
Statins to prevent cardiovascular events in hypertensive patients. The ASCOT-LLA study
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Introduction
The recently published Lipid-Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes Study Trial (ASCOT-LLA) [1] provides interesting evidence for the use of statins in hypertensive patients with average cholesterol levels and other cardiovascular risk factors. In this study, 19,342 hypertensive patients with at least three other cardiovascular risk factors were randomized to two antihypertensive regimes (amlodipine and/or perindopril vs atenolol and/or clorthalidone) and were planned to be followed for 5 years.

The LLA was comprised of those patients with baseline total cholesterol levels ≤6.5 mmol/l (≤260 mg/dl), who were also randomized to receive daily atorvastatin 10 mg vs placebo. A total of 10,305 patients entered in the LLA, which was stopped prematurely by the safety committee after a mean follow-up of only 3.3 years due to a significantly lower incidence of the primary objective (non-fatal acute myocardial infarction and fatal coronary artery disease) in the atorvastatin group. The results showed that 100 patients in the atorvastatin arm and 154 in the placebo arm met criteria for the primary end-point (relative risk reduction 36%, P = 0.0005). The analysis
also demonstrated that the clinical benefit started after only a year of treatment, similarly to secondary prevention randomized studies with statins. The study also showed a significant reduction in both fatal and nonfatal stroke in the atorvastatin group (relative risk reduction of 27%) [1]. Average serum cholesterol levels in the atorvastatin group decreased by 1.3 and 1.1 mmol/l after 1 and 3 years, respectively, with a total follow-up of 3 years compared with the placebo group.

Comparison of the ASCOT-LLA trial with other major clinical statin trials

These data confirm and expand the benefit of statin treatment in patients at high risk of developing cardiovascular events. A high-risk patient profile was initially considered to be represented by those with previous myocardial infarction [2], a patient population known to have a higher incidence of events than the general population. The benefit of statin treatment was later expanded to those without a history of myocardial infarction and either moderate hypercholesterolaemia [3] or low levels of high-density lipoprotein-cholesterol [4]. The emerging new concept that the ASCOT-LLA study addresses is the clinical management of hypertensive patients without overt hypercholesterolaemia but with at least three other cardiovascular risk factors, a common finding in clinical practice. In this regard, both the ASCOT-LLA and the recently published Heart Protection Study (HPS) [5] show clear benefit of statin treatment in patients at high risk of developing cardiovascular events, even those with normal baseline cholesterol levels in primary prevention. However, differences between the two studies need to be pointed out. The ASCOT-LLA targeted hypertensive patients meeting criteria for high risk due to the concurrence of many risk factors, a well-known prognostic marker. The presence of prior atherosclerotic disease or diabetes (as a surrogate) was not required. The use of a low dose of atorvastatin showed clinical benefit after a mean follow-up of 3.3 years. The HPS study patients had previous atherosclerotic vascular disease or diabetes (known to have a similar risk profile). In them, a relatively high statin dose was associated with clinical benefit after a 5-year follow-up, since this study was not finished prematurely. Patients in the ASCOT-LLA study were apparently at lower risk than those in the HPS study. Also, the ASCOT-LLA study design selected a relative low dose of statin compared with the HPS, so a low incidence of adverse effects would be anticipated, making it an attractive long-term preventive therapy for a wide range of physicians. The results of the ASCOT-LLA trial proved to be independent of the degree of blood pressure reduction associated with intense lipid lowering [6], as both the atorvastatin and the placebo group showed a similarly good blood pressure control.

Mechanisms involved in the benefit of statin treatment in hypertensive patients

The clinical benefit of atorvastatin in this patient population is probably explained by both lipid-dependent and lipid-independent effects of atorvastatin. These so-called pleiotropic effects of statins [7] may contribute to alter the progression of atherosclerosis, independently of cholesterol lowering. Statins are known to improve endothelial function [8], reduce blood thrombogenicity [9] and exert anti-inflammatory actions [10]. These non-lipid-related actions could be due to the inhibition of isoprenoid intermediates of the cholesterol biosynthetic pathway, such as farnesylpyrophosphate (FPP) and geranylgeranylpiphosphatate (GGPP) [7]. FPP and GGPP mediate the post-translational modification (prenylation) of many proteins, including the small G proteins (Ras, Rac, Rab and Rho), which are involved in cell growth regulation/apoptosis, actin cytoskeleton organization, membrane trafficking and gene expression [7]. The statin-induced inhibition of the prenylation of these proteins impairs their submembranous localization, limiting their activation and full functionality. In vascular smooth muscle cells, we and others have shown that statins regulate the cellular localization and activation of Ras and Rho proteins [11].

Table 1 summarizes the potential benefit of statin treatment in hypertensive patients. The statin-induced inhibition of Rho and its downstream target Rho-kinase function may have beneficial effects in hypertensive patients. Angiotensin-II (AngII), acting through AT1 receptors, plays a key role in the progression of vascular damage associated with hypertension. AngII regulates cell growth, hypertrophy, the production of extracellular matrix proteins and pro-inflammatory mediators [12]. AT1 receptors are coupled to G proteins and require functional small G proteins, including RhoA, Rac, RasG and the Rho/kinase system [12], to exert responses such as actin reorganization, vasoconstriction, hypertrophy, and monocyte chemoattractant protein 1 (MCP-1) and connective tissue growth factor (CTGF) expression. Experimental studies have established that statins regulate several AngII responses. In cultured vascular smooth muscle cells and monocytes, we have observed that atorvastatin decreased the activation of transcription factors.

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<th>Improved endothelial function</th>
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<td>Lower AT1-mediated angiotensin II signal involving:</td>
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<td>Decreased AT1 receptor density</td>
<td>Pro-inflammatory activity, i.e. NF-κB activation, MCP-1, IL-8 expression</td>
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<td>Pro-fibrotic stimulus, i.e. CTGF expression</td>
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AP-1 and NF-κB and inhibited the induction of pro-inflammatory genes [MCP-1 and interleukin-8 (IL-8)] caused by AngII [13]. These effects were reversed by intermediary compounds of the cholesterol pathway, such as mevalonate and the isoprenoids FPP and GGPP. We recently observed that in vascular smooth muscle cells, statins decreased AngII-induced CTGF production, mediated by inhibition of isoprenoids [14]. Statins also show antioxidant properties and restore nitric oxide bioactivity [15]. The AT1 receptor regulates reactive oxygen species (ROS) production through stimulation of NAD(P)H oxidase. Statins decrease the level of AT1 receptors [16], the expression of NAD(P)H oxidase subunits [17] and AngII-induced ROS production [18]. On the other hand, hypercholesterolaemia is associated with elevated AT1 receptor levels, suggesting a major biological response to AngII [16]. All these observations point to a direct interaction between statins and AngII-elicited intracellular signals that could have important clinical consequences.

Unresolved issues in the ASCOT-LLA trial

The safety committee board prematurely discontinued the ASCOT-LLA trial, considering that stopping rules for the primary end-point were significantly exceeded, although no significant reduction in total mortality was shown. This fact also left some unresolved issues open to discussion [19]. For instance, although women on atorvastatin treatment had 20% fewer events, this difference did not reach significance probably due to the limited power of the analysis (there were only 36 primary end-points among women) at the time the trial was stopped. A comparable pattern was described in diabetic patients, in whom no clear benefit of atorvastatin was found despite a 23% reduction in cardiovascular events and procedures in the atorvastatin group. Similarly, other important subgroups such as patients with left ventricular hypertrophy, those ≤60 years old, patients without renal dysfunction and patients with the metabolic syndrome showed no benefit with atorvastatin. The low statistical power of some of the available data for pre-specified subgroups is therefore amenable to interpretation. However, as Trewby et al. [20] pointed out, the absolute risk reduction for preventive treatments such as statins, β-blockers, some antihypertensive treatments, angiotensin-converting enzyme inhibitors and antiplatelet drugs is <1% per year even in high risk patients, and of the same order of magnitude as atorvastatin in the ASCOT-LLA trial. Therefore, the possibility of improving the prognosis of hypertensive patients has to be welcome, despite the need for further research to show better treatment options for our patients.

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Conflict of interest statement. None declared.

References

Diabetogenic effect of antihypertensive treatment: primum nil nocere

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Introduction

Hypertension and diabetes mellitus have been shown to exhibit a complex and multifactorial interrelationship. As part of this, the incidence of diabetes is enhanced in hypertensive patients and this finding is only in part explained by the higher percentage of overweight and obese patients in both populations [1–3]. Moreover, evidence suggests that the rate of new-onset diabetes mellitus in hypertensive patients may also depend on the choice of antihypertensive treatment [4–15]. Among the more modern trials comparing antihypertensive treatment strategies, the Captopril Prevention Project (CAPPP) observed a statistically higher rate of new-onset diabetes mellitus in patients randomized to treatment with conventional therapy (diuretics and β-blockers) as compared with those receiving the angiotensin-converting enzyme (ACE) inhibitor captopril [16]. The present review analyses more studies that reported differences in the incidence of new-onset diabetes mellitus when comparing antihypertensive treatment strategies, and attempts to define the magnitude and possible clinical significance of the observed differences.

Evidence from randomized controlled trials

Since the CAPPP trial, several studies have described differences in the rate of new-onset diabetes mellitus in hypertensive patients treated with various antihypertensive strategies. Table 1 summarizes results from five prospective, randomized hypertension trials (CAPPP [16], INSIGHT [17], LIFE [18], ALLHAT [19] and INVEST [20]) in which different treatment strategies were compared on various morbidity and mortality end points and from one study investigating an ACE inhibitor vs placebo in patients with high cardiovascular risk (HOPE) [21]. In all hypertension studies analysed, there was a significant difference in the incidence of new-onset diabetes mellitus between patients treated with β-blockers or diuretics as compared with more modern antihypertensive agents. Interestingly, in the HOPE trial, ACE inhibition—when compared with placebo—was associated with significantly less new-onset diabetes in a population at high cardiovascular risk, in which β-blockers and diuretics were used at a rate of ~40 and 15%, respectively [21]. Table 2 gives the calculated ‘numbers needed to treat’ (NNT) [22] for new-onset diabetes mellitus in the cited trials. Data are also corrected for the respective observation periods and expressed as NNT/year.

Two studies have provided information about the time course of the manifestation of new-onset diabetes mellitus in treated hypertensive patients. In the LIFE study, an apparently linear increase in the incidence of diabetes over the 5 year period of the study could be observed in the patients randomized to either atenolol or losartan-based antihypertensive treatment. Accordingly, the difference in the incidence of diabetes