Antihypertensive Therapy in Diabetic Hypertensive Patients

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Background: We analyzed the available data to assess the benefits of antihypertensive therapy in hypertensive patients with diabetes mellitus.

Procedure: A MEDLINE search of English-language articles published until June 1999 was undertaken using the terms diabetes mellitus, hypertension or blood pressure (BP), and therapy. 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.

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 to 2.77 for cardiovascular events, 2.25 to 3.66 for cardiovascular mortality, and 1.73 to 2.18 for total mortality). Intensive BP control to levels lower than 130/85 mm Hg was beneficial in diabetic hypertensive patients. All four 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 BP.

Conclusions: Intensive control of BP 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. Combination of more than one drug is frequently required to control BP and may be more beneficial than monotherapy. Am J Hypertens 2001;14:12S–16S © 2001 American Journal of Hypertension, Ltd.

Key Words: Diabetes mellitus, cardiovascular morbidity, mortality, hypertension, antihypertensive therapy.
Methods

Data Collection

We searched the MEDLINE database for English-language articles published before May 1999; we used the terms diabetes mellitus, hypertension or BP, and treatment or therapy. Pertinent articles cited in the identified papers were also reviewed.

We included only prospective randomized studies of more than 12 months' duration that compared the effects of active treatment with placebo, or two 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 remaining on monotherapy, and 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 events, and all-cause mortality are doubled in diabetic hypertensive patients when compared with nondiabetic ones (Table 1, Fig. 1). Elevated BP has been identified as a major risk factor in progression of diabetic nephropathy. Elevated BP has been identified as a major risk factor in progression of diabetic nephropathy. The risk of retinopathy, left ventricular hypertrophy, and cardiovascular morbidity and mortality is also doubled in hypertensive patients when diabetes is present.

Goal Blood Pressure Levels in Diabetic Patients

Guidelines recommended lowering BP to below 130/85 mm Hg in diabetic patients. 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.\(^6\)–\(^8\),\(^30\)–\(^32\) However, results from recent studies (Hypertension Optimal Treatment [HOT]\(^{20}\) and UKPDS\(^{5,16}\)) suggest that lowering BP in diabetic hypertensive patients to below 130/85 mm Hg is beneficial. Indeed the recent guidelines\(^{34}\) suggest lowering BP to below 130/80 mm Hg.

### Prospective Studies Among Diabetic Hypertensive Patients

We identified eight studies that reported outcome in diabetic hypertensive patients.\(^{13–20,35}\) Three studies compared the effects of two active treatments in diabetic hypertensive patients\(^{13,14,35}\) and one 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 (SHEP) compared a diuretic (chlorthalidone) with placebo,\(^{17}\) Syst-Eur and Systolic Hypertension in China (Syst-China) compared dihydropyridine calcium antagonist (nitrendipine) with placebo,\(^{15,18,19}\) and UKPDS\(^{5,16}\) compared tight BP control with either captopril or atenolol versus less tight control of BP.

In two studies that compared calcium antagonists with ACE inhibitors, a significantly higher incidence of cardiovascular events was observed in patients assigned therapy with calcium antagonists. Group analysis for patients with diabetes in the Captopril Prevention Project (CAPP) study showed that patients assigned captopril-based therapy had fewer primary end points and fewer fatal and nonfatal myocardial ischemic attacks than those assigned conventional treatment.\(^{35}\) In the HOT study, lowering BP to diastolic target level of ≤80 mm Hg with calcium antagonist-based therapy, lowered cardiovascular events by 51%.\(^{20}\)

In all four prospective, randomized, double-blind studies that compared the effects of active treatment with placebo, antihypertensive treatment reduced cardiac end points, stroke, and total mortality (Table 2, Fig. 2).\(^{5,15–19}\) A comparison between the study results is of questionable validity as the studies differed in the inclusion criteria, initial BP, age, and time of follow-up. However, it seems that all four drugs effectively reduced cardiovascular events and mortality. The profile of side effects of all drugs was comparable.

### Table 2. Reduction of cardiovascular morbidity by various drugs

<table>
<thead>
<tr>
<th>End Point</th>
<th>Cardiac End Points</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor (captopril)(^{5,16})</td>
<td>16%</td>
<td>40%</td>
</tr>
<tr>
<td>β-blocker (atenolol)(^{5,16})</td>
<td>27%</td>
<td>55%</td>
</tr>
<tr>
<td>Diuretic (chlorthalidone)(^{17})</td>
<td>56%</td>
<td>22%</td>
</tr>
<tr>
<td>Calcium antagonist (nitrendipine)(^{15,18,19})</td>
<td>69%</td>
<td>70%</td>
</tr>
</tbody>
</table>

ACE = angiotensin converting enzyme.
*Because patient populations are different in various studies, the benefits conferred by antihypertensive drugs are not directly comparable.

\(^{14}\text{S}\) AJH – May 2001 – VOL. 14, NO. 5, PART 2

**FIG. 2.** Efficacy of antihypertensive therapy in hypertensive diabetic patients. ACE = angiotensin converting enzyme; UKPDS = UK Prospective Diabetes Study; other abbreviations as in Fig. 1.
Discussion

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 results from the four large prospective studies showed that diuretics, ACE inhibitors, β-blockers, and calcium antagonists effectively reduced morbidity and mortality in diabetic hypertensive patients. The prospective studies were not homogeneous as the initial BP, age, and time of follow-up were different in the various studies. The UKPDS recruited relatively young patients with hypertension and type 2 diabetes and followed them up for 8 years, whereas 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 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 risk of the patient population at the onset of the study. Therefore, elderly patients with highest systolic and pulse pressure, such as in the SHEP, Syst-Eur, and Syst-China, will have the highest absolute risk and, as a consequence, benefit most from antihypertensive therapy. Of note, less than 40% of the diabetic hypertensive patients treated with diuretic, ACE inhibitor, and β-blocker continued to receive monotherapy throughout the study, whereas 55% of the patients treated with calcium antagonists continued with monotherapy.

Combination Therapy Required to Achieve 130/85 mm Hg BP

To achieve a BP of less than 130/85 mm Hg, more than 60% of the patients will require combination therapy with two or more drugs. In the HOT study, 76% of the patients assigned to the lowest target diastolic BP ≤80 mm Hg required combination therapy. In the UKPDS, 62% of those who were assigned intensive BP control required combination therapy. Combination therapy may also be more beneficial than monotherapy in reducing the risk of cardiovascular events. In the Fosinopril Versus Amiodopine Cardiovascular Events Randomized Trial, those who received the combination of amiodopine and fosinopril had fewer cardiovascular events than those who received either drug alone. Also, patients receiving the combination had the best overall survival percentages, well into 30 months of therapy (Fig. 3). Similarly, Bakris et al. documented that at comparable BP levels the combination of an ACE inhibitor (either lisinopril or trandolapril) and verapamil was more effective than either drug alone in attenuating both albuminuria and the rate of decline in glomerular filtration rate. The use of a combination of an ACE inhibitor and calcium antagonist is strongly recommended to maximally protect the kidney in diabetic hypertensive patients with nephropathy.

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 four 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. It appears that combinations, such as ACE inhibitor plus calcium channel blocker, may be more effective than individual monotherapies in terms of reducing cardiovascular events and providing renal protection.

References


