Journal of Drug Discovery, Development and Delivery

Austin Publishing Group

Open Access Full Text Article

Letter to the Editor

Hypotensive Statin Effect - from Pathophysiology to Treatment

Agnieszka M Tycinska*

Department of Cardiology, Medical University of Bialystok, Poland

***Corresponding author:** Agnieszka M Tycinska, Department of Cardiology, Medical University of Bialystok, ul. M. Sklodowskiej-Curie 24A, 15-276 Bialystok, Poland

Received: August 28, 2014; **Accepted:** August 30, 2014; **Published:** September 01, 2014

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, supressing 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

Citation: Tycinska AM. Hypotensive Statin Effect - from Pathophysiology to Treatment. J Drug Discov Develop and Deliv. 2014;1(2): 2.

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.

References

1. Vanhoutte PM. Endothelial dysfunction: the first step toward coronary arteriosclerosis. Circ J. 2009; 73: 595-601.
2. Higashi Y, Noma K, Yoshizumi M, Kihara Y. Endothelial function and oxidative stress in cardiovascular diseases. Circ J. 2009; 73: 411-418.
3. Drexler H, Hornig B. Endothelial dysfunction in human disease. J Mol Cell Cardiol. 1999; 31: 51-60.
4. Ozdogan M, Bozcuk H, Coban E. Low-grade inflammation in white-coat hypertension. Med Sci Monit. 2007; 13: CR570-573.
5. Schlaich MP, Lambert E, Kaye DM, Krozowski Z, Campbell DJ, Lambert G, et al. Sympathetic augmentation in hypertension: role of nerve firing, norepinephrine reuptake, and Angiotensin neuromodulation. Hypertension. 2004; 43: 169-175.
6. Campelo M, Polónia J, Serrão P, Cerqueira-Gomes M. Evaluation of the sympathetic nervous system using heart rate variability and plasma hormones in hypertensive patients treated with cilazapril and atenolol. Cardiology. 1996; 87: 402-408.
7. Esler M, Lambert G, Brunner-La Rocca HP, Vaddadi G, Kaye D. Sympathetic nerve activity and neurotransmitter release in humans: translation from pathophysiology into clinical practice. Acta Physiol Scand. 2003; 177: 275-284.
8. Banach M, Mikhailidis DP, Kjeldsen SE, Rysz J. Time for new indications for statins? Med Sci Monit. 2009; 15: MS1-5.
9. Koh KK, Quon MJ, Waclawiw MA. Are statins effective for simultaneously treating dyslipidemias and hypertension? Atherosclerosis. 2008; 196: 1-8.
10. Mahalwar R, Khanna D. Pleiotropic antioxidant potential of rosuvastatin in preventing cardiovascular disorders. Eur J Pharmacol. 2013; 711: 57-62.
11. Tycinska A, Janica J, Mroczko B, Musial WJ, Sawicki R, Sobkowicz B, et al. Hypotensive effect of atorvastatin in hypertensive patients: the association among flow-mediated dilation, oxidative stress and endothelial dysfunction. Arch Med Sci. 2011; 7: 955-962.
12. Zhou MS, Tian R, Jaimes EA, Raij L. Combination therapy of amlodipine and atorvastatin has more beneficial vascular effects than monotherapy in salt-sensitive hypertension. Am J Hypertens. 2014; 27: 873-880.
13. Borghi C, Dormi A, Veronesi M, Sangiorgi Z, Gaddi A. Brisighella Heart Study Working Party Association between different lipid-lowering treatment strategies and blood pressure control in the Brisighella Heart Study. Am Heart J. 2004; 148: 285-292.
14. Williams B, Lacy PS, Cruickshank JK, Collier D, Hughes AD, Stanton A, et al. Impact of statin therapy on central aortic pressures and hemodynamics: principal results of the Conduit Artery Function Evaluation-Lipid-Lowering Arm (CAFE-LLA) Study. Circulation. 2009; 119: 53-61.
15. Mancia G, Parati G, Revera M, Bilo G, Giuliano A, Veglia F, et al. Statins, antihypertensive treatment, and blood pressure control in clinic and over 24 hours: evidence from PHYLLIS randomised double blind trial. BMJ. 2010 25; 340:c1197.
16. Banach M, Nikfar S, Rahimi R, Bielecka-Dabrowa A, Pencina MJ, Mikhailidis DP, et al. The effects of statins on blood pressure in normotensive or hypertensive subjects--a meta-analysis of randomized controlled trials. Int J Cardiol. 2013; 168: 2816-2824.
17. Briasoulis A, Agarwal V, Valachis A, Messerli FH. Antihypertensive effects of statins: a meta-analysis of prospective controlled studies. J Clin Hypertens (Greenwich). 2013; 15: 310-320.
18. Correa V Jr., Fuchs FD, Moreira LB, Gerhardt M, Fuchs SC, Sloczinski CR, et al. Blood pressure-lowering effect of simvastatin: a placebo-controlled randomized clinical trial with 24-h ambulatory blood pressure monitoring. J Hum Hypertens. 2014; 28: 62-67.

J Drug Discov Develop and Deliv - Volume 1 Issue 2 - 2014
ISSN : 2471-0288 | www.austinpublishinggroup.com

Citation: Tycinska AM. Hypotensive Statin Effect - from Pathophysiology to Treatment. J Drug Discov Develop and Deliv. 2014;1(2): 2.