The role of statins in patients with arterial hypertension

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Abstract

Several primary and secondary prevention studies have shown that statin (HMG-CoA reductase inhibitors) interventions have an effect on both cardio- and cerebrovascular events, regardless of blood pressure status. In hypertensive patients, studies have shown that primary intervention with statin treatment significantly reduces the risk of both cardio- and cerebrovascular diseases and even death, even though cholesterol levels were considered to be within the normal range. This was particularly so in patients with both hypertension and diabetes. Therefore hypertensive patients with established cardiovascular disease or diabetes should be treated with statins as secondary prevention. Hypertensive patients without overt cardiovascular disease should be considered for treatment with statins if their risk of cardiovascular events is markedly elevated: The 2007 European Society of Hypertension and European Society of Cardiology guidelines suggest intervening at the level of 20% risk over 10 years.

Key words: statin, hypertension, lipid lowering, cardiovascular disease, primary prevention, secondary prevention.

Introduction

Cardiovascular diseases are among the most common causes of mortality and morbidity worldwide, with hypertension, hypercholesterolaemia and smoking being the major risk factors. In patients with hypertension, the most important aim of treatment is to reduce the cardiovascular complications, both by blood pressure lowering therapy and by treatment of other risk factors. Several primary and secondary prevention studies have shown that statin (HMG-CoA reductase inhibitors) interventions have an effect on both cardio- and cerebrovascular events, regardless of blood pressure status. In the present review, the beneficial effects of statins both in secondary and in primary prevention of patients with hypertension are discussed.

Benefits of statins in secondary prevention

Several randomized secondary and primary prevention trials have allowed an analysis of the effect of lipid-lowering interventions with statins [1-3]. Although epidemiological data show serum cholesterol concentration to be closely associated with coronary events but not with stroke [4], statins have been shown to be effective in preventing both coronary and cerebrovascular events, prevention of both outcomes being similar in hypertensives and normotensives [1-3].

In the largest randomized trial so far performed with a statin, the Heart Protection Study [5], administration of simvastatin to patients with established cardiovascular disease markedly reduced cardiac and cerebrovascular events compared to placebo. The effects were manifest in the hypertensive subpopulation (41% of the total cohort) regardless of the type of antihypertensive treatment employed. Similar results were obtained with pravastatin in the elderly patients of the PROSPER study [6], 62% of whom were hypertensive. Effective prevention was also found with another statin, atorvastatin, in patients with a previous stroke [7].

The VALUE trial [8] of 15,245 hypertensive patients with stable cardiac or peripheral vascular disease, previous cerebral stroke, transient ischaemic attacks or left ventricular hypertrophy, with or without diabetes, demonstrated that hypertensive patients with diabetes have greater risk of myocardial infarction and congestive heart failure than patients without diabetes. This result was also seen among patients who developed diabetes during the trial, emphasizing the importance of treating such patients at an early stage. Long-standing diabetes among hypertensive patients had 2-fold increased risk of cardiac mortality.

Therefore, for hypertensive patients up to the age of at least 80 years with established cardiovascular disease, the goal for total and LDL serum cholesterol should be set at <4.5 mmol/L (174 mg/dL) and <2.5 mmol/L (97 mg/dL) respectively, and lower goals may also be considered, i.e. <4.0 and <2 mmol/L (155 and 80 mg/dL). For hypertensive patients with diabetes the aim for LDL cholesterol levels should be as low as <1.8 mmol/L (70 mg/dL) when treatment is given as secondary prevention.

Benefits of statins in primary prevention in hypertensive patients

Two trials, ALLHAT and ASCOT, have evaluated the benefits associated with the use of statins specifically among patients with hypertension. In ALLHAT, the administration of 40 mg/day of pravastatin to 10,000 hypertensive patients (about two thirds of whom had established vascular disease) reduced serum total and LDL cholesterol (by 11 and 17%, respectively) compared to usual care, but had no significant effect on coronary heart disease, stroke or all-cause mortality [9]. In contrast, in ASCOT [10] administration of 10 mg/day of atorvastatin in over 10,000 hypertensive patients (ASCOT-LLA) (untreated BP >160/100 mmHg, treated BP <140/90 mmHg) at intermediate cardiovascular risk and with a serum total cholesterol <6.5 mmol/L reduced serum total cholesterol and LDL cholesterol by 19.9 and 28%, respectively, compared to placebo (Figures 1 and 2). This was accompanied by substantial benefits both with regard to fatal and non-fatal myocardial infarction (primary endpoint, 36% reduction) (Figure 3) and stroke (27% reduction). There were also significant reductions in other secondary endpoints including total cardiovascular events (21% reduction), total coronary events (29% reduction) and the primary endpoint excluding silent myocardial infarction (38%). All-cause mortality was non-significantly reduced by 13% (Figure 4). The blood pressure control throughout the trial was similar in the patients receiving atorvastatin compared to placebo.

The lipid-lowering arm of the ASCOT study was prematurely discontinued after 3.3 years' follow-up due to the highly significant reduction in the primary end-point and stroke. The beneficial effect seen in the ASCOT study as compared to the lack of benefit reported in ALLHAT might depend on the

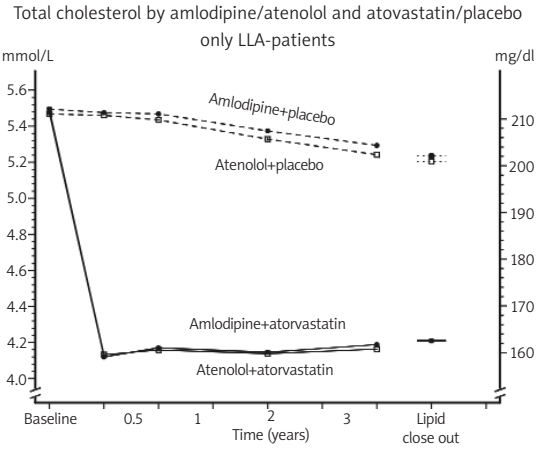

Figure 1. Total cholesterol reduction induced by atorvastatin 10 mg vs. placebo in the ASCOT Study

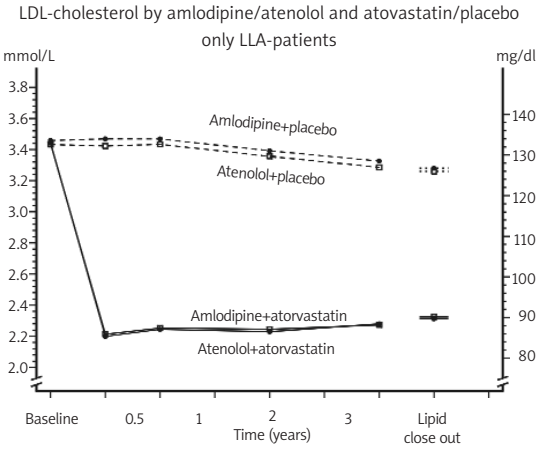

Figure 2. LDL cholesterol reduction induced by atorvastatin 10 mg vs. placebo in the ASCOT Study

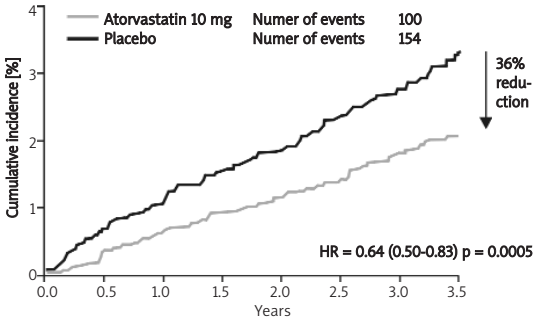

Figure 3. Kaplan-Meier curves showing 36% reduction in the primary endpoint of myocardial infarction or fatal coronary heart disease of treatment with atorvastatin 10 mg vs. placebo

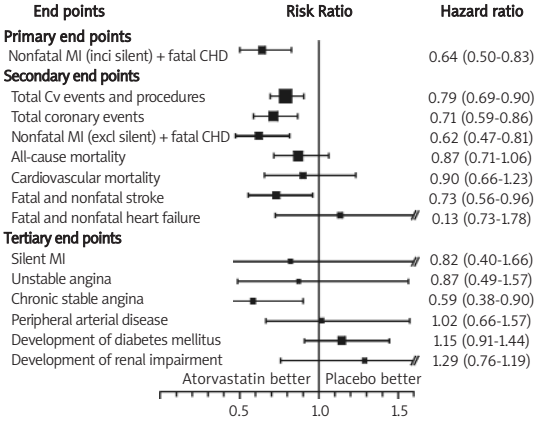

Figure 4. Point estimates and confidence intervals regarding atorvastatin vs. placebo for all pre-specified endpoints in the lipid-lowering arm in the ASCOT Study

greater relative difference in total and LDL cholesterol achieved among the actively treated versus the control group.

The ASCOT study population was randomized into one out of two antihypertensive regimens. The first group received amlodipine with perindopril added as required (amlodipine-based) and the second group received atenolol with bendroflumethiazide added as required (atenolol-based). Compared with placebo, allocation to atorvastatin [11] reduced the relative risk of the primary endpoint of non-fatal myocardial infarction plus fatal coronary heart disease by 53% ($p<0.0001$) among those allocated to the amlodipine-based regimen, whereas it reduced the incidence of this outcome by 16% (p: n.s) among those allocated to the atenolol-based regimen (Figure 5). The difference between these risk reductions with atorvastatin was significant (test for heterogeneity $p=0.025$). Allocation to atorvastatin reduced the relative risk of total cardiovascular events and procedures by 27% ($p<0.005$) among those allocated to amlodipine and by 15% (p: n.s) among patients allocated to atenolol. The difference between these effects was not significant (heterogeneity $p=0.25$) and was due entirely to the observed differences in the primary endpoint. There was no significant difference (heterogeneity $p=0.73$) between the effects of atorvastatin on non-fatal or fatal strokes among those assigned amlodipine (p: n.s.) or atenolol (p: n.s.).

Benefits of statins in primary prevention in patients with both hypertension and diabetes

The ASCOT study included 2,532 patients with hypertension and type 2 diabetes in the lipid-lowering arm or in the statin part of the trial [12]. The outcome of these patients showed significant reductions in major cardiovascular events and procedures by 23% ($p=0.04$) in the group treated with 10 mg atorvastatin compared to the placebo group. This was similar to the proportional reduction observed among participants in the same trial without diabetes, but given that diabetic patients are at a higher absolute risk of cardiovascular events than those without diabetes, the absolute benefit of the lipid-lowering intervention was even greater for the diabetic sub-population. There were also fewer fatal and non-fatal coronary myocardial infarctions (16%, $p=0.25$) and strokes (33%, $p=0.1$) although statistically not significantly reduced compared to placebo. The lack of statistical power may be due to the fact that the study was not designed to exclusively treat diabetic patients and hence the number of participants in this sub-population was limited. The prescription of open-labelled statin (14% of the patients in the diabetic sub-group vs. 9% for the whole ASCOT-LLA) and the relatively short follow-up time may have contributed to the insignificant results.

In the CARDS study [13] 2,838 patients with type 2 diabetes with no history of cardiovascular disease and at least one additional risk factor were randomized to treatment with 10 mg atorvastatin or placebo to assess the effectiveness of statin therapy versus placebo. Almost all (84% of the participants) had hypertension as a risk factor alone or as one of several risk factors. All had fasting LDL and triglycerides below 4.14 and 6.78 mmol/L respectively. Allocation to atorvastatin was associated with a 36% reduction in incidence of acute coronary events, 31% reduction in coronary revascularisation events and 48% reduction in stroke. There was also a 27% fall in all-cause mortality in patients allocated to atorvastatin. This study was prematurely discontinued because the pre-specified early stopping rule for

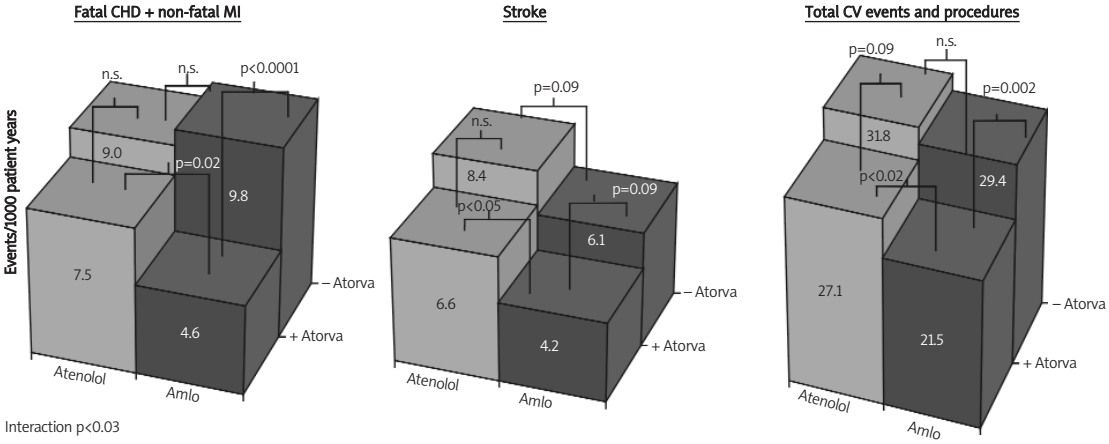

Figure 5. Interaction between lipid-lowering treatment and blood pressure lowering treatment in the ASCOT Study: the interaction was statistically significant for the primary endpoint but not for the secondary endpoints stroke and all cardiovascular events and procedures

efficiency had been met. The investigators concluded that the debate in the future should focus on whether any diabetic patients can be identified as being at sufficiently low risk to withhold statin treatment.

Discussion

According to the results in several randomized clinical trials [1-7], patients with established cardiovascular disease will benefit from statin treatment. In view of the results of the ASCOT study [10] 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. There are reports that the benefits of statin administration in hypertensive patients may include some blood pressure reduction [14], although in the ASCOT [10] and the PHYLLIS [15] studies, addition of statin to antihypertensive treatment was not accompanied by further blood pressure lowering effect. Target levels should be a serum total and LDL cholesterol of respectively <4.5 mmol/L (174 mg/dL) and <2.5 mmol/L (97 mg/dL) and among diabetic patients with established cardiovascular disease: <4.5 mmol/L (174 mg/dL) and <1.8 mmol/L (70 mg/dL) respectively. The majority of patients will reach these targets using a statin at appropriate doses in combination with non-pharmacological measures. For patients who do not reach targets or whose HDL cholesterol or triglyceride levels remain abnormal (e.g. <1.0 mmol/L or >2.3 mmol/L, respectively), and addition of ezetimibe [16] or other therapies as well as referral to a specialist service may be indicated. The apparent interaction between atorvastatin and the two antihypertensive regimens used in ASCOT in the prevention of coronary events could have important implications for primary prevention strategies in hypertensive patients. According to the CARDS study [13] it is reasonable to consider statin therapy in all diabetic patients whether they are normo- or hypertensive with total cholesterol >3.5 mmol/L (135 mg/dL).

Recommendations in the 2007 Guidelines for the Management of Arterial Hypertension [17] and in the 2007 Guidelines on Diabetes and Cardiovascular Disease [18] are summarized in the accompanying Table I.

Table I. Summary of ESH-ESC 2007 hypertension guidelines and ESC-EASD 2007 guidelines on diabetes and cardiovascular disease: position statement regarding treatment with lipid-lowering agents

• All hypertensive patients with established cardiovascular disease should be considered for statin therapy aiming at serum total and LDL cholesterol levels of, respectively, <4.5 mmol/L (174 mg/dL) and <2.5 mmol/L (97 mg/dL), even lower if possible.
• Hypertensive patients without overt cardiovascular disease but with high cardiovascular risk (≥20% risk of events in 10 years) should also be considered for statin treatment even if their baseline total and LDL serum cholesterol levels are not elevated.
• Diabetic patients with or without cardiovascular disease should be considered for statin treatment with the goal for total and LDL cholesterol of <4.5 mmol/L (174 mg/dL) and <1.8 mmol/L (70 mg/dL), respectively.

References

1. Gotto AM Jr. Review of primary and secondary prevention trials with lovastatin, pravastatin, and simvastatin. Am J Cardiol 2005; 96: 34F-8F.
2. Clearfield M. Statins and the primary prevention of cardiovascular events. Curr Atheroscler Rep 2006; 8: 390-6.

3. Thavendiranathan P, Bagai A, Brookhart MA, Choudhry NK. Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. Arch Intern Med 2006; 166: 2307-13.
4. Gorelick PB, Schneck M, Berglund LF, Feinberg W, Goldstone J. Status of lipids as a risk factor for stroke. Neuroepidemiology 1997; 16: 107-15.
5. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002; 360: 7-22.
6. Shepherd J, Blauw GJ, Murphy MB, et al. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. Lancet 2002; 360: 1623-30.
7. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006; 355: 549-59.
8. Aksnes TA, Kjeldsen SE, Rostrup M, et al. Impact of new-onset diabetes mellitus on cardiac outcomes in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial population. Hypertension 2007; 50: 467-73.
9. 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-LLT). JAMA 2002; 288: 2998-3007.
10. Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary events and stroke with atorvastatin in hypertensive subjects with average or below average cholesterol levels. The Anglo-Scandinavian Cardiac Outcomes Trial: Lipid Lowering Arm (ASCOT-LLA). Lancet 2003; 361: 1149-58.
11. Sever PS, Dahlöf B, Wedel H, et al. Potential synergy between lipid lowering and blood pressure lowering treatments in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm. Eur Heart J 2006; 27: 2982-8.
12. Sever PS, Poulter NR, Dahlöf B, et al. Lipid- Lowering Arm (ASCOT-LLA): reduction in cardiovascular events with atorvastatin in 2532 patients with type 2 diabetes. Diabetes Care 2005; 28: 1151-7.
13. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomized placebo-controlled trial. Lancet 2004; 364: 685-96.
14. Borghi C, Dormi A, Veronesi M, et al. Use of lipid-lowering drugs and blood pressure control in patients with arterial hypertension. J Clin Hypertens (Greenwich) 2002; 4: 277-85.
15. Zanchetti A, Crepaldi G, Bond MG, et al. Different effects of antihypertensive regimens based on fosinopril or hydrochlorothiazide with or without lipid lowering by pravastatin on progression of asymptomatic carotid atherosclerosis: principal results of PHYLLIS-a randomized double-blind trial. Stroke 2004; 35: 2807-12.
16. Kosoglou T, Statkevich P, Johnson-Levonas AO, Paolini JF, Bergman AJ, Alton KB. Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. Clin Pharmacokinet 2005; 44: 467-94.
17. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and of the European Society of Cardiology. J Hypertens 2007; 25: 1105-87.
18. Rydén L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J 2007; 28: 88-136.