



Invited commentary

Can renin inhibition by Aliskiren prove itself in atherosclerosis prevention?

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The renin-angiotensin-aldosterone system (RAAS) regulates inflammation and vascular remodeling thus playing an important role in atherosclerosis, kidney disease and heart failure. As an example of this, the effector hormone Angiotensin II (AngII) was shown to promote oxidative stress, endothelial dysfunction and vascular inflammation [1], all of which would be detrimental. However, inhibiting the RAAS now goes beyond blood pressure reduction and is an important component of the baseline treatment of heart failure, cardiorenal syndrome and diabetic nephropathy. As an example of its protective role in atherosclerosis, the HOPE (Heart Outcomes Prevention Evaluation) trial showed a 37% risk reduction in cardiovascular death by Ramipril in people with diabetes [2].

Angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) reduce effectively the production of AngII, but consequently increase plasma renin concentration because of the loss of negative feedback by AngII on renin. On one hand this might lead to a limited blockade of the RAAS, on the other it could lead to activation of possible alternative pathways by renin [3]. This issue raised the demand for different RAAS inhibitors. In 2007 the US Food and Drug Administration first approved Aliskiren. This orally active drug acts a direct renin antagonist, thereby antagonizing the rate-limiting step of the RAAS without raising the plasma renin activity. Plasma renin activity has

previously been discussed as biomarker to predict cardiovascular events [4], so the pre-conditions for Aliskiren seemed to be promising. However to date, Aliskiren has failed to prove itself in cardiovascular outcome studies. The ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-renal Disease Endpoints) study was terminated prematurely due to the concerns of higher stroke risk and apparently no beneficial effects of Aliskiren. However, in experimental setups, Aliskiren was shown to be protective and reduced early atherosclerotic lesions [5].

In this issue of Atherosclerosis Wu and colleagues [6] investigate the effect of RAAS inhibition by Aliskiren on neovessel formation and atherosclerotic plaque development in an apolipoprotein E-deficient (ApoE $-/-$) mouse model of late atherosclerosis. The key feature of this study is a roughly 54% reduction of intima/media ratio as indicator of plaque size as well as a significant reduction of neovascularization in aortic roots of Aliskiren-treated mice in a blood pressure-independent matter. The physiological process of new vessel formation restores normoxia in the vessel wall, whereas pathologically increased neovascularization leads to the vicious cycle of disease progression by inflammation, wall thickening and hypoxia [7]. Wu et al. [6] further found an increased collagen and elastin plaque content indicating a more stable plaque, while macrophage infiltration, the expression of cathepsin S protein (CatS) and toll-like receptor (TLR) 2 were reduced. TLR play an important role in the innate immune system and several lines of evidence indicate an association with atherosclerosis [8]. CatS is an excreted lysosomal protease which is linked to extracellular matrix degradation such as elastin and collagen and therefore potentially responsible for plaque destabilization [9].

To further evaluate the effect of CatS on atherosclerosis, the authors went on and generated ApoE $-/-$ CatS $-/-$ mice. CatS-lacking mice showed significantly less plaques, which strengthens the potential role of CatS on atherogenesis, and particularly on plaque destabilization. However, additionally, the authors demonstrated that treatment with Aliskiren did not have further effects on plaque reduction in ApoE $-/-$ CatS $-/-$ mice indicating CatS being a downstream target of the RAAS. As would be expected, Aliskiren treatment reduced serum AngII. In human umbilical vein endothelial cells (HUVECs) Wu et al. demonstrated that CatS expression was induced by AngII, whereas RAAS inhibition as well as siRNA

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treatment targeting TLR2 antagonized CatS expression. This *in vitro* finding supports a potential pathway of CatS being a downstream target of AngII via a TLR2-mediated cascade.

Overall this study advances our understanding of the RAAS in the context of atherosclerosis and vascular remodeling. Particularly the link between Angiotensin, TLR2 and CatS is interesting and promises future interventional targets. However, several issues remain still unclear. In an earlier publication the same group had already demonstrated that RAAS inhibition via AngII type 1 receptor blockade by Olmesartan resulted in reduction of plaque size in ApoE^{-/-} mice as well as reduced CatS tissue levels [10]. These findings make clear that the effect of Aliskiren in this study is most likely due to the inhibition of RAAS, but possible effects of Aliskiren other than reduction of AngII remain to be elucidated.

Interestingly, Wu et al. [6] showed a reduction of (pro) renin receptor (PRR) in plaques of Aliskiren-treated mice. The PRR has recently been discovered with its intracellular downstream cascade and is particularly expressed in vascular smooth muscle cells of heart and kidney [3]. Therefore PRR might play a potential role in atherosclerosis. PRR can be activated by prorenin and also by renin itself. ARBs and ACEIs increase, whereas Aliskiren reduces plasma renin activity, so effects on the PRR –and therefore possibly on atherosclerosis– might be contrary, but remain to be elucidated.

Another aspect that requires further investigation is whether Aliskiren acts also at the tissue level. In fact, recently there has been some evidence that Aliskiren inhibits tissue RAAS more efficiently due to direct antagonism of the non-proteolytically activated prorenin [3]. Wu and colleagues [6] have only focused on local effects of RAAS, but discrimination between the tissue-specific and the systemic effects of Aliskiren need further evaluation and could help explain the results of clinical outcome studies. Interestingly, in a different study using a model of metabolic syndrome, mice lacking renin expressed a favorable phenotype due to higher energy expenditure and resistance to diet-induced obesity [11]. In the current study a different mouse model has been used, but at least with a similar setup also using a high fat diet on mice with a C57BL/6 genetic background. Wu et al. did not notice an effect of Aliskiren as direct renin antagonist on weight gain, however the energy expenditure was not tested. Further experiments are needed to reveal if Aliskiren might increase energy expenditure and would be favorable in patients with metabolic syndrome. As a final point, the authors state, supported by their *in vitro* experiments using a PI3K inhibitor, that the PI3K/Akt pathway might be involved in AngII mediated CatS expression. This finding is interesting, but weakly supported. Previous studies have showed few pathways in this matter might be involved. Therefore more studies are eventually needed to understand the actual cascades.

In conclusion, Aliskiren has shown promising results in an experimental setup like this study, which also highlights the importance of the RAAS in atherogenesis. Especially the resulting difference of low plasma renin activity compared to treatment with ARBs and ACEIs seems interesting, but additional investigations are

needed to distinguish between RAAS- and non-RAAS-related effects of those substances. In the ALTITUDE trial Aliskiren combined with an ACEI failed to prevent cardiovascular outcomes in patients with Type 2 Diabetes, showing possible harmful effects. Previously, ARBs and ACEIs in combination have failed as well [12]. It is intriguing to hypothesize that a tissue-specific effect of Aliskiren explains the negative performance in diabetic patients, but it may also be a promising treatment option in specific patients independently from ARBs and ACEIs.

Disclosures

The authors have no conflict of interest to disclose regarding the content of this manuscript.

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