The effects of statins on blood pressure: current knowledge and future perspectives

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Statin therapy has gained interest in the field of hypertension due to the potential role of different statin agents in blood pressure (BP) lowering [1-3]. The potential mechanisms involved include the downregulation of the angiotensin II-type 1 receptor, the decrease of vasoconstrictor endothelin-1 levels, and the increase in the endothelial production of nitric oxide (NO), an effect that is correlated with the upregulation of endothelial NO synthase expression [4-6]. Furthermore, we have recently reported the effects of statin treatment on endothelial function, oxidative stress and inflammation in patients with hypertension and normal cholesterol levels [7]. Yet, despite the beneficial effects shown by statins in hypertensive animal models as well as in small clinical studies, the results from meta-analyses and large clinical trials have been controversial.

Indeed, the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) [8] demonstrated that the combination of amlodipine-based therapy and atorvastatin was highly effective in preventing cardiovascular (CV) endpoints in hypertensive patients at risk of CV disease, but the authors did not report any significant effect on BP [8]. However, it should be highlighted that the use of anti-hypertensive agents was left to the discretion of physicians during the trials [8]. Additional information comes from post-hoc analyses and meta-analyses, suggesting that statins could lower systolic blood pressure, particularly in patients with high blood pressure [9]; however, most studies had small sample sizes, were not blinded, and the time of observation was not long enough.

In addition, several authors have emphasized that hypertension and hyperlipidaemia seem to be interrelated through common pathophysiological pathways [10] and it has been recently reported [11] that lipoprotein size and subclass concentrations, especially small, dense low-density lipoproteins (LDL), are associated with incident hypertension and may provide additional information to traditional CV risk factors [11]. In this view, it should be highlighted that the most important link between lipid metabolism and atherosclerosis is based on the formation of foam cells (the first step of plaque generation) from oxidized, small dense LDL [12]. Indeed, LDL are very heterogeneous particles, which comprise multiple distinct subclasses that differ in size, density, physico-chemical composition, metabolic and oxidative behaviour, as well as atherogenicity [13]. Increasing evidence suggests that both the "quality", and probably especially the "quantity" of plasma lipids and lipoproteins influence CV risk, as reflected in the pro-atherogenic alterations that give rise to elevated levels of

small, dense LDL. The pathophysiology, atherogenicity and clinical significance of these LDL particles have already been highlighted in the recent consensus statement of a European panel of experts [14, 15].

Owczarek *et al.* in the present issue of *Archives of Medical Science* [16] report no beneficial effects of simvastatin after 4 weeks of therapy on BP and heart rate after metoprolol injection in animal models (rats). The authors have already observed similar effects in two other studies with a 2-week period of statin administration [17, 18]. Yet, a reduction in heart rate and BP has been reported in patients with hypertension and type-2 diabetes with the concomitant administration of simvastatin and metoprolol [19], and other studies evaluated the effects of such combined therapy on C-reactive protein levels [20]. We cannot exclude that therapeutic modulation of enhanced inflammation and/or atherogenic dyslipidaemia may contribute to the beneficial effect shown by simvastatin on blood pressure, especially considering that the study by Owczarek *et al.* has some important limitations connected to the length of the intervention (only 4 weeks), the dose and the type of statin, and finally with the selection of hypertension drug: metoprolol, an old β_1 receptor blocker without a nitric oxide-potentiating vasodilatory effect [16, 21].

In conclusion, as recently highlighted, there is more to predicting vascular disease than just established risk factors [22]. Patients with hypertension benefit from statin administration, independently of their plasma lipid levels, and independently of the influence on their BP. Inflammation and atherogenic dyslipidaemia may play a role [23-25]. Future well-designed clinical trials with carefully selected endpoints are needed in order to demonstrate whether statins definitely have an anti-hypertensive effect. Such studies should also investigate the synergistic effects of hypertension and atherogenic lipoproteins on CV risk.

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