

# Aliskiren and the kidney: beyond hypertension

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## Abstract

Aliskiren is a novel drug with the ability to lower plasma renin activity, reducing proteinuria in hypertension and in diabetic nephropathy. In primary and secondary glomerular diseases, important causes of end-stage kidney disease, proteinuria is a hallmark. Moreover, urinary protein is a marker of renal disease progression. The renin-angiotensin-aldosterone system is generally activated in these patients. A complete blockade with the use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers with or without aldosterone receptor blockers is not easy to achieve, and side effects are not uncommon. Plasma renin activity is even increased in patients with this approach. Aliskiren should be considered as a new therapeutic option to be assessed in glomerular diseases, as plasma renin activity can be reduced and a better control of the renin-angiotensin system could be achieved with the consequent reduction in the amount of urinary protein excretion.

## Introduction

The ability of a saline sample of renal tissue to produce an increase in blood pressure, noted by Tigerstedt and Bergman in 1898,<sup>1</sup> was probably the turning point to unravel the inherent complexity of the pathophysiology of hypertension. Their discovery suggested the presence of the circulating renin-angiotensin-aldosterone system (RAAS). This intriguing system consists of an array of blood-borne and locally generated components which functions to maintain salt and water homeostasis and blood pressure regulation. The feedback loops can be turned on or off at different steps by several factors or mechanisms, with the ultimate outcome of maintaining normal cardiovascular function. However, tissular or local RAAS may be more important than the circulating RAAS to control vascular tone and arterial wall homeostasis.

increase aldosterone levels to certain degrees, rendering these inflammatory molecules free to play an active role in tissue remodeling and scarring.<sup>7</sup>

Furthermore, ACEIs and ARBs can inhibit the synthesis and secretion of many cytokines and inflammatory mediators involved in the pathophysiology of many glomerulopathies, (angiotensin II, aldosterone, endothelin, plasminogen activator inhibitor-1, transforming growth factor- $\beta$ , platelet derived growth factor, platelet activated factor, interleukin-6, tumor necrosis factor, fibroblast growth factor). This important effect, although clinically relevant, is also still incomplete. This partial inhibition of the RAAS can explain the failure of ACEIs and/or ARBs to completely control the progression of renal failure in the glomerular arena.

## Renin-angiotensin system, angiotensin converting enzyme inhibitors and receptor blockers

Inhibition of the RAAS with angiotensin converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs) has proved to be a successful strategy for the treatment of hypertension and related cardiovascular disorders. The evidence of this approach to control blood pressure is beyond question, regardless of the level of activation of the circulating plasma renin activity. However, by reducing feedback inhibition of renin release, the effects of ACEIs and ARBs lead to an increase in plasma renin concentration and activity, limiting a complete inhibition of the RAAS system.<sup>2,3</sup> Moreover, inhibition of ACE causes an increase in angiotensin I, which is then available for conversion to angiotensin II by ACE-independent pathways not blocked by ACEIs, namely cathepsins and tonins.<sup>4,6</sup> Consequently, despite an adequate control of blood pressure, angiotensin II levels will

## Renin-angiotensin system and the kidney

One of the organs that is compromised by this partial inhibition of the RAAS is the kidney. Angiotensin II increases efferent arteriole vasoconstriction and glomerular filtration rate, therefore increasing the traffic of macromolecules along the mesangial surface and the influx of cytokines and macrophages. This harmful circuit leads to glomerular basement membrane derangements that, if they become chronic, result in proteinuria which when reabsorbed by proximal tubular cells causes tubulo-interstitial injury, oxidative-stress, hypertension, and chronic and progressive renal failure.

## Aliskiren and the (pro)renin receptor

It is, therefore, tempting and reasonable to assess the effects of a different pharmacological strategy that completely blocks the RAAS upstream. Aliskiren is an octanamide, the first known representative of a new class of non-

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peptide orally active renin inhibitor that blocks the RAAS at its rate-limiting step and induces a net reduction in plasma renin activity, angiotensin II and aldosterone levels.<sup>8,9,10</sup> Upon inhibition of the RAAS at this initial step, there is a compensatory rise in plasma renin concentration.<sup>11</sup> The increase in plasma renin concentration that occurs after ACEIs, ARBs or aliskiren has been used as an indirect means to quantify the inhibitory effects of any anti-angiotensin II drug on the RAAS.<sup>12</sup> Aliskiren acts as a pure direct renin inhibitor that binds to the enzymatically active site of renin. A (pro)renin receptor signals exposure to either renin or prorenin, the inactive form of renin.<sup>13</sup> The (pro)renin receptor in turn enhances renin catalytic activity and allows prorenin to display catalytic activity without its proteolytic conversion to renin. This (pro)renin receptor-induced prorenin activation could explain how prorenin exerts pathological effects in diabetic patients, where prorenin represent  $\leq 95\%$  of total circulating renin.<sup>14</sup> Interestingly, recent data has shown that renin and prorenin induce activation of the extracellular signal-regulated kinase (ERK) pathway, independent of angiotensin II. In this respect, aliskiren has no (pro)renin receptor blocking action. Therefore, ACEIs, ARBs and aliskiren all increase renin concentration which could conceivably induce (pro)renin receptor signaling without the involvement of angiotensin II. This suggests that blockade of the (pro)renin receptor might be an alternative or an adjunct to the renin-angiotensin system inhibition, particularly in conditions with high renin and/or prorenin levels.<sup>14</sup> High prorenin levels are closely associated with the severity of diabetic complications. However, aliskiren still blocks the tissue renin angiotensin system, because aliskiren would immediately act on activated prorenin so that angiotensin II production does not occur.<sup>14</sup> Interestingly, renin bound to the (pro)renin receptor presents much greater catalytic activity than soluble renin.<sup>15</sup>

The cloning of a functional receptor for both renin and prorenin suggests that renin and prorenin may exert direct angiotensin II-independent tissue damaging effects by increasing the expression of profibrotic pathways and molecules such as transforming growth factor- $\beta$ .<sup>16</sup> Additionally, the receptor may amplify renin-induced angiotensin II-dependent effects.

## Aliskiren and renin angiotensin system

One concern is the potential adverse effect of high circulating renin concentrations after aliskiren therapy. As mentioned previously, aliskiren binds to the active site of renin, reducing its activity (plasma renin activity)

and angiotensin II production. Diminished angiotensin II levels stimulate renin secretion (plasma renin concentration). The potential negative consequence of high renin concentration is that renin may bind to a renin receptor and trigger yet unknown events.<sup>15</sup> However, an important contributor to the exaggerated renin response is the interference by the renin inhibitor in the renin assay causing overestimation of the renin concentration.<sup>17</sup> Thus, this renin response may not actually represent an increase in enzymatically active renin molecules in plasma. The question as to whether this increase in renin concentration has any effect remains unanswered. Although aliskiren lowers plasma renin activity, renin concentration rises, while both are increased by ACEIs and ARBs.<sup>18,19</sup> High levels of renin could activate the prorenin/renin receptor, which aside from activating prorenin, can possibly initiate ERK1/2 (extracellularly regulated kinase) signaling, transforming growth factor- $\beta$  activation, and other potentially serious complications.<sup>17,20</sup> However, ACEIs and ARBs also leave these issues unresolved with a partial inhibition of angiotensin II concentration, despite good blood pressure control. Authors have argued against renin inhibition, because plasma renin concentrations after aliskiren are higher than those obtained after ARBs.<sup>21</sup> However, in some studies in mice, ARBs have caused higher plasma renin concentrations than aliskiren. This discrepancy could be partly explained by the method used to measure renin concentrations in mice and in humans.<sup>22</sup>

Plasma renin activity is blocked only by aliskiren. Elevated baseline plasma renin activity in untreated patients has been associated with end-organ damage, such as left ventricular hypertrophy and renal dysfunction,<sup>23,24</sup> probably due to high angiotensin II levels.<sup>25</sup> Renin inhibition with aliskiren, therefore, offers the chance of enhanced RAAS suppression and improved end-organ protection, alone or in combination with other antihypertensive drugs.<sup>12,26</sup>

## Aliskiren and the kidney

The kidney is an important site of uptake of renin inhibitors, and aliskiren has been found in renal glomeruli, renal arteries and capillaries.<sup>27,28</sup> Aliskiren may act directly on the renin-secreting juxtaglomerular cell to influence prorenin processing and renin release.<sup>17</sup>

Diabetes mellitus, essential hypertension, primary glomerular diseases and autosomal dominant polycystic kidney disease account for the vast majority of adult cases of stage 5 renal insufficiency. Glomerulonephritis, a

setting in which proteinuria plays a major role both in pathogenesis and prognosis, accounts for 12% of end-stage renal disease cases; coupled with diabetes mellitus and hypertension they represent 80% of the causes of end-stage renal disease and the need for dialysis.<sup>29</sup> Many renal patients, particularly those with primary glomerulopathies, may present with heavy proteinuria and normotension.

## Aliskiren in pre-clinical studies

Of note, in an interesting paper published by Nussberger et al, aliskiren and irbesartan were administered separately to mice and significantly prevented atherosclerosis progression. The mice showed thinner fibrous cap, smaller lipid core, decreased media degeneration and local macrophage infiltration when compared with untreated animals or with those treated with atenolol or calcium channel blockers, despite similar results in successfully controlling blood pressure. Interestingly, aliskiren significantly increased vascular smooth muscle. This shows a specific role of the renin angiotensin system in atherogenesis.<sup>22</sup>

It has been shown that reducing angiotensin II action with ACEIs and/or ARBs can even reduce proteinuria to a lower level after normotension has been achieved, suggesting that in normotensive rats, proteinuria can be caused by angiotensin II through inflammatory (glomerulosclerosis and interstitial sclerosis) and not just hemodynamic mechanisms. In other words, proteinuria is not exclusively caused by hypertension. In this respect, aliskiren normalized blood pressure and coronary resistance and prevented cardiac hypertrophy and albuminuria in double transgenic rats. The renoprotective effects of aliskiren were, at least in part, due to improved renal hemodynamics and distal tubular function.<sup>30</sup>

In diabetic transgenic mice, Kelly *et al.* showed that aliskiren did not reduce blood pressure as much as perindopril, but both drugs successfully reduced albuminuria and glomerulosclerosis. However, the magnitude of interstitial fibrosis was reduced to a greater degree with aliskiren. This is an important observation since in glomerulonephritis the degree of interstitial fibrosis determines the prognosis of kidney function.<sup>31</sup> Authors conclude that therapies directed to different targets within the renin angiotensin system may not have the same effects in reducing histological injury.<sup>32</sup>

Finally, in streptozotocin-diabetic rats, Feldman *et al.* demonstrated that aliskiren reduced (pro)renin receptor expression in glomeruli, tubules, and cortical vessels. However, in *in vitro* studies with human

mesangial cells, aliskiren bound to the active site of prorenin did not inhibit binding of renin to the (pro)renin receptor, nor did it alter the receptor gene expression or affect the activation of the ERK pathway.<sup>33</sup>

To our knowledge, aliskiren has not been tested in primary glomerulonephritis in pre-clinical studies.

## Aliskiren in clinical studies

Aliskiren, alone or in combination, has been proved to efficiently reduce proteinuria in diabetic patients.<sup>34,35</sup> Moreover, in clinical trials in patients with mild-to-moderate hypertension, direct renin inhibition with aliskiren in combination with other antihypertensive drugs such as ARBs, ACEIs, diuretics or calcium channel blockers, further reduced blood pressure compared with the respective monotherapies.<sup>36</sup> There is evidence that increased blockade of the RAAS can lead to improved clinical outcomes.<sup>37</sup> Higher doses of ARBs provide modest, but significantly greater renoprotection in patients with diabetic nephropathy.<sup>38,39</sup> In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Added trial, addition of candesartan to ACEIs significantly reduced the rate of cardiovascular events in patients with chronic heart failure.<sup>40</sup> Similarly, the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) demonstrated that the combination of eplerenone with standard ACEI or ARB provided significant additional reductions in cardiovascular morbidity and mortality in post-myocardial infarction patients with left ventricular dysfunction.<sup>41</sup> Therefore, when proteinuria due to glomerular damage is considered, dual and even higher-dose renin-angiotensin-aldosterone system inhibition appears to be of benefit to reduce the progression of kidney failure.<sup>42</sup> In this respect, aliskiren may be a useful drug which should be carefully assessed in this setting.

However, the recently published ONTARGET study has raised some concerns about the simultaneous use of ACEIs plus ARBs in patients at high vascular risk.<sup>43,44</sup> Although the combination therapy reduced proteinuria to a greater extent than monotherapy, it worsened major renal outcomes, mainly due to hypotension and renal hypoperfusion. However, the population that could benefit most from a dual blockade of the renin-angiotensin system represented a minority in the ONTARGET study. As remarked by the authors, the occurrence of dialysis, hyperkalemia and doubling of creatinine was low and the effect estimates for the renal events were of borderline significance. It is possible that combined therapies with

aliskiren may prevent progressive renal failure and dialysis better than ACEI or ARB alone in people with specific proteinuric renal diseases. Whether aliskiren alone or in combination is superior to ACEIs and/or ARBs to reduce proteinuria and improve outcomes in glomerular diseases needs to be determined.

The ongoing Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALITUDE) will address whether aliskiren in combination with ACEIs or ARBs will reduce morbidity and mortality in diabetics with proteinuria and stage 3 chronic renal failure patients.<sup>45</sup> Until these results are known, we believe these combinations must be used with appropriate and judicious caution.

## Aliskiren side effects

With respect to side effects, aliskiren appears to be a safe drug. No episodes of cough have been reported, as aliskiren is not involved with the catalyses of bradykinin, unlike ACEIs.<sup>46</sup> However, aliskiren has been reported to be involved in an episode of acute renal failure and hyperkalemia in an elderly patient, when replacing irbesartan while spironolactone was continued.<sup>47</sup> Being a novel drug, more information needs to be known about aliskiren in order to understand its side effects, and it should be used with caution.

## Aliskiren and target populations

Populations that could benefit from aliskiren alone or in combinations include glomerular proteinuric subjects and patients with moderate to high-cardiovascular risk, particularly diabetics. As high plasma renin activity is regarded as a risk factor for myocardial infarction in untreated hypertensive and normotensive patients, this population could benefit from aliskiren prescription.<sup>48</sup> While diuretics,  $\beta$ -blockers and calcium channel blockers appear to be good options for combinations, ACEIs or ARBs should be reserved for proteinuric patients, although more data needs to be obtained before recommendations can be made.

## Conclusions

Besides lowering systemic blood pressure and blocking the circulating and tissue renin-angiotensin system, aliskiren may be anti-fibrotic because of (pro)renin receptor-mediat-

ed actions: suppression of the receptor may cause less receptor number and dampen intracellular fibrotic pathways induced by prorenin, preventing the activation of prorenin in renal tissue and impeding the catalytic activity of receptor-bound renin.<sup>33</sup> Clinically, it would be interesting to assess aliskiren effects alone and in combination mainly with ACEIs and/or ARBs in glomerulonephritis, as the RAAS plays a critical role in the worldwide pandemic that renal failure comprises and that ends up recruiting annually thousands of patients to dialysis, despite current available treatments.<sup>29</sup>

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