

## RESEARCH HIGHLIGHT

# Renin blockade: a double-edged sword?

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**Aliskiren, a direct renin inhibitor, blocks the first step of the renin–angiotensin–aldosterone system (RAAS), thereby reducing plasma renin activity and the circulating levels of angiotensin I, angiotensin II, and aldosterone. Extensive RAAS blockade can be achieved through the administration of aliskiren; however, renin blockade is a double-edged sword because the renin/prorenin receptor-associated pathway is also reportedly modulated by direct renin inhibitor. This research highlight discusses the findings of a recent clinical study of aliskiren and explores the complex interactions of key molecules in the RAAS pathway in response to aliskiren administration.**

**Keywords:** Direct renin inhibitor; renin/proreninreceptor; endothelial function

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The renin–angiotensin–aldosterone system (RAAS) plays a key role in the development of arteriosclerosis; therefore, blocking several steps in the RAAS pathway is reported to be protective against the progression of this disease. However, attempts to block the RAAS pathway have been unsatisfactory because each blockade is associated with a specific set of problems, such as a reciprocal increase in serumangiotensin (Ang) II concentration after Ang II receptor blocker (ARB) treatment [1], or aldosterone breakthrough [2]. Therefore, the complete blockade of the RAAS pathway remains an unattainable goal.

Aliskiren is a direct renin inhibitor that blocks the first step in the RAAS pathway, thereby reducing plasma renin activity (PRA) and the circulating levels of Ang I, Ang II, and aldosterone [3]. Hence, this agent offers a broad suppression of the RAAS pathway. However, there have

been some unanticipated pitfalls associated with this agent. For example, aliskiren has been unsuccessful in blocking RAAS-independent intracellular signaling pathways through prorenin receptors (PRRs). At instances where this agent is reported to effectively suppress PRA, the reciprocal increase in plasma renin concentration may enhance the PRR activity [4].

In our recent report titled “Effect of add-on aliskiren to type1 angiotensin receptor blocker therapy on endothelial function and autonomic nervous system in hypertensive patients with ischemic heart disease,” we discuss the results of a study based on comparative therapy of aliskiren and ARB on the effects of endothelial function and the autonomic nervous system response [5]. ARB monotherapy increased PRA, Ang I, and Ang II levels, while the addition of aliskiren to ARB eliminated the compensatory increase in PRA and Ang II caused by ARB

administration [6]. The results of the study demonstrated that aliskiren reduced PRA significantly, but did not improve endothelium-dependent vasodilation as measured by flow-mediated dilation (FMD), which was in contrast to the results of previous reports [7-10]. For instance, Virdis *et al.* [11] reported that aliskiren improved endothelial function compared with ramipril, probably due to decrease of reactive oxygen species via the suppression of RAAS pathway. Bonadei *et al.* [8] also demonstrated the add-on effect of aliskiren with angiotensin converting enzyme inhibitor (ACEi) or ARB pretreatment. It seems reasonable that reinforcement of RAAS suppression by aliskiren leads to an improvement in the endothelial function. However, similar to our study, Flammer *et al.* [12] demonstrated that aliskiren-induced endothelial dysfunction in patients with early atherosclerosis. Therefore, the effect of aliskiren on vascular function remains controversial. In the current study, the negative finding may be the result of inadequate aliskiren dosage because aldosterone concentration did not decrease either with the combination therapy of aliskiren and ARB or with ARB monotherapy [2]. However, the effects on the sympathetic nervous system and heart rate were clearly demonstrated and enhanced parasympathetic nervous system activity usually leads to an improvement in FMD in the clinical setting of RAAS inhibition [13-14]. The failure in improving endothelial function by adding aliskiren suggests some opposite effects of aliskiren on vascular function, which may imply that renin blockade is a double-edged sword.

It remains unclear whether aliskiren exerts adverse effects; however, the correlative relationship between changes in PRA and FMD also strongly supports the hypothesis that this result was derived from the contribution of the PRR pathway. PRA suppression is believed to promote an increase in renin concentration and the effect of PRA suppression may correspond to the enhanced activity of a PRR-associated pathway [15]. In addition, the study included patients with significant coronary artery stenosis, which is supposed to correspond to increased PRA as compared to other study populations [16-17]. As a result, the aliskiren-induced increase in PRR activity may have been enhanced.

In regard to the effects associated with PRRs, several reports demonstrated pro-atherosclerotic features induced by the PRR pathway. Liu *et al.* [18] found that the binding of prorenin to PRR induced the proliferation of human umbilical artery smooth muscle cells, and this pathway is mediated by the generation of reactive oxygen species and extracellular-signal regulated kinase 1/2 (ERK1/2) activation. In addition, in diabetic rats, PRR expression was upregulated, which contributed to the development of glomerulosclerosis, diabetic nephropathy, and increased

blood pressure [19]. However, the PRR pathway has not been sufficiently explored and its path physiological implications have not been concisely elucidated. Furthermore, the effects of aliskiren on the PRR pathway also remain unknown [20-21]. The balance of the RAAS and PRR pathways significantly differs in each clinical condition; thus, clarifying the regulation of these pathways may contribute to a better understanding of the hemodynamic effect in the clinical setting of RAAS inhibition.

### Conflicting interests

The authors declare that they have no conflicting interests.

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