

## STATINS AND HYPERTENSION

Renata Cifková, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; Peter M. Nilsson, Department of Clinical Sciences, Lund University, University Hospital, Malmö, Sweden

Cardiovascular disease (CVD) remains the leading cause of death in developed countries [1]. Hypertension and dyslipidaemia are two major CVD risk factors highly prevalent either alone or in combination [2]. Hypertension often clusters with other CVD risk factors associated with a markedly increased risk of CV events. The interaction among CVD risk factors is such that the probability of a CV event is frequently greater in patients with only moderate BP and cholesterol abnormalities in the presence of additional risk factors than in patients with isolated marked elevation in BP or cholesterol levels alone [3]. In addition, the majority of CV events in the population occur among individuals with modest levels of several risk factors rather than among those rare persons with extreme values of one risk factor. A major aim of treating hypertension is a maximal decrease in long-term total CV risk. This could only be achieved by treatment of all reversible risk factors and associated conditions in addition to treatment of raised BP *per se*.

### Lipid abnormalities and hypertension

There is evidence that normotensive subjects with hypercholesterolaemia have an excessive BP response to a mental arithmetic stress test [4]. Furthermore, up to 40% of patients with essential hypertension and many patients with borderline hypertension already have lipid abnormalities. An analysis of the Physicians' Health Study prospectively examined data from 3110 participants who were free of hypertension, CVD, and cancer at baseline [5]. Over an average of 14 years of follow-up, approximately one third of the men developed hypertension. Elevated levels of total cholesterol, non-HDL-cholesterol, and the total cholesterol/HDL-cholesterol ratio were independently associated with an increased risk of hypertension in middle-aged and older men. Furthermore, higher levels of cholesterol were associated with a higher risk of hypertension.

Genetic studies in humans and in animal models suggest that a predisposition to the development of both hypertension and dyslipidaemia may result from the inheritance of shared genetic factors.

### Effect of statins on BP in clinical studies

In addition to their beneficial effects on lipids, statins may reduce systolic, diastolic, and mean arterial BP in normotensive, hypercholesterolaemic [6] men and kidney transplant patients [7]. These effects were independent of their lipid actions.

The capacity of statins to lower BP has been reported to be superior to that of other lipid-lowering drugs. In the Brisighella Heart Study [8], a total of 1356 hypercholesterolaemic individuals were randomly treated with a low-fat diet, cholestyramine, gemfibrozil or simvastatin for 5 years. Participants were divided at baseline into four quartiles based upon systolic BP. A significant decrease in BP was observed in the two upper quartiles of systolic BP, and was greater in subjects treated with lipid-lowering drugs. In particular, the BP reduction was greater in patients treated with a statin despite a comparative reduction in LDL-cholesterol (reduction by 13% in both systolic and diastolic BP at the highest quartiles after 5 years of treatment with a statin as compared with 10% after treatment with non-statin drugs).

The BP-lowering effect of statins is not consistent. Milionis et al. [9] summarised, in an elaborate review of the available data regarding the BP-lowering effect of statins, the effect of statin treatment on BP. This review included studies within a broad spectrum of patients (normotensives, hypertensives, individuals with normal lipids and dyslipidaemia, diabetic patients) published up to 2005. The effect on BP varied from neutral to most favourable ( $\Delta$  systolic BP 8–13 mm Hg;  $\Delta$  diastolic BP 5–7.8 mm Hg).

A meta-analysis of all studies that reported BP data during treatment with statins was published recently [10]; 20 randomised controlled trials (828 patients) published up to 2005 were included. The

duration of the studies ranged from one to 12 months. Systolic BP was significantly lower in patients on statins than in those on placebo or a comparative lipid-lowering drug (mean difference:  $-1.9$  mm Hg; 95% CI:  $-3.8$  to  $-0.1$ ). The effect was greater when the analysis was restricted to studies with a baseline systolic BP  $> 130$  mm Hg ( $\Delta$  systolic BP  $-4.0$  mm Hg; 95% CI:  $-5.8$  to  $2.2$ ). There was a trend for lower diastolic BP in patients receiving statin therapy compared with controls:  $-0.9$  mm Hg (95% CI:  $2.0$  to  $0.2$ ) overall, and  $-1.2$  mm Hg (95% CI:  $-2.6$  to  $0.1$ ) in studies with a baseline diastolic BP  $> 80$  mm Hg.

### Reduction in BP due to statin therapy: pathophysiological mechanisms

Statins induce consistent and predictable reductions in circulating LDL-cholesterol and triglycerides, and have a small effect on HDL-cholesterol. In addition, these agents exhibit ancillary actions which have been attributed to reductions in isoprenoid cholesterol intermediates and reductions in dolichols, geranylgeranoic acid, and farsenylfarsenoic acid. It can be hypothesised that these actions may provide a pleiotropic mechanism by which statins exert actions on BP as well as target organ damage associated with hypertension. Statins improve endothelial function by increasing the bioavailability of NO, promoting re-endothelialisation, reducing oxidative stress, and inhibiting inflammatory responses [11]. Increased angiotensin II sensitivity predisposes to hypertension and plaque instability. It has been reported that the increased sensitivity to angiotensin II in healthy young subjects with isolated hypercholesterolaemia can be partly restored by therapy to reduce the levels of LDL-cholesterol using statins. There is evidence that statins downregulate AT<sub>1</sub>-receptor expression [12]. There is also some evidence that statins may reduce the levels of circulating aldosterone [13].

### Renal function, hypertension, lipids and statins

Recent clinical trials have demonstrated that aggressive treatment with statins improves serum creatinine, glomerular filtration rate and urate levels [14, 15]. This effect is probably another consequence of improved blood flow following treatment with statins. The effect of statin use on the development of renal dysfunction was examined in 197,551 patients (Department of Veterans Affairs, Veterans Integrated Service Network [16]). The odds for developing renal dysfunction were decreased by 13% in statin users [16]. The beneficial effect of statins in preventing the development of renal dysfunction seems to be independent of their lipid-lowering effect.

### Statins and BP: implications of large clinical outcome trials

Treatment of hypertension is associated with a reduction in stroke and, to a lesser extent, coronary events. It is also well known that elevated serum total cholesterol significantly increases CHD risk. Therefore, it is logical that co-existing vascular risk factors, including abnormal lipid profiles, should be an integral part of hypertension management.

Statins were prescribed for a long time to various subgroups in large landmark primary and secondary prevention trials. The overall benefit in CVD risk reduction was similar among hypertensive and normotensive individuals. Although a sizeable number of hypertensive subjects were included among these studies, there are no data as to whether statin treatment produced any significant BP reductions. However, we should keep in mind that 1) the effect of statin treatment on BP was not included in the study design; 2) the inclusion of large numbers of normotensive participants could have attenuated any beneficial effect on BP, which could have also been masked by 3) the use of specific antihypertensive therapy. Only statins within the class of lipid-lowering agents have been shown to induce a consistent 20–25% reduction in the risk of stroke or transient ischaemic attacks [17].

The benefit of lowering both BP and cholesterol was evaluated in two large-scale trials, ALLHAT [18] and ASCOT-LLA [19].

Part of ALLHAT was designed to determine whether pravastatin compared with usual care would reduce all-cause mortality in 10,355 patients with hypertension and moderate hypercholesterolaemia, plus at least one additional CHD risk factor [18]. At four years total cholesterol was reduced by 17.2% with pravastatin vs. 7.6% with usual care. All-cause mortality was similar in the two groups, and CHD event rates were not different between the two groups; six-year CHD event rates were 9.3 (pravastatin) and 10.4 (usual care). These results could be attributed to the small difference in total cholesterol (9.6%) and LDL-cholesterol (16.7%) between pravastatin and usual care compared with other statin trials. Adherence to the treatment assigned declined over time. For those assigned to pravastatin, adherence dropped from 87.2% at year 2 to 80% at year 4, and 77% at year 6, although the number of participants was small. On the other hand, in the usual care group, cross-overs to statin treatment increased from 8% at year 2 to 17% by year 4. This increase continued at year 6, but the number of participants was small.

In the ASCOT-BPLA trial [20], 19,342 men and women with hypertension and at least three other CV risk factors were randomised to amlodipine (5–10 mg/d) ± perindopril (4–8 mg/d) or to atenolol (50–100 mg/d) ± bendroflumethiazide (1.25–2.5 mg/d). A total of 10,305 of these patients with normal or slightly elevated total cholesterol were randomised to atorvastatin 10 mg/d or placebo [19]. The atorvastatin arm was stopped prematurely at 3.3 years due to a significant reduction in the primary endpoint (–36%;  $p = 0.0005$ ). The benefit of atorvastatin treatment was apparent within the first year of treatment. Fatal/non-fatal stroke and total CV/coronary events were also reduced with atorvastatin. At one year, atorvastatin reduced total cholesterol by 24% and LDL-cholesterol by 35%. However, in the period between 6 weeks and 18 months, a significant 1.1/0.7 mmHg difference in BP was seen in favour of atorvastatin despite titration of doses and numbers of drugs. Overall, amlodipine-perindopril therapy was superior to atenolol-bendroflumethiazide therapy [20], and a recent analysis of early monotherapy data comparing amlodipine with atenolol has suggested a positive interaction between atorvastatin and amlodipine [21].

The latest meta-analysis so far of large clinical trials, including only those with more than 1000 patients followed for more than 2

years, was published by Messerli et al. [22]. Beside ASCOT-LLA and ALLHAT-LLT, 12 trials enrolling 69,284 patients met the inclusion criteria. Overall, in these 12 trials, statin therapy decreased cardiac death by 24% (RR 0.76; 95% CI 0.71–0.82). There was no evidence of a difference in RR estimates for hypertensive and normotensive patients. In conclusion, statin therapy effectively decreased CV morbidity and mortality to the same extent in hypertensive and normotensive patients.

### Compliance with antihypertensive and lipid-lowering treatment

The critical issue of any long-term medication is adherence, which varies according to diagnosis. Real-world compliance rates tend to average between 50 and 60%, but they can be much lower. The compliance rate for antihypertensive medication, as reported by the US National Council on Patient Information and Education, is 53%. In a retrospective cohort study [23], adherence to medication was analysed in 8406 enrollees in a US managed care plan which initiated treatment with antihypertensive and lipid-lowering drugs within a 90-day period. Adherence to concomitant antihypertensive and lipid-lowering therapy is poor, with only 35.9% of patients adherent to both medications at 6 months. A single pill containing an antihypertensive and lipid-lowering compound may increase patient adherence to these medications and thus improve the simultaneous management of hypertension and dyslipidaemia, which may also improve clinical outcome [24].

### Conclusions

The 2007 ESH/ESC guidelines for the management of arterial hypertension [25] recommend considering lipid-lowering agents in all hypertensive patients with established cardiovascular disease or with Type-2 diabetes, aiming at serum total and LDL-cholesterol levels of < 4.5 mmol/l (175 mg/dl) and < 2.5 mmol/l (100 mg/dl), respectively, or lower, if possible.

In view of the results of the ASCOT trial [19], it seems reasonable to consider statin therapy in hypertensive patients aged less than 80 years who have an estimated 10-year risk of cardiovascular disease ≥ 20% or of cardiovascular death (based on the SCORE model) of 5% or more. Target levels should be serum total cholesterol and LDL-cholesterol levels of < 5 mmol/l (190 mg/dl) and < 3 mmol/l (115 mg/dl), respectively.

### References

1. Rosamond W, Flegal K, Furie K, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics — 2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008; 117: e25–e146.
2. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial research group. *Arch Intern Med* 1992; 152: 56–64.
3. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J* 1991; 121: 293–298.
4. Sung BH, Izzo JL Jr, Wilson MF. Effects of cholesterol reduction on BP response to mental stress in patients with high cholesterol. *Am J Hypertens* 1997; 10: 592–599.
5. Halperin RO, Sesso HD, Ma J, Buring JE, Stampfer MJ, Gaziano M. Dyslipidemia and the risk of incident hypertension in men. *Hypertension* 2006; 47: 45–50.
6. Terzoli L, Mircoli L, Raco R, Ferrari AU. Lowering of elevated ambulatory blood pressure by HMG-CoA reductase inhibitors. *J Cardiovasc Pharmacol* 2005; 46: 310–315.
7. Prasad GV, Ahmed A, Nash MM, Zaltzman JS. Blood pressure reduction with HMG-CoA reductase inhibitors in renal transplant recipients. *Kidney Int* 2003; 63: 360–364.
8. Borghi C, Dormi A, Veronesi M, et al.; for the Brisighella Heart Study Working Party: association with different lipid-lowering treatment strategies and blood pressure control in the Brisighella Heart Study. *Am Heart J* 2004; 148: 285–292.
9. Milionis HJ, Liberopoulos EN, Elisaf MS, Mikhailidis DP. Analysis of antihypertensive effects of statins. *Curr Hypertens Rep* 2007; 9: 175–183.
10. Strazzullo P, Kerry SM, Barbato A, Versiero M, D'Elia L, Cappuccio FP. Do statins reduce blood pressure? A meta-analysis of randomized, controlled trials. *Hypertension* 2007; 49: 792–798.
11. Wolfrum S, Jensen KS, Liao JK. Endothelium-dependent effects of statins. *Arterioscler Thromb Vasc Biol* 2003; 23: 729–736.
12. Wassmann S, Faul A, Hennen B, et al. Rapid effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition on coronary endothelial function. *Circ Res* 2003; 93: e98–e103.
13. Ide H, Fujiya S, Ananuma Y, Agishi Y. Effects of simvastatin, an HMG-CoA reductase inhibitor, on plasma lipids and steroid hormones. *Clin Ther* 1990; 12: 410–420.
14. Collins R, Armitage J, Parish S, et al.; for the Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; 361: 2005–2016.
15. Athyros VG, Elisaf M, Papageorgiou AA, et al.; for the GREACE Study Collaborative group: effects of statins versus untreated dyslipidemia on serum uric acid levels in patients with coronary heart disease: a subgroup analysis of the GREACE Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Am J Kidney Dis* 2004; 43: 589–599.
16. Sukhija R, Bursac Z, Kakar P, et al. Effects of statins on the development of renal dysfunction. *Am J Cardiol* 2008; 101: 975–979.
17. Amarenco P, Tonkin AM. Statins for stroke prevention: disappointment and hope. *Circulation* 2004; 109: III44–III49.
18. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2998–3007.
19. Sever PS, Dahlof B, Poulter NR, et al.; for the ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; 361: 1149–1158.
20. Dahlof B, Sever PS, Poulter NR, et al.; for the ASCOT Investigators. 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 multicenter randomised controlled trial. *Lancet* 2005; 366: 895–906.
21. Sever P, Dahlöf B, Poulter N, et al.; on behalf of the ASCOT Steering Committee Members. Potential synergy between lipid-lowering and blood-pressure-lowering in the Anglo-Scandinavian Cardiac Outcomes Trial. *Eur Heart J* 2006; 27: 2982–2988.
22. Messerli FH, Pinto L, Tang SSK, Thakker KM, Cappelleri JC, Sichrovsky T, Dubois RW. Impact of systemic hypertension on the cardiovascular benefits of statin therapy — a meta-analysis. *Am J Cardiol* 2008; 101: 319–325.
23. Chapman RH, Benner JS, Petrilla AA, Tierce JC, Collins SR, Battleman DS, Schwartz JS. Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med* 2005; 165: 1147–1152.
24. Flack JM, Victor R, Watson K, et al. Improved attainment of blood pressure and cholesterol goals using single-pill amlodipine/atorvastatin in African Americans: the CAPABLE trial. *Mayo Clin Proc* 2008; 83: 35–45.
25. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension. *J Hypertens* 2007; 25: 1105–1187.