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Lipophilic Statins and Aldosterone Secretion: A Bridge Too Far?

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Statins have been hypothesized to have pleiotropic effects that may mitigate the risks of developing arterial and venous thromboembolic events,[1, 2] heart failure,[3] and immune-related diseases including pneumonia.[4] Statins have been observed also to lower blood pressure in short-term, double-blinded, randomized clinical trials,[5–7] and to attenuate cardiac remodeling in mice with myocardial infarction or hypertension.[8–10] While the latter effects may relate to improvements in vascular stiffness (secondary to reduced lipid accumulation within the arterial intima-media layer), other biological features of statins that are distinctive from their cholesterol-lowering effects may contribute to both the attenuation of blood pressure elevation and cardiac remodeling.[11]

In the current issue of *Circulation*, Dr. Baudrand and colleagues explore a potential novel mechanism of statin pleiotropy by focusing on the impact of lipophilic versus hydrophilic statins on endogenous aldosterone secretion.[12] Previous studies of humans evaluating this premise have yielded conflicting results, with both a lowering[13] and no effect[14] on circulating aldosterone levels being reported. Prior experimental observations in Dahl salt-sensitive rats provide some support for an aldosterone-lowering effect of simvastatin (both at the tissue level and in the circulation).[15]

Current Study

In an elegantly designed two-step investigation the authors evaluate if blood and 24-hour urinary aldosterone levels are affected by statin use. First, the investigators used data on adrenal hormone secretion from two separate interventional studies of people with hypertension and diabetes, respectively, who were not treated with renin-angiotensin-aldosterone system (RAAS) inhibitors. The authors observed that people on statin treatment

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had a lower blood pressure, and up to a third lower blood aldosterone levels compared with people who were not on statin treatment, both at baseline and following stimulation with angiotensin II (Ang II); these observations were paralleled by lower 24-hour urinary aldosterone levels in statin-treated individuals. In contrast, plasma and 24-hour urine cortisol levels were unaffected by statin use suggesting a preferential cross-talk between statins and the mineralocorticoid pathway as opposed to with the corticosteroid pathway. Of note, blood aldosterone levels were significantly lower in people using lipophilic compared with hydrophilic statins. In a second step, the investigators conducted an *in vitro* study of aldosterone secretion in rat adrenal glomerulosa cells to strengthen the plausibility of their initial observations. In this study, aldosterone secretion following stimulation with potassium and Ang II was observed to be lower in cells exposed to lipophilic (but not to hydrophilic) statins, compared with cells not exposed to statins, whereas corticosteroid secretion remained unaffected.

The carefully performed study by Dr. Baudrand and colleagues adds novel and interesting data to the current literature on the effect of statins on aldosterone metabolism.[12] Aldosterone secretion is influenced by several factors, including physical activity, posture, and dietary sodium intake. Therefore, blood aldosterone concentration measurements following stimulation with Ang II need to be undertaken under highly standardized conditions. It is conceivable that failure to adequately control for these factors contributed to the inconsistent results in the literature regarding the effect of statins on circulating aldosterone levels.[13, 14] The two interventional studies analyzed by the investigators were undertaken under very well-controlled conditions: all study participants were provided a sodium-, potassium-, and calcium- regulated diet that was also free from caffeine and alcohol, and blood and 24-hour urinary samples were obtained during in-patient visits. This rigorous study protocol increased the likelihood of revealing a true inverse association between blood/urinary aldosterone concentrations and statin use in individuals on both a low and a high salt diet. The consistency of the observations in two separate intervention studies, and both in patients on low salt and high salt diets, the demonstration of a graded statin dose-response relationship, and the specificity of the association for aldosterone (and not corticosterone) support the possibility of a causal relationship underlying the reported observations. However, additional studies are required to elucidate the underlying biological mechanisms for the observed effects of statins, including on blood pressure. For instance, statins may reduce blood pressure by mechanisms not directly related to alteration of aldosterone secretion, such as by decreasing the expression of Ang II receptors, inhibiting Ang II-dependent intracellular signaling, and by reducing the RAAS-dependent inflammation and oxidative stress.[16].

Clinical Implications

The intriguing observations raise several important questions from a clinical perspective. For instance, it is unclear if the effects of lipophilic statins on aldosterone metabolism are ‘clinically’ relevant, and if so, should lipophilic statins be preferred over hydrophilic statins in clinical practice? Moreover, could statins be used as an adjuvant therapy to conventional blood pressure lowering and anti-remodeling medications in high-risk patients with average levels of serum low-density lipoprotein (LDL) cholesterol? Aldosterone is a well-known key

regulator of sodium and potassium balance, blood pressure, endothelial function, and cardiovascular remodeling, and may independently predict incident hypertension and mortality in the general population.[17, 18] Further, blood aldosterone concentrations are directly and positively associated with the risk of ischemic events and mortality in patients with coronary artery disease and myocardial infarction.[19, 20] Aldosterone blockers improve survival in severe heart failure and in patients with myocardial infarction with a reduced left ventricular ejection fraction (LVEF),[21, 22] and are superior to other antihypertensive medications in reducing blood pressure in patients with diabetes and refractory hypertension.[23] Yet such aldosterone blockade may not have beneficial effects in other settings. Of note, there are no data to support the notion of aldosterone antagonism in patients without hypertension, myocardial infarction, heart failure or primary hyperaldosteronism, i.e., in individuals with average or lower cardiovascular risk.

The investigators report a blood pressure lowering effect and lesser salt sensitivity in patients on statin therapy. It is unclear if an approximately 30% reduction in blood aldosterone levels as observed by Baudrand et al. will translate into clinically meaningful reductions in risk of cardiovascular risk in general. Moreover, the analyses undertaken by the investigators were restricted to individuals with hypertension and/or diabetes who were not using RAAS inhibitors, and the studies were undertaken under highly controlled conditions of dietary sodium intake and during stimulation with potassium or Ang II. Whether long-term statin use under normal, physiological conditions in ambulatory high-risk individuals on a random sodium diet (and possibly on RAAS blockers) would also translate into an up to 30% reductions in blood aldosterone levels and if such lowering contributes to lower cardiovascular rates remains, therefore, to be determined. Additionally, it is unclear if the blood aldosterone levels will remain lowered over a sustained period (chronic statin usage) or if an ‘aldosterone escape’ will set in eventually in high-risk individuals, as has been reported in heart failure patients.[24]

There is some indirect evidence consistent with the notion that lipophilic statins may have clinically important effects on the mineralocorticoid pathway. A meta-analysis of 6,214 heart failure patients from 19 trials suggested that lipophilic statins were superior to hydrophilic statins in reducing blood B-type-natriuretic peptide (BNP) concentrations and improving LVEF (both $p<0.0001$).[25] Moreover, in a short-term randomized clinical trial of patients with non-ischemic, dilated cardiomyopathy, those treated with simvastatin (the most lipophilic statin available) experienced improved symptoms, increased LVEF, and lowered circulating BNP, compared with the placebo group over 14 weeks of treatment.[26] In contrast, another study that compared atorvastatin (a lipophilic statin) with pravastatin (a hydrophilic statin) did not report any differences in deaths or major adverse cardiovascular events, or surrogate measures such as circulating BNP or serum creatinine concentrations in post-myocardial infarction patients over a 2-year period.[27] Because of the burgeoning numbers of people treated with statins worldwide (estimated to exceed a billion[28]), even a small reduction in aldosterone secretion and/or a modest decrement in blood pressure due to statin intake could, in theory, translate into a large reduction in numbers of cardiovascular events in the community, a premise that warrants further investigation. Undoubtedly, however, the inhibitory effects of statins on mineralocorticoid synthesis (deemed favorable from a cardiovascular perspective) must be juxtaposed against the reported risk of unintended side

effects of these agents.[29] Overall, statin use should therefore be restricted to lower elevated LDL cholesterol levels and to lower cardiovascular in high-risk individuals; at least until robust evidence suggests clinically beneficial effects beyond the lipid-lowering mechanisms.

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