Direct renin inhibitors: the dawn of a new era, or just a variation on a theme?

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**Keywords:** chronic kidney disease; direct renin inhibitors; renin-angiotensin-aldosterone system

**Renin-angiotensin-aldosterone system (RAAS) inhibitors in chronic kidney disease (CKD): benefits and limitations**

Numerous studies have demonstrated that the renin-angiotensin-aldosterone system (RAAS) plays an important role in the progression of chronic kidney disease (CKD). Angiotensin (Ang) II generates intrarenal haemodynamic and inflammatory changes that promote proteinuria, growth of glomerular and tubular cells, inhibition of NO synthesis, stimulation of extracellular matrix synthesis and induction of chemokines, reactive oxygen species and apoptosis [1]. In addition, in animal models of renal diseases, aldosterone is also involved in endothelial dysfunction, inflammation, proteinuria and fibrosis [2]. In clinical trials, treatment with angiotensin-converting enzyme (ACE) inhibitors and Ang II AT1 receptor blockers (ARBs) was proved to slow down the evolution of both diabetic and non-diabetic nephropathies and, therefore, it is currently regarded as the cornerstone of what we call ‘nephroprotection’.

A controversial issue is whether these agents are superior to other antihypertensive drugs in terms of nephroprotection—in other words, do they possess so-called ‘pleiotropic’ effects? A large meta-analysis [3] suggested that the benefit seen with ACE inhibitors was related to the blood pressure (BP) decrease alone. The truth, as Sarafidis et al. [4] pointed out in a very recent review, is that, indeed, ACE inhibitors exhibit a BP-independent renoprotective effect, but only in patients with proteinuria and advanced CKD (i.e. stage 3 or 4), and also that the higher the baseline urine protein excretion and its subsequent decrease, the more pronounced the beneficial effect of these drugs is likely to be [4].

However, it is not sufficiently appreciated that, due to the remarkable complexity of the RAAS, neither ACE inhibitors nor ARBs alone can completely suppress its activity (Figure 1). The main limitations of these agents in that regard can be summarized as follows:

(i) A substantial proportion of Ang II is generated in the kidneys from Ang I via non-ACE pathways, such as chymase [5], which are not susceptible to the actions of ACE inhibitors.

(ii) ACE inhibition and ARB, by interrupting negative feedback-loops, result in high plasma (and most likely tissue-) renin concentrations and high plasma renin activity (PRA), which may overcome the drugs’ effectiveness. The reactivation of Ang II (or ‘Ang II escape’) has been described with both ACE inhibitors and ARBs [6]; however, its clinical significance is not yet fully understood.

(iii) Renin can also bind to specific receptors in the mesangium and in the subendothelium of the renal arteries. This binding leads on one hand, to a substantial increase in the catalytic efficiency of conversion of angiotensinogen to Ang I, and, on the other hand, to stimulation of mitogen-activated protein kinases, ERK-1 and ERK-2 [7]. In animal models of nephrotic syndrome, treatment with ACE inhibitors was associated with a reduction in glomerular injury and proteinuria, but also with tubulo-interstitial lesions [8]. These findings support a direct profibrotic role for renin, independent of its Ang-generating effect.

(iv) ACE inhibitors induce an acute decrease in plasma aldosterone. This effect, however, is often only transient and followed by a progressive rise in aldosterone levels that ultimately, with long-term ACE inhibition, can reach normal or even elevated concentrations. This ‘aldosterone
escape' is not well explained, but it might be the result of aldosterone secretion stimulation by high potassium levels induced by ACE inhibition. Aldosterone breakthrough also occurs during long-term ARB treatment, through an AT2-dependent mechanism [9].

(v) The ARBs leave the AT2 receptors unblocked, and some experimental data suggest that these receptors are involved in renal inflammation, by activation of NF-κB in mesangial and endothelial cells and induction of chemokines [6].

Taking all of these mechanisms together, one can see that there is at least the potential for additional benefit from alternative or complementary approaches to RAAS blockade.

Combination therapy: more effective, more risks

One way in which this last point has been addressed is by dual RAAS blockade with ACE inhibitors and ARBs together. This stratagem is now advocated by many nephrologists, as it has been shown to decrease proteinuria and slow kidney disease progression more effectively than using each of the two drug classes alone [6]. However, such combination therapy carries, undoubtedly, an increased risk of side effects, particularly in certain patients such as the elderly, the salt-depleted, those receiving cyclooxygenase inhibitors, those with renal artery stenosis and during anaesthetic induction [10]. In the CHARM-Added trial, patients with congestive heart failure treated with an ARB and an ACE inhibitor experienced significantly more episodes of hypotension, acute renal failure and hyperkalaemia, compared with those receiving an ACE inhibitor alone [11]. The risk of hyperkalaemia was also increased when the baseline glomerular filtration rate was <35 ml/min [12].

Another useful combination could be the addition of an aldosterone receptor antagonist to patients already receiving an ACE inhibitor or an ARB [13]. In small studies (reviewed by Sarafidis et al. [4]), the use of either spironolactone or eplerenone, on top of ACE inhibitors or ARBs, further decreased proteinuria. However, it is not known whether the addition of an aldosterone antagonist can retard the long-term progression of CKD to end-stage renal failure, but
promising data have been recently published by Bianchi et al. [14]. On the other hand, such combinations may dangerously increase the serum potassium levels in CKD patients [14].

**Direct renin inhibition: an ‘old–new’ strategy of RAAS blockade**

A new and promising development in RAAS blockade has been initiated with the introduction of the first direct renin inhibitor (DRI), aliskiren, recently approved by the USA Food and Drug Administration for the treatment of hypertension. While this is indeed an exciting progress, it should not be forgotten that beta-blockers (BBs) also induce a significant reduction in plasma renin synthesis, by about one-third. However, as it has been recently discussed at length, their other properties may not make them first-line therapy choices for hypertensive patients [15].

Research on DRIs started over 30 years ago and several agents have been synthesized over this period, but low efficacy, lack of oral availability and high cost prevented their therapeutic application [16]. Aliskiren is the only orally active DRI that progressed to phase-III clinical trials and, is in fact the first new treatment for hypertension since the introduction of ARBs in 1994. As there is only one such compound that has undergone significant clinical trial exposure, we are restricted to discussing this to try to understand the potential effects, benefits and safety-concerns of DRIs, but it should be borne in mind that there will most likely be other DRIs in time.

Unlike ACE inhibitors and ARBs, DRIs induce a marked and sustained reduction in PRA, and, as a result, the serum levels of Ang I, Ang II and aldosterone dramatically decrease [16]. DRIs do not block other Ang I-releasing enzymes, such as cathepsin D or tonins, but these enzymes appear to be of minor physiological importance [17]. Several studies in animal models by Fisher et al. [18] showed that DRIs cause a significantly higher increase in renal plasma flow than ACE inhibitors, despite similar BP falls, which suggests a more complete inhibition of the renal RAAS. In clinical trials, the addition of aliskiren to PRA-increasing drugs like diuretics, ACE inhibitors and ARBs was shown to prevent the raise or even to lower the PRA [19]. Suppressing the RAAS at the earliest stage with DRIs may be expected to limit the Ang II and the aldosterone escape phenomena, by avoiding the accumulation of their precursors [20]. Although BBs are also capable of reducing the PRA, their influence on Ang I, Ang II and aldosterone is unknown [21]. However, most BBs either decrease (non-selective BBs) or have no influence (β1-selective BBs) on the renal blood flow and the glomerular filtration rate [22].

Aliskiren’s average half-life of 24 h [23] and its 98% trough to peak ratio [24] makes it appropriate for a once daily administration. Since <1% of the drug is excreted by the kidneys [16], there is no need for adjustment of the starting dose in patients with renal insufficiency. Aliskiren concentrations in the kidneys are particularly high and persistent up to 3 weeks after discontinuation of the drug, suggesting that long-term effects could be derived at the tissue level [25].

Aliskiren monotherapy demonstrated significant, dose-dependent antihypertensive effects in several placebo-controlled clinical trials [23]. Compared with other drugs, the BP lowering effect of aliskiren 150 mg/day was similar to that of irbesartan 150 mg/day [26] and hydrochlorothiazide 12.5 mg/day [27], whereas at a dose of 300 mg/day, aliskiren was as potent as hydrochlorothiazide [27], but more effective than ramipril 10 mg/day [28]. Combinations of aliskiren with diuretics [27], calcium-channel blockers [29], ACE inhibitors [28] and ARBs [30] provided greater reductions in BP than any of these drugs alone.

Aliskiren is, generally, well tolerated by hypertensive patients. In contrast to ACE inhibitors, it does not induce accumulation of substance P or bradykinin, therefore side effects like cough and angioedema are implausible [16]. Angioedema does not occur more often with aliskiren than with placebo, and whereas the incidence of cough is slightly increased with aliskiren, it is still much lower than with ACE inhibitors [23]. Increases in serum potassium >5.5 mmol/l were seldom reported with aliskiren alone; however, when used in combination with an ACE inhibitor in a diabetic population, hyperkalaemia was more frequent [23]. Minor increases in blood urea nitrogen or serum creatinine were observed in <7% of patients treated with aliskiren alone, vs 6% on placebo [23]. Yet, since subjects with significant renal dysfunction, dialysis, nephrotic syndrome or renovascular hypertension were excluded from clinical trials of aliskiren in hypertension, caution is required when prescribing the drug in such patients [23]; clearly, there is an urgent need to investigate DRIs in these special conditions.

**Better renoprotection with renin inhibitors?**

From a nephrologist’s point of view, renin inhibition seems an interesting new approach for preventing the progression of CKD. Just like ACE inhibitors and ARBs, DRIs were shown to diminish renal vascular resistance and increase renal blood flow. On the other hand, by predominantly dilating the efferent arteriole, the net result is a decrease in the filtration fraction, without a change (or even an increase) in the glomerular filtration rate and the fractional sodium excretion. These effects were seen in animals [31–33], as well as in humans [34,35], and may provide renoprotective benefits, similar to ACE inhibitors and ARBs. Moreover, particular advantages may result from direct renin inhibition, if the Ang-independent profibrotic role of renin (discussed earlier) is considered relevant.
Direct evidence of favourable effects of renin inhibitors on kidney disease is very scarce; however, a few experimental and clinical trials have yielded notable results. Several researchers studied the renal effects of aliskiren in double transgenic rats, which carry human renin and angiotensinogen genes and spontaneously develop malignant hypertension, leading to multiple organ damage and death, if left untreated. In these animals, aliskiren significantly lowered the BP and albuminuria, in a dose-dependent manner, and normalized the serum creatinine [36]. The antiproteinuric effect of aliskiren persisted even 2 weeks after stopping the treatment [37]. The drug reduced intrarenal inflammation (cell infiltration, C-reactive protein, tumour necrosis factor-α and complement) and fibrosis, to the same extent as losartan did [38].

In six patients with renal dysfunction, a short-acting renin inhibitor, remikiren, reduced proteinuria by 27% ($P < 0.01$) from a median baseline level of 5.8 g/day [35]. Preliminary data from an ongoing clinical study indicate a more substantial reduction in microalbuminuria with aliskiren (−61%) compared with ramipril (−50%) [39].

**Conclusion**

DRIs may have a significant future as renoprotective agents, besides their utility as antihypertensives. The ability to decrease renin concentration and PRA, the more complete inhibition of the RAAS, the expected limitation of Ang II and aldosterone escape phenomena, and the prevention of possible renal-damaging direct effects of renin make DRIs appealing drugs for nephrologists. Certainly though, DRIs have a very long way to go before eventually overtaking the well-established ACE inhibitors and ARBs, with their long track record of reducing not just the intermediate end-point proteinuria, but also the progression of CKD, and conferring cardioprotection and increased survival to many groups of patients with heart failure, diabetes or myocardial infarction. To start with, DRIs may find their place as adjunctive therapies, in combinations with ACE inhibitors or ARBs, or less commonly still, in patients intolerant to these.

In the next few years, the results of the first phase III trials with aliskiren in patients with CKD will become available. The ongoing AVOID study (Aliskiren in the Evaluation of Proteinuria in Diabetes) is a 6-month study of aliskiren in addition to losartan in 496 patients with controlled hypertension, type 2 diabetes and proteinuria, with the change in urinary albumin to creatinine ratio as primary endpoint. ALTITUDE (Aliskiren Trial in Type 2 Diabetic Nephropathy) is a type 2 diabetes outcomes study that will be carried out in approximately 6000 subjects, to determine whether aliskiren delays time to diabetic complications in patients with diabetes mellitus and nephropathy [39].

Finally, other DRIs are expected to join aliskiren in clinical use in the years to come, since some of these new agents are currently undergoing animal and pre-clinical investigation [21].

**Acknowledgements.** The authors wish to address special thanks to Dr Jan A. Staessen, MD, PhD, FESC, FAHA, Laboratory of Hypertension, Leuven, Belgium, for granting them the permission to reproduce the picture ‘The renin-angiotensin-aldosterone system’ [21].

**Conflict of interest statement.** Dr D.J.A.G. receives honoraria and speaker fees from Novartis, Astellas, Shire, Genzyme, Roche, Amgen and Abbott. Dr A.C. is a member of the speakers’ bureau for Hoffmann La Roche and member of the advisory board of Fresenius Medical Care. Dr L.S. has no conflict of interests to declare.

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