



## TREATMENT OF HYPERTENSION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Peter M. Nilsson<sup>1</sup>, Renata Cifkova<sup>2</sup>, Sverre E. Kjeldsen<sup>3</sup>

<sup>1</sup>Department of Clinical Sciences, Lund University, University Hospital, Malmö, Sweden

<sup>2</sup>Department of Preventive Cardiology, Charles University, Prague, Czech Republic

<sup>3</sup>Department of Cardiology, Ullevaal University Hospital, Oslo, Norway

### Introduction

Hypertension in diabetes is one of the most widespread, important, and treatable cardiovascular risk factors in clinical practice. Data from randomised trials have shown the benefits of improved blood pressure control in patients with type 2 diabetes [1], but the blood pressure goal is still not well established due to lack of evidence. Recent international and national guidelines and recommendations have emphasised the screening, evaluation, and vigorous treatment of elevated blood pressure (BP) if combined with diabetes [2–4], especially systolic BP. Epidemiological data indicate some improving trends in blood pressure control reflecting increased awareness and more appropriate treatment over time [5].

### Randomised clinical trials including hypertensive patients with diabetes

Several intervention trials have formed the evidence-base for treatment of hypertension in diabetes. In the Systolic Hypertension in the Elderly Program (SHEP) low-dose, diuretic-based treatment (chlorthalidone) was found to be effective compared with placebo in preventing CV complications in elderly patients with type 2 diabetes mellitus and isolated systolic hypertension [6]. Similarly, the Systolic Hypertension in Europe (Syst-Eur) Trial compared calcium-antagonist based treatment (nitrendipine) with placebo in elderly patients with isolated systolic hypertension and in a 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 [7], i.e. approximately 6 patients had to be treated for five years to prevent one major CV event.

The Hypertension Optimal Treatment Study (HOT) [8] investigated the intensity of antihypertensive treatment using a calcium-antagonist (felodipine) as baseline therapy in hypertensive patients averaging 62 years of age and 170/105 mm Hg in baseline BP, including 1501 patients with type 2 diabetes. In HOT [8] the incidence of major CV events was lowered ( $p = 0.005$ ) from 24.4 to 18.6 and 11.9 events/100 patient-years, respectively, in the randomised tertiles of diabetes patients who had achieved 85, 83, and 81 mm Hg, respectively, in diastolic BP. 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 mm Hg in these patients. Tight BP control to prevent macro- and microvascular complications was also successful after more than 8 years of follow-up of 1148 hypertensive patients in the United Kingdom Prospective Diabetes Study (UKPDS), especially for prevention of stroke and retinopathy [9]. However, no significant effect difference was found between captopril and atenolol [10], but patients on atenolol needed significantly more oral anti-glycaemic drugs due to weight increase.

The Captopril Prevention Project (CAPPP) [11] compared the effects of an 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 mortality was the same on standard therapy, ACE inhibition, or calcium-antagonist treatment [12].

In addition, nearly normotensive subjects with diabetes may sometimes benefit from the use of drugs with blood pressure lowering properties. The results of the Heart Outcomes Prevention

Evaluation (HOPE) Study and the Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO) HOPE substudy [13] 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, including 56% with a history of hypertension. Uncontrolled diabetic hypertensives (BP >160/90 mm Hg) were, however, not randomised. HOPE was not a hypertension trial, but gives a strong argument in favour of blockade of the renin-angiotensin-system in CV risk patients with diabetes.

In the Losartan Intervention For Endpoint reduction (LIFE) trial [14] a subgroup of 1195 patients with diabetes, hypertension, and signs of left-ventricular hypertrophy (LVH) on electrocardiograms were randomised to either losartan-based or atenolol-based treatment. Mortality from all causes was 63 and 104 in the losartan and atenolol groups, respectively; RR 0.61 (0.45–0.84),  $p = 0.002$ . In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [15] a subgroup of 12,063 patients (36%) with diabetes were randomised to treatment with chlorthalidone, amlodipine, or lisinopril. There were no differences in the primary composite CV outcome between these three drugs, used in a very heterogeneous study population. A similar result of equity between treatment arms for the primary composite CV end-point was found in the Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) based on a sub-analysis of 1302 patients with hypertension and diabetes randomised to either nifedipine slow-release or conventional therapy [16].

The Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) has shown substantial benefits in patients randomised to a treatment based on amlodipine, with perindopril as add-on therapy if needed, versus atenolol-based treatment, with thiazide as add-on therapy if needed, for the reduction of stroke and total mortality [17]. The ASCOT study was stopped prematurely because of the difference in all-cause mortality, indicating the benefits of an amlodipine-based treatment in comparison to older drug alternatives after 5.5 years' median follow-up. Though not significant, compared with the atenolol-based regimen, fewer individuals on the amlodipine-based regimen had a primary endpoint (429 vs. 474; unadjusted HR 0.90, 95% CI 0.79–1.02,  $p = 0.1052$ ), fatal and non-fatal stroke (327 vs. 422; 0.77, 0.66–0.89,  $p = 0.0003$ ), total cardiovascular events and procedures (1362 vs. 1602; 0.84, 0.78–0.90,  $p < 0.0001$ ), and all-cause mortality (738 vs. 820; 0.89, 0.81–0.99,  $p = 0.025$ ). Patients with diabetes had the same benefits of this treatment as non-diabetics, with no heterogeneity between subgroups [17].

In the ADVANCE trial it was shown that addition of the combination of perindopril and indapamide to patients on antihypertensive treatment was associated with substantial clinical benefits versus placebo treatment [18]. The relative risk of a major macrovascular or microvascular event was reduced by 9% (861 [15.5%] active vs. 938 [16.8%] placebo; hazard ratio 0.91, 95% CI 0.83–1.00,  $p = 0.04$ ). The separate reductions in macrovascular and microvascular events were similar but were not independently significant. The relative risk of death from cardiovascular disease was reduced by 18% (211 [3.8%] active vs. 257 [4.6%] placebo; 0.82, 0.68–0.98,  $p = 0.03$ ) and death from any cause was reduced by 14% (408 [7.3%] active vs. 471 [8.5%] placebo; 0.86, 0.75–0.98,  $p = 0.03$ ). The actively treated group had a mean systolic blood pressure under treatment of 135 mm Hg.

In the Accomplish trial (60% patients with diabetes) it was shown that the fixed combination of benazepril and amlodipine resulted in a relative risk reduction of cardiovascular events compared to the fixed combination of benazepril and hydrochlorothiazide [19].

Finally, in the Action to Control Cardiovascular Risk in Diabetes-Blood Pressure (ACCORD-BP) study a total of 4733 participants with type 2 diabetes were randomly assigned to intensive therapy, targeting a systolic pressure of less than 120 mm Hg, or standard therapy, targeting a systolic pressure of less than 140 mm Hg [20]. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years. After 1 year, the mean systolic blood pressure was 119.3 mm Hg in the intensive-therapy group and 133.5 mm Hg in the standard-therapy group. The annual rate of the primary outcome was 1.87% in the intensive-therapy group and 2.09% in the standard-therapy group (hazard ratio with intensive therapy, 0.88; 95% confidence interval [CI], 0.73 to 1.06;  $p = 0.20$ ). The annual rates of death from any cause were 1.28% and 1.19% in the two groups, respectively (hazard ratio, 1.07; 95% CI 0.85 to 1.35;  $p = 0.55$ ). The annual rates of stroke, a pre-specified secondary outcome, were 0.32% and 0.53% in the two groups, respectively (hazard ratio, 0.59; 95% CI, 0.39 to 0.89;  $p = 0.01$ ). Serious adverse events attributed to antihypertensive treatment occurred more often in the intensive-therapy group (3.3%) than in the standard-therapy group (1.3%) ( $p < 0.001$ ). Thus, in patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of major cardiovascular events.

## Summary

The general consensus for treatment of hypertension in type 2 diabetes is now to aim for a well controlled SBP of 130–139 mm Hg and, if possible, closer to the lower values in this range, but the exact BP goal has not been fully established [4]. Such a strategy is usually based on polypharmacy with synergistic drug combinations. This should be part of an overall risk factor control, also addressing smoking, dyslipidaemia, microalbuminuria, and hyperglycaemia to optimise the control [21]. Treatment with an RAS blocking agent has been shown to be effective in preventing macro- and microvascular events in high-risk diabetics with controlled hypertension.

## Conclusions

1. Patients with type 2 diabetes should be treated for hypertension when BP is above 140 and/or 90 mm Hg, aiming at a systolic BP well below this threshold but not below 120 mm Hg. 2. These patients usually need two or more drugs/combination therapy to reach the BP target, especially for systolic BP. 3. Though ACE inhibitors have been proven to be cardiovascular-protective and some angiotensin-II receptor blockers nephroprotective, there is no consensus on the "drug of choice" for all hypertensive type 2 diabetic patients. 4. Most studies support the notion that blood pressure reduction *per se* is more important than individual properties of specific drugs in most cases. 5. Blockade of the renin-angiotensin system seems to be an appropriate choice as one of the partner drugs in offering combination therapy to hypertensive patients with diabetes or glucose intolerance. 6. It is recommended that trends be followed in the quality of health care for patients with hypertension and diabetes, for example by local, regional, or national registers.

## References

1. Zanchetti A, Ruilope LM. Antihypertensive treatment in patients with type-2 diabetes mellitus: what guidance from recent controlled randomized trials? *J Hypertens* 2002; 20: 2099–2110.
2. Chobanian AV, Bakris GL, Black HR, et al. and the National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 Report. *JAMA* 2003; 289: 2560–2571.
3. Williams B, Poulter NR, Brown MJ, et al. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004 — BHS IV. *J Hum Hypertens* 2004; 18: 139–185.
4. Mancia G, Laurent S, Agabiti-Rosei E, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens*. 2009; 27: 2121–2158.
5. Nilsson PM, Gudbjörnsdóttir S, Eliasson B, Cederholm J; for the Steering Committee of the National Diabetes Register, Sweden. Hypertension in diabetes — trends in control and relation to macrovascular morbidity in repeated national surveys from Sweden. *J Hum Hypertens* 2003; 17: 37–44.
6. 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: 1886–1892.
7. 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: 677–684.
8. 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: 1755–1762.
9. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular complications in type-2 diabetes: UKPDS 38. *BMJ* 1998; 317: 703–713.
10. 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: 713–720.
11. Niklason A, Hedner T, Niskanen L, Lanke J; Captopril Prevention Project Study Group. Development of diabetes is retarded by ACE inhibition in hypertensive patients — a subanalysis of the Captopril Prevention Project (CAPPP). *J Hypertens* 2004; 22: 645–652.
12. Lindholm LH, Hansson L, Ekblom T, et al. Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. *J Hypertens* 2000; 18: 1671–1675.
13. 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: 253–259.
14. Lindholm LH, Ibsen H, Dahlöf B, et al; LIFE Study Group. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359: 1004–1010.
15. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. *JAMA* 2002; 288: 2981–2997.
16. Mancia G, Brown M, Castaigne A, et al.; INSIGHT. Outcomes with nifedipine GITS or Co-amilofide in hypertensive diabetics and nondiabetics in Intervention as a Goal in Hypertension (INSIGHT). *Hypertension* 2003; 41: 431–436.
17. Dahlöf B, Sever P, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; 366: 895–906.
18. Patel A; ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet*. 2007; 370: 829–840.
19. Weber MA, Jamerson K, Bakris GL, et al.; for the ACCOMPLISH Investigators. Cardiovascular events in patients with diabetes and hypertension receiving renin-angiotensin system blockade plus diuretic or a calcium channel blocker. *J Am Coll Cardiol* 2010 (accepted for publication).
20. ACCORD Study Group, Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; 362: 1575–1585.
21. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med*. 2008; 358: 580–591.