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"Statins in hypertension. Are they a new class of antihypertensive agents?"

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There is considerable evidence that hypertension and dyslipidemia are inter-related metabolically, epidemiologically, and clinically[1,2]. The association of hypertension and dyslipidemia confers a greater increase in cardiovascular risk than would be expected with either risk factor alone[3]. With regard to this relationship, a recent analysis of data of the National Health and Nutrition Examination Survey 2003-2004 showed that the prevalence of hypertension was ranged from 23.1% in those without cardiovascular comorbidities to 51.8% to 81.8% in those with cardiovascular comorbidities (in chronic kidney disease: 81.8%; in diabetics: 76.8%; in peripheral artery disease: 73.7%; in coronary artery disease: 73.0%; in congestive heart disease: 71.4%; in stroke:69%; in metabolic syndrome: 61.5%; in dyslipidemia: 51.8%). In spite of higher rates of hypertension treatment in patients with cardiovascular comorbidities (83.4%-89.3%) than in those without these conditions (66.5%), control rates for treatment remained low (23.2%-49.3%)[4]. The remarkable benefit achieved with statin treatments in patients with a wide range of cholesterol levels cannot be attributed only to their cholesterol lowering effect alone. The effectiveness and rapidity of statin-induced decreases in coronary events led to the assumption that these agents possess also cholesterol-independent effects. These beneficial effects that are partly independent of their lipid-lowering actions were named pleiotropic effects. A summary of pleiotropic effects of statins is displayed on Table 1. They especially take aim to the concept of 'vascular failure', including the improvement of vascular endothelial function, inhibition of vascular smooth muscle cell proliferation and migration, anti-inflammatory actions, anti-oxidative effects or stabilization of vulnerable plaques, and improve arterial compliance[5,6]. It has been suggested that the mechanisms of pleiotropic effects involves also the inhibition of 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase, an enzyme crucial to cholesterol synthesis. By means of that statins reduce not only cholesterol but also non steroidal isoprenoid intermediates production. Since these isoprenoids, such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate, regulate the small signaling proteins, Ras and Rho, inhibition of these prenylated proteins by statins might account for their non-lipid-related effects[7]. It has been suggested that other factors than those widely recognized, as chronic low-grade inflammation may also be implicated in the development of hypertension, either as a primary or secondary effect[8]. Sesso et al[9] have demonstrated increased levels of high-sensitivity C reactive protein (hsCRP), a sensitive marker of vascular inflammation is increased in patients with hypertension, even after adjustment for potential confounding factors. Even more, elevated hsCRP levels were documented in subjects with prehypertension[10]. It has been demonstrated that statins reduce hsCRP levels independently of LDL-C levels [9]. Pleiotropic effects of statins raise the possibility that these agents may directly lower BP in addition to reducing serum cholesterol levels. It would imply a further cardiovascular protective effect of these agents. Statins activate endothelial nitric oxid synthase[12], downregulate angiotensin II type 1 receptors[13], reduce levels of endothelin-1[14] and decrease the vascular production of reactive oxygen species[15], These changes are accompanied by increase in arterial compliance[16,17]. The question

about the possible antihypertensive effect of statins remain unanswered, and raises the possibility that statins may directly lower blood pressure in addition to reduce cholesterol levels. However, many gaps exist within our knowledge and there is limited guidance regarding the evaluation of statins as antihypertensive agents.

Table 1.- Pleiotropics effects of Statins

Enhance of Endothelial function and Increase Vascular Relaxation
Up regulate eNOS expression
Decrease release of reactive oxygen species (ROS)
Reduce levels of Endothelin-1
Decrease subunit P22 of NAD(P)H oxidase
Down-regulate Ang AT-1 receptor expression
Increase PI 3-kinase/Akt activity
Hyperpopolarize calcium-activated potassium channels

Inhibition of Inflammatory responses
Decrease pro-inflammatory cytokines
Decrease MHC class II antigen expression
Inhibition of leukocyte function antigen-1
Decrease leukocyte-endothelial cell adhesion
Decrease nuclear factor- κB activation
Lower C-reactive protein levels
Lower Homocysteine levels

Antithrombotic effects
Inhibition of platelet activation and adhesion
Increase t-PA
Decrease PAI-1
Decrease Tissue-Factor expression

Plaque stabilization
Decreased macrophage cholesterol accumulation
Reduced production of matrix metalloproteinases
Decrease inflamatory cell infiltrate
Decrease collagen synthesis
Reduce Angiogenesis
Improvement of coronary remodeling

Immunomodulation

Animal studies

In normocholesterolemic, spontaneously hypertensive rats atorvastatin 50 mg/kg per day, a dose that produce plasma concentrations comparable to those achieved after administration of ordinary doses of atorvastatin in humans, systolic blood pressure (SBP) was significantly decreased. This hemodynamic effect was accompanied by an improvement of endothelial dysfunction and a reduction of Ang II-induced vasoconstriction[18]. In Atorvastatin-treated rats there was a decreased aortic AT1 receptor mRNA expression and a reduction in mRNA expression of the NAD(P)H oxidase subunit p22phox. Some experimental evidences pointed out that in experimental Ang II hypertension statins may have a beneficial effect. In Sprague-Dawley rats increases in heart weight index and carotid cross-sectional area induced by Ang II were blotted out by simvastatin[16].

Do Statins Lower Blood Pressure in Clinical Studies on Hypertensive patients?

Data on the BP–lowering effects of statins in humans have been mixed and highly controversial. Some studies have reported significant BP reduction, but others have not. Goode et al.[11] showed indirect evidences from several studies that cholesterol-lowering regimens may simultaneously reduce BP by between 2 and 5 mm Hg. In a cross-sectional study of 2584 hypertensive patients with no known cardiovascular disease from the National Health and Nutrition Examination Survey 1999-2002[19] compared with people not receiving a statin medication, significantly more statin users had BP <140/90 mm Hg (52.2% vs. 38.0%), complied with low-salt diet, were using antihypertensive medication, and were non-smokers. Nevertheless, in studies performed in hypercholesterolemic subjects without hypertension there was no any significant reduction in BP[20,23]. Very few, relatively small studies have investigated the antihypertensive effect of statins in hypertensive patients with or without hypercholesterolemia with an adequate design[24,29]. Only in few studies participants did not receive other drugs than statins during the whole period of treatment[17,23,24] while the majority received concomitantly antihypertensive drugs and were not specifically designed to evaluate the statins antihypertensive effects (Table 2). Frequent methodological flaws in trials were inclusion of normotensive and hypertensive subjects, they were uncontrolled or unblended, some of them allowed adjustment of antihypertensive medications during the treatment phase, and the treatment period may be too short. In hypercholesterolemic patients with controlled hypertension addition of statins to an ACE inhibitor, an ARB, a calcium channel blocker or a beta-blocker did not significantly decrease BP levels[29,32]. On the other hand, in those patients with uncontrolled hypertension when a statin was added to antihypertensive agents led to a greater reduction in BP. In a double-blind, placebo-controlled crossover trial of untreated hypertensive patients with hypercholesterolemia pravastatin significantly lowered BP independently of age and gender, and of more importance, unrelated to baseline plasma LDL-C and HDL-C levels[26]. Spósito et al[27] compared BP reduction between hypertensive subjects with hypercholesterolemia receiving ACE inhibitors (enalapril or lisinopril) alone and those in whom a statin (lovastatin or pravastatin) was added. The statin–treated group showed a greater reduction in BP and total cholesterol levels. In another study that included patients with isolated systolic hypertension and normal levels of cholesterolemia that were treated with a high dose of atorvastatin (80 mg/d) or placebo without any antihypertensive, SBP was significantly lower after statin than on placebo[17]. Ikeda et al[28] observed an additional lowering effect of pravastatin only on SBP in patients undergoing long-term treatment with antihypertensive agents. However, there were considerable discrepancies with results of other studies that did not showed any significant effect of statins on BP. Here are some examples. O´Gallaghan et al. did not find any significant

short-term effect of low doses of pravastatin on BP in hypertensive patients when adding to a previous treatment with ACE inhibitors or calcium channel blockers[29]. In the Plaque Hypertension Lipid Lowering Italian Study (PHYLLIS)[33] which was the largest study using office determination of BP, included 508 hypertensive hypercholesterolemic patients treated with hydrochlorothiazide or fosinopril for 2.6 years, there was no any additional effect on BP when pravastatin (20 mg/d) was added.

Table 2. BP effects of statins in studies that included only hypertensive patients

Author (year)	Subjects	Duration (mg/d)	Statin (mm Hg)	Change in BP	Diagnosis
Straznicky, 1995	14	8 weeks	Pravastatin 40 vs Placebo	No differences	HTN + HC
Ikeda, 2004	52	24 weeks	Pravastatin 10 vs Probucol 500 mg/d	-4.7/-0.7	Treated HTN + HC
Glorioso, 1999	25	32 weeks	Pravastatin 20-40	-8.0/-5.0	Untreated HTN + HC
Spósito, 1999	70	16 weeks	Lovastatin 20/ Pravastatin 10+diet or only diet,	-7.0/-4.0	Treated HTA + HC
Ferrier, 2002	22	12 weeks	Atorvastatin 80 vs. Placebo	-6.0/2.0	Untreated Systolic HTN+ NC
Fogari, 2004	45	12 weeks	Atorvastatin 20	-2.8/-3.8	Treated HTN + HC
Koh, 2004	47	8 weeks	Simvastatin 20	-3.0/-3.0	Treated HTN + HC

Studies with Ambulatory Blood Pressure Monitoring (ABPM)

In above studies BP was measured only by the traditional clinic approach whose reproducibility and ability to consistently document small BP differences may be limited. Results of studies using ABPM are displayed in Table 3. Terzoli et al.[34] in hypertensive subjects with hypercholesterolemia from both genders, compared their ABPM response to different statins versus soy lecithin. Statins therapy resulted in a non significant tendency to reduce casual SBP and DBP but average daytime SBP and DBP dropped significantly without significant changes in nighttime BP and in the circadian profile of BP. In another study that compared the effects of adding a moderate dose of atorvastatin or diet to antihypertensive agents in hypertensive hypercholesterolemic patients, there was a great reduction in SBP and DBP with the statin[35]. In hypercholesterolemic patients with resistant hypertension adding a moderate dose of atorvastatin to antihypertensive agents 24-h SBP and DBP were more reduced than in the group that only added diet[36] achieved a significant lowering of BP. However, a discrepant results was showed in the largest double-blind trial in hypertensive patients with hyperlipidemia evaluated with ABPM comparing valsartan alone and combinations with a low a a high dose of simvastatin[37]. Valsartan/simvastatin combinations had not incremental effect on 24-hour ambulatory BP compared with valsartan alone. Nevertheless, valsartan plus high–dose simvastatin lowered hs-CRP more effectively than valsartan alone or a combination of valsartan plus low dose of simvastatin[37].

Table 3. Statins effects on BP measured by ABPM

Author (year)	Subjects	Duration	Statin	Change in BP (mm Hg)	Diagnosis
Abetel, 1998	23	12 weeks	Fluvastatin 40 mg/d	-6.2/-5.3	Untreated HTN+ HC
Magen, 2004	48	8 weeks	Atorvastatin 20 mg/d vs. Vitamin C 500 mg/d orPlacebo	-13.7/-7.8	ResistantHTN + HC
Kanbay, 2005	49	12 weeks	Atorvastatin 20 mg/d vs.Diet	-5.1/-5.2	HTN + HCNo placebo
Terzoli, 2005	31	8 weeks	Simvastatin or Pravastatin10-20 mg/d, or Atorvastatin 5-10 mg/d	in HTN: -6.5/-3.2	NT e HTN+ HC
Rajagopalan, 2007	404	12 weeks	Valsartan 160 mg or Valsartan 160 mg plus Simvastatin 20 mg or 80 mg	-0.36/-0.53	HTN+HC

Large Scale Clinical studies

The majority of studies with large population were not specifically designed to determine the antihypertensive effects of statins and that was an ancillary consequence of their analysis. Those studies that included high proportion of normotensive subjects make lowering BP effects of statins difficult to detect. The possible heterogeneity of the BP effects of statins in different group of subjects according to their age, gender, marked versus mild or no hypercholesterolemia, well controlled or uncontrolled BP with antihypertensives, etc, may also explain the discrepancies in BP lowering effects of statin results. In the Brishigella Heart Study, Borghi et al[38] studied 1356 normotensive and hypertensive hypercholesterolemic patients (total cholesterol levels exceeding 239 mg/dL) randomly treated for 5 years with low fat-diet, cholestyramine, gemfibrozil, or simvastatin. In 93% of the hypertensive patients antihypertensive agents were continued unchanged during the whole trial. Significant decreases of BP by about 5% to 10% were found only in those patients whose SBP at baseline were at the 2 highest quartiles. Lowering of BP was greater in subjects treated with statins than in those receiving non-statin lipid-lowering agents. In the UCSD statin study[39] normotensive and hypertensive subjects were included and not discriminatively analyzed, and even in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering-Arm (ASCOT-LLA) trial extra antihypertensive drug use in the placebo group obscured atorvastatin BP effect[40]. Affected by the same limitations, the ALLHAT study[41] did not demonstrate a benefit of addition of pravastatin 40 mg/d to antihypertensive agents on cardiovascular morbidity and mortality.

Statins Treatment of Hypertensive patients with comorbidities

The importance of lowering the impact of hypertension in diabetic patients is remarkable. In a study performed in a group of type 2 diabetic patients with dyslipidemia and hypertension, maintaining antihypertensive agent doses, the addition of low dose of atorvastatin (10 mg/d) lowered DBP levels[42].

In a long-term cross-over study in type 2 diabetic patients with hypertension and microalbuminuria, only simvastatin (20 mg/d) but not cholestyramine (6 g, three times a day) lowered DBP and microalbuminuria, though both hypolipidemic agents similarly decreased serum cholesterol levels[43]. However, there were discrepancies with another study that did not find any significant lowering in BP when added to after controlled BP with ramipril[44].

Meta-Analyses of the antihypertensive effects of statins

A recent meta-analysis of 20 randomized, controlled trials with a total of 828 patients in which concomitant antihypertensive treatment (if any) remained not modified throughout the study showed that SBP was only modestly but significantly lower in patients on statins than in those who received placebo or control hypolipidemic agent. The antihypertensive effect of statins was greater when the analysis was restricted to studies with baseline SBP >130 mm Hg. There was also a non-significant trend for lower DBP in patients receiving statins compared with control[45]. These authors suggested that in general, the higher the baseline BP, the greater the effect of statins on BP. Even this well–performed meta-analysis study demonstrated significant heterogeneity between studies (nondiabetics, diabetics, non diabetics; design protocols with different trial sizes and durations, crossover design, double blind or open-label trials), they were carried out in a variety of settings, with different methods particularly of BP determination, and treatment regimens. These factors can greatly affect the interpretation of the results. Another meta-analysis was focussed on the overall efficacy of statins in hypertensive and nonhypertensive patients. It evaluated results of 14 major randomized clinical trials, that at least followed ≥1000 patients for ≥ 2 years showing that statin therapy effectively decreased cardiovascular morbidity and mortality to the same extent in hypertensive and nonhypertensive patients[46].

Benefits of Combination Therapy with Statins and Antihypertensive Agents

There are experimental evidences of the interaction between LDL-C and mediators of vasoconstriction. With regard to this LDL-C up regulates the expression of both Ang AT-1 receptor[47] and the Endothelin-1 (ET B) receptor[48]. Statins increase the inhibitory effect of AEC inhibitors and ARBs on atherosclerosis through reduction of malondialdehide, monocyte chemoattractant protein-1, levels[44] and hs PCR. Besides, statins prevent heart alterations induced by Ang II[18]. In salt-loaded Dahl-sensitive hypertensive rats pravastatin and olmesartan improved endothelial function through different mechanisms. The statin increased eNOS activity through phosphatidylinositol-3-kinase (PI3K)-protein kinase B (Akt) phosphorylation, while the ARB produced downregulation on dihydrofolate reductase (DHFR), regardless the serum cholesterol and blood pressure levels[49,50]. Experimental results suggested a potential benefit in combining statin with ARB for vascular diseases of salt-sensitive hypertension. Despite no synergistic impact of a combination of a statin with a RAS inhibitor, it does seem to lower inflammatory mediator concentration like TNF- and IL-6 as well as IL-6-induced CRP and PAI-1 production in hepatocytes[51]. In spite of experimental evidences, the clinical benefit of the combination of a renin-angiotensin system (RAS) blocker with a statin in hypertensive patients remains contradictory. Even though insulin resistance that is present in approximately 50% of patients with essential hypertension with or without obesity[52] decreases by the action of RAS inhibitors[53] the addition of simvastatin neither enhanced the BP-lowering effect of losartan in hypertensive hypercholesterolemic patients[33] nor ramipril lowering BP effect in type 2 diabetics with hypertension[45].

In a double blind crossover study the combination of a calcium channel blocker and a statin in normocholesterolemic obese hypertensive patients resulted in greater reduction of BP, TNF, IL-6 and insulin resistance than that produced by the calcium channel blocker alone (54). Those patients that received single pill containing amlodipine/atorvastatin were 2 to 3 times more likely to be adherent than those receiving either co administered amlodipine and atorvastatin or other 2-pill combination of a calcium channel blocker and a statin[55,56].

Conclusions

So far it is unclear whether statins are effective in lowering BP. The available data support only a modest BP-lowering effect of statins that is most prominent in those patients with not well-controlled hypertension. Nevertheless they only produce minor reduction in BP their effects may be relevant from the point of view of cardiovascular prevention. From the available results it appears consistent that statins may be useful in hypertensives with high serum total cholesterol, in those whose hypertension is not well controlled with antihypertensive agents even without high serum total cholesterol, in hypertensive subjects well controlled with antihypertensives, without high serum cholesterol when they have high PCR levels, in those who require preventive measures because other concomitant cardiovascular risk factors, or when they require secondary prevention.

Future research could further characterize the impact of statin use alone or in combination with antihypertensive agents to delay the development of stage 1 hypertension in prehypertension.

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