

Letter to the Editor

# Hypotensive Statin Effect - from Pathophysiology to Treatment

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## Letter to the Editor

The pathophysiology of essential arterial hypertension (HTN) is multifactorial and complex. Recently great interest has been directed toward investigating the role of endothelial dysfunction and oxidative stress, which act as important factors disturbing vascular homeostasis. Vascular endothelial cell dysfunction leads to the reduction of endothelium-derived relaxing factors, of which Nitric Oxide (NO) seems to play the most important role. Indeed, as it was shown endothelial release of NO reduced in HTN [1]. On the other hand, increased production of contracting factors, like oxygen-derived free radicals (reactive oxygen species, ROS) and oxidized low density lipoprotein (ox-LDL) as markers of oxidative stress, could also play important role in the development and consolidation of HTN. ROS production is associated with endothelial dysfunction [2]. Therefore, an imbalance of enhanced oxidative stress and reduced NO production may account for reduced vasodilation, which in turn can favor the development of HTN [3]. Low grade inflammation, measured as elevated levels of hs-C-reactive protein (hs-CRP), may be implicated in the development of endothelial dysfunction, which leads to arterial hypertension [4]. Hs-CRP is an important biomarker in hypertensive patients plays a role in the diagnosis, assessment of risk and prediction of complications. There is growing evidence that the primary abnormality in HTN may be related to sympathetic nervous activation. Although augmented sympathetic drive in the pathogenesis of HTN is well documented, the exact pathophysiology of the nervous dysfunction, as well as its clinical implications remains unclear [5]. It has been proposed that the primary abnormality in HTN may be related to sympathetic nervous activation [6]. Probably, there is a concurrent impact of epinephrine and norepinephrine [7].

Statins – lipid lowering 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors – significantly decrease and limit cardiovascular morbidity and mortality in patients with cardiovascular diseases.

Several experimental and clinical studies indicate that statins could influence Blood Pressure (BP) control [8]. This is due to, independent of lipid-lowering, pleiotropic statin effect [9]. Experimental and clinical data suggest that statins, beyond their hypolipemic effect, exert anti-inflammatory and anti-proliferative actions.

What could be the mechanism of the hypotensive statin effect? A number of mechanisms have been proposed to explain the pleiotropic hypotensive statin effect. Some studies demonstrated statins as reducing ROS mediated oxidative stress. Statins may maintain the balance between oxidant generation and removal by reducing ROS, suppressing endothelial Nitric Oxide Synthase (eNOS) as well as inducing and upregulating antioxidant defense mechanism [10]. According to recent studies, statins reduce cholesterol level and improve endothelium-dependent vasodilation, inflammation and oxidative stress. Flow-Mediated Dilation (FMD) improvement was related to a trend towards increase in total antioxidant status, which was less evident, but still present, after the withdrawal of statin therapy [11]. This may suggest lasting antioxidant statin effect. The hypotensive statin effect could be associated with the endothelial improvement- atorvastatin decreased BP values in parallel with FMD improvement [11]. Increased sympathetic outflow and diminished cardiac vagal tone are characteristic for cardiovascular diseases including HTN. However, the influence of statins on the sympathetic tone activity is unclear. Statins may reduce aortic hyperthrophy, plasma CRP, normalize eNOS with mild Systolic Blood Pressure (SBP) reduction [12]. In experimental studies it has been shown that statins decrease BP through increased NO oxide bioavailability.

Still, hypotensive statin effect seems to be ambiguous.

In the Brisighella Heart Study – a large randomized controlled trial [13], among 1356 patients with hypercholesterolemia a significant decrease in BP was observed in the two upper quartiles of SBP and was greater in patients treated with statin drugs. Thus, it has been suggested that statins significantly lower BP in patients with uncontrolled hypertension, but not in patients with controlled hypertension or normotension. However, in the CAFE-LLA (The Conduit Artery Function Evaluation-Lipid-Lowering Arm) – a substudy of an Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) – 891 patients with HTN were randomized to atorvastatin 10 mg daily or placebo. Statin therapy did not influence central aortic BP or hemodynamics [14]. And finally PHYLLIS (Plaque Hypertension Lipid-Lowering Italian Study) – a randomized double blind trial – discovered that the addition of pravastatin to anti-hypertensive treatment did not cause reduction in SBP values in patients with low blood pressure at baseline [15]. In the meta-analysis of 18 trials assessing hypotensive statin effect in normotensive and hypertensive patients revealed statin therapy did not lead to significant reduction in both- systolic and diastolic pressures [16]. In a huge meta-analysis small, but statistically significant reduction of SBP in patients taking statins was found [17]. Authors concluded that the observed decrease in BP values might be caused by pleiotropic statins effect. Hypercholesterolemia is often accompanied by hypertension. It has been showed that simvastatin decrease ambulatory BP values in patients with HTN, but particularly in the presence of higher levels of cholesterol [18]. It has been observed that statins lower BP values

in patients with elevated, but not normal BP regardless of cholesterol level [9].

The variety of results could be related to various BP measurement techniques, various statins used, small sample size of study populations, confounding effects of concomitant anti-hypertensive therapy, different comparative groups and, finally, various populations studied.

A large randomized double-blind study should be conducted to confirm objectively hypotensive statin effect.

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