TREATMENT OF HYPERTENSION IN PATIENTS WITH TYPE-2 DIABETES MELLITUS

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Introduction: Recently, the results of the Heart Outcomes Prevention Evaluation (HOPE) Study and the Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO) HOPE substudy (1) showed that treatment with the angiotensin-converting-enzyme (ACE) inhibitor ramipril compared with placebo significantly lowered the risk of cardiovascular (CV) events (by 25%) and overt nephropathy in people with type-2 diabetes with a previous CV event or at least one other CV risk factor. Although 56% of the HOPE diabetics (n=3577) had a history of hypertension (1), uncontrolled diabetic hypertensives (BP >160/90 mmHg) were not randomized. HOPE was not a hypertension trial, and the HOPE results were not mainly attributable to the BP change (1); thus the discussion of the best treatment of hypertension in patients with type-2 diabetes is ongoing.

Randomized Clinical Trials With Hypertensive Diabetics: In the Systolic Hypertension in the Elderly Program (SHEP) low-dose, diuretic-based treatment (chlorthalidone 12.5-25 mg with a step-up to atenolol 25-50 mg or reserpine 0.05-0.10 mg daily if needed) was found to be effective compared with placebo in preventing CV complications in elderly patients with type-2 diabetes mellitus (n=583) and isolated systolic hypertension (2). Similarly, the Systolic Hypertension in Europe (Syst-Eur) Trial (3) compared calcium-antagonist based treatment (nitridinepine) with placebo in elderly patients with isolated systolic hypertension and in a rather large subgroup with type-2 diabetes (n=492). In Syst-Eur, treatment for five years prevented 178 major CV events in every 1000 diabetic patients treated (3), i.e. approximately 6 patients had to treated for 5 years to prevent one major CV event.

The Hypertension Optimal Treatment Study (HOT) (4) investigated the intensity of antihypertensive treatment with calcium-antagonist as baseline therapy in hypertensive patients averaging 61.5 years of age and 170/105 mmHg in baseline BP of whom 1,501 had type-2 diabetes. In HOT (4) major CV events was lowered from 24.4 to 18.6 and 11.9 events/1000 patient-years, respectively, in the randomized tertiles of diabetic patients who had achieved 84, 82 and 81 mmHg, respectively, in diastolic BP; i.e. approximately 20 patients needed to be treated for 5 years to prevent one major CV event when BP was further lowered from 84 to 81 mmHg in the diabetic patients. Tight BP control to prevent all macro- and microvascular complications was also successful after more than 8 years of follow-up of 1148 patients in the United Kingdom Prospective Diabetes Study (UKPDS) (5); however, no significant difference was found between captopril and atenolol (6).

Two studies in type 2 diabetics with hypertension suggested benefits of ACE inhibitors compared with calcium antagonists in prevention of CV disease (7,8). The Captopril Prevention Project (CAPPP) (9) compared the effects of ACE inhibitor with diuretic/beta-blocker treatment in middle-aged hypertensive patients of whom 572 had type-2 diabetes at baseline; there were fewer CV events on captopril and (as in HOPE) fewer hypertensive patients developed type-2 diabetes on ACE inhibitor compared to "standard therapy". In the Swedish Trial Old Patients with Hypertension-2 (STOP-2) Study all patients were above the age of 70 years and as many as 719 of them had type-2 diabetes at baseline; however, CV death was the same on standard therapy, ACE inhibition or calcium antagonist treatment (10).

Summary: The consensus for treatment of hypertension in type 2 diabetes is now aggressive BP lowering treatment (<130/85 mmHg), usually with polypharmacy. Although treatment with ACE inhibitors has been shown effective in preventing macro- and microvascular events in high risk diabetics with controlled hypertension, we are awaiting the results of ongoing randomized hypertension trials with large subpopulations of type-2 diabetics like ALLHAT (11), ASCOT (12), CONVINCE (13), INSIGHT (14), LIFE (15), VALUE (16) and nephropathy studies (ABCD-2V, CSGTEI, IDNT, RENAAL) to clarify the preferred drug (s) of choice for the treatment of hypertension in these patients. Altogether these trials have randomized >30,000 hypertensive patients with type-2 diabetes. They are being monitored closely; ALLHAT has the largest subset of type-2 diabetics (n>15,000) and there has not been any need of early termination (17) except that the alpha-blocker arm was stopped (18).

Conclusions: 1. Patients with type-2 diabetes should be aggressively treated for hypertension when BP is above 140 and/or 90 mmHg aiming at BP <130/85 mmHg. 2. These patients usually need 2 or more drugs/combination therapy to reach the BP target. 3. Though ACE inhibitors have been proven protective there is no consensus on the «drug of choice» for hypertensive type-2 diabetic patients. 4. The best treatment (class or regimen of drugs) may be clarified in ongoing trials with sufficient statistical power.
References:


