</td>
<td>501</td>
</tr>
</tbody>
</table>

### Comment

The coexistence of hypertension and diabetes almost doubles the risk of cardiovascular events. Data from the Hypertension Detection and Follow-up Program showed that 5-year mortality rates were 1.5 to 1.8 times higher for hypertensive patients with evidence of diabetes than for those without. Intensive lowering of BP in diabetic hypertensive patients is associated with significantly reduced risks of cardiovascular events and total mortality. In these patients, intensive BP control is more beneficial than tight glucose control. Thus, even drugs that partially impair glucose control can reduce cardiovascular morbidity and mortality if they lower BP effectively. The ACE inhibitors were considered the drugs of choice in diabetes-hypertension since they have beneficial effects on renal function above and beyond those simply due to BP control.

An ACE inhibitor, lisinopril, also has been shown to slow the progression of renal disease in normotensive insulin-dependent diabetic patients, even if they have no albuminuria. In a meta-analysis of 100 studies providing data on renal function, proteinuria, or both, before and after treatment with an antihypertensive agent, Kasiske et al showed that ACE inhibitors decreased proteinuria independent of changes in BP, treatment duration, and the type of diabetes or stage of nephropathy. Indeed, 2 studies published recently showed that ACE inhibitors are superior to calcium antagonists in reducing cardiovascular events in diabetic hypertensive patients. However, both studies have some weaknesses that make the conclusions doubtful. In the Appropriate Blood Pressure Control in Diabetes study, significantly more patients assigned to enalapril maleate required additional therapy with diuretics and β-blockers than those assigned to the calcium antagonist. Moreover, significantly more patients in the enalapril group discontinued the study because of uncontrolled BP. The Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial was small, uncontrolled, and open labeled and has been extensively criticized.

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received diuretics if their BP did not reach the goal. Therefore, one cannot firmly conclude from the Captopril Prevention Project that ACE inhibitors are superior to either β-blockers or diuretics in diabetic hypertensive patients. The ACE inhibitors and calcium antagonists were recently found to be as effective as the conventional therapy in reducing morbidity and mortality in diabetic patients, but the results were not analyzed separately for β-blockers and diuretics.

The results from the 4 large prospective studies showed that diuretics, ACE inhibitors, β-blockers, and calcium antagonists effectively reduced morbidity and mortality in diabetic hypertensive patients. The UKPDS recruited relatively young patients with hypertension and type 2 diabetes and followed them up for 8 years, while the other studies recruited elderly patients with isolated systolic hypertension and followed them up for a shorter period. A statistical comparison between the studies was therefore not deemed to be appropriate, but it seems that, in elderly diabetic patients with isolated systolic hypertension, calcium antagonist-based treatment gives good protection against cardiovascular events. It must be emphasized, however, that any reduction of events is dependent on the absolute

### Table 3. Studies in Diabetes With Hypertension*

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>No. of Patients</th>
<th>Age, Mean, y</th>
<th>Follow-up, y</th>
<th>Initial BP, Mean, mm Hg</th>
<th>Change in BP, Mean, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCD14</td>
<td>Enalapril maleate</td>
<td>235</td>
<td>57.7</td>
<td>5</td>
<td>156/98</td>
<td>NA</td>
</tr>
<tr>
<td>FACET13</td>
<td>Nisoldipine</td>
<td>235</td>
<td>57.2</td>
<td>3.5</td>
<td>155/98</td>
<td>13/8</td>
</tr>
<tr>
<td></td>
<td>Fosinopril sodium</td>
<td>189</td>
<td>62.8</td>
<td>3.5</td>
<td>170/95</td>
<td>19/8</td>
</tr>
<tr>
<td></td>
<td>Amlodipine besylate</td>
<td>191</td>
<td>63.3</td>
<td>3.5</td>
<td>171/94</td>
<td>NA</td>
</tr>
<tr>
<td>HOT22</td>
<td>Felodipine</td>
<td>1501</td>
<td>61.5</td>
<td>3.8</td>
<td>170/105</td>
<td>4/4†</td>
</tr>
<tr>
<td>CAPP34</td>
<td>Captopril</td>
<td>309</td>
<td>55.0</td>
<td>6.1</td>
<td>163.6/97.1</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>β-Blocker or diuretic</td>
<td>263</td>
<td>55.7</td>
<td>6.1</td>
<td>163.3/97.3</td>
<td>NA</td>
</tr>
<tr>
<td>SHEP17</td>
<td>Chlorthalidone</td>
<td>283</td>
<td>70.2</td>
<td>2</td>
<td>170.2/76.9</td>
<td>9.8/2.2‡</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>300</td>
<td>70.5</td>
<td>2</td>
<td>170.2/74.8</td>
<td></td>
</tr>
<tr>
<td>Syst-Eur15</td>
<td>Nitrendipine</td>
<td>252</td>
<td>≥60</td>
<td>2</td>
<td>175.3/84.5</td>
<td>8.6/3.8‡</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>240</td>
<td>≥60</td>
<td>2</td>
<td>175.3/84.5</td>
<td></td>
</tr>
<tr>
<td>Syst-China18,19</td>
<td>Nitrendipine</td>
<td>51</td>
<td>≥60</td>
<td>3</td>
<td>172.5/86.0</td>
<td>6.0/4.7‡</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>47</td>
<td>≥60</td>
<td>3</td>
<td>172.5/86.0</td>
<td></td>
</tr>
<tr>
<td>UKPDS5,16</td>
<td>Captopril</td>
<td>400</td>
<td>56.3</td>
<td>8.4</td>
<td>159/94</td>
<td>9/4‡</td>
</tr>
<tr>
<td></td>
<td>Atenolol</td>
<td>358</td>
<td>56.0</td>
<td>8.4</td>
<td>159/93</td>
<td>10/5‡</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>390</td>
<td>56.5</td>
<td>8.4</td>
<td>160/94</td>
<td></td>
</tr>
</tbody>
</table>

*BP indicates blood pressure; ABCD, Appropriate Blood Pressure Control in Diabetes Study; NA, not available; FACET, Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial; HOT, Hypertension Optimal Treatment Study; CAPP, Captopril Prevention Project; SHEP, Systolic Hypertension in the Elderly Program; Syst-Eur, Systolic Hypertension in Europe; Syst-China, Systolic Hypertension in China; and UKPDS, UK Prospective Diabetes Study.
†Between the target diastolic blood pressure group of 90 or less and 80 mm Hg or less.
‡Active treatment vs control.

### Table 4. Comparison of Calcium Antagonist and ACE Inhibitors in Diabetic Hypertensive Patients*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCD14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>235</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td>Enalapril</td>
<td>maleate</td>
<td>235</td>
<td>11</td>
</tr>
<tr>
<td>Risk ratio (95% CI)†</td>
<td>5.5 (2.1-14.6)</td>
<td>1.6 (0.6-4.2)</td>
<td>1.3 (0.6-2.8)</td>
</tr>
<tr>
<td>FACET13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine besylate</td>
<td>191</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Fosinopril sodium</td>
<td>189</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Risk ratio (95% CI)†</td>
<td>1.3 (0.57-2.94)</td>
<td>2.56 (0.81-8.30)</td>
<td>1.24 (0.28-5.61)</td>
</tr>
</tbody>
</table>

*ACE indicates angiotensin-converting enzyme; MI, myocardial infarction; ABCD, Appropriate Blood Pressure Control in Diabetes Study; CI, confidence interval; and FACET, Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial.
†Nisoldipine vs enalapril.
‡Amlodipine vs fosinopril.

### Table 5. Reduction of Cardiovascular Morbidity and Total Mortality by Various Drugs*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Cardiac End Points, %</th>
<th>Stroke, %</th>
<th>Total Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor (captopril)5,16</td>
<td>16</td>
<td>40</td>
<td>12</td>
</tr>
<tr>
<td>β-Blocker (atenolol)5,16</td>
<td>27</td>
<td>55</td>
<td>23</td>
</tr>
<tr>
<td>Diuretic (chlorthalidone)7</td>
<td>56</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td>Calcium antagonist (nitrendipine)5,16</td>
<td>69</td>
<td>70</td>
<td>56</td>
</tr>
</tbody>
</table>

*Since patient populations are different in various studies, the benefits conferred by antihypertensive drugs are not directly comparable. ACE indicates angiotensin-converting enzyme.
received either drug alone. Similarly, Bakris et al.44,45 documented that, at comparable BP levels, the combination of an ACE inhibitor and calcium antagonist was strongly recommended to maximally protect the kidney in diabetic hypertensive patients with nephropathy.16,67

We conclude that, in diabetic hypertensive patients, intensive control of BP to levels lower than 130/85 mm Hg reduces the risk of cardiovascular events. All 4 drug classes—diuretics, β-blockers, ACE inhibitors, and calcium antagonists—were effective in reducing morbidity and mortality. Most diabetic hypertensive patients will require combination therapy to achieve goal BP.

Accepted for publication March 17, 2000.

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Table 6. Main Adverse Effects in Diabetic Hypertensive Patients

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>ACEI (n = 635)†</th>
<th>CCB (n = 235)†</th>
<th>Diuretics (n = 283)†</th>
<th>β-Blockers (n = 358)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaise and fatigue</td>
<td>21 (3.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>16 (4.5)</td>
</tr>
<tr>
<td>Edema</td>
<td>11 (1.7)</td>
<td>20 (8.5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gastrointestinal tract disease</td>
<td>9 (1.4)</td>
<td>4 (1.7)</td>
<td>0 (0)</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>6 (0.9)</td>
<td>2 (0.9)</td>
<td>13 (4.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cough</td>
<td>29 (4.6)</td>
<td>8 (3.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>3 (0.5)</td>
<td>2 (0.9)</td>
<td>34 (11.9)</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (0.3)</td>
<td>10 (4.3)</td>
<td>0 (0)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (0.2)</td>
<td>0 (0)</td>
<td>11 (3.9)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (0.2)</td>
<td>1 (0.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>7 (1.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>15 (4.2)</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>22 (6.2)</td>
</tr>
<tr>
<td>Cold and numb hand</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>70 (24.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypokalemia (potassium, &lt;3.2 mmol/L)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6 (2.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hyponatremia (sodium, &lt;130 mmol/L)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>22 (7.9)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*ACEI indicates angiotensin-converting enzyme inhibitors; data based on Appropriate Blood Pressure Control in Diabetes14 and UK Prospective Diabetes16 studies. CCB indicates calcium-channel blockers; data based on the Appropriate Blood Pressure Control in Diabetes14 Study. For diuretics, data are based on the Systolic Hypertension in the Elderly Program.17 For β-blockers, data are based on the UK Prospective Diabetes Study.18
†Number of patients included in the analysis.

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