



TREATMENT OF HYPERTENSION IN PATIENTS WITH TYPE-2 DIABETES MELLITUS

Sverre E. Kjeldsen and Ingrid Os, Departments of Cardiology and Nephrology, Ullevaal University Hospital, Oslo, Norway; Csaba Farsang, St. Emerie Teaching Hospital, Budapest, Hungary; Jean-Michel Mallion, Department of Medicine and Cardiology, University Hospital of Grenoble, France; Lennart Hansson, Clinical Hypertension Research, University of Uppsala, Sweden; and Peter Sleight, Department of Cardiovascular Medicine, John Radcliffe Hospital, University of Oxford, United Kingdom.

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 (nitrendipine) 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 be 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 in 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), CONVINCENCE (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:

1. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253-9.
2. Curb JD, Pressel SL, Cutler JA et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease in older diabetic patients with isolated systolic hypertension. *JAMA* 1996;276:1886-92.
3. Tuomilehto J, Rastenyte D, Birkenhäger WH et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. *N Engl J Med* 1999;340:677-84.
4. Hansson L, Zanchetti A, Carruthers SG et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;351:1755-62
5. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;317:703-13.
6. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes. UKPDS 39. *BMJ* 1998;317:713-20.
7. Tatti P, Pahor M, Byington RP et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET). *Diabetes Care* 1998;21:597-603.
8. Estacio RO, Jeffers BW, Hiatt WR et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998;338:645-52.
9. Hansson L, Lindholm LH, Niskanen L et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999;353:611-6.
10. Hansson L, Lindholm LH, Ekblom T et al. Randomised trial of old and new antihypertensive drugs in elderly patients. Cardiovascular mortality and morbidity in the Swedish Trial in Old patients with Hypertension-2 study. *Lancet* 1999;354:1751-6.
11. Davis BR, Cutler JA, Gordon DJ et al. Rationale and design for the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT). *Am J Hypertens* 1996;9:342-60.
12. Dahlöf B, Sever PS, Poulter NR et al. The Anglo-Scandinavian Cardiac Outcomes trial (ASCOT). *Am J Hypertens* 1998;11:9A.
13. Black HR, Elliott WJ, Grandits G et al. Baseline characteristics of the first 14,242 patients enrolled in the CONVINCe Study. *Am J Hypertens* 1999;12:141A.
14. Brown M, Castaigne A, de Leeuw PW et al. Study population and treatment titration in the international Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *J Hypertens* 1998;16:2113-6.
15. Dahlöf B, Devereux RB, Julius S et al. Characteristics of 9194 patients with left ventricular hypertrophy. The LIFE Study. *Hypertension* 1998;32:989-97.
16. Mann J, Julius S. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) Trial of Cardiovascular Events in Hypertension. Rationale and design. *Blood Press* 1998;7:176-83.
17. Cutler JA. Calcium-channel blockers for hypertension - uncertainty continues. *N Engl J Med* 1998;338:679-81.
18. Davis BR, Furberg CD, Wright JT et al. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone. The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT). *JAMA* 2000;283:1967-1975.