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IM - REVIEW

Renin–angiotensin–aldosterone system blockade in chronic kidney disease: current strategies and a look ahead

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Abstract The Renin–Angiotensin–Aldosterone System (RAAS) is profoundly involved in the pathogenesis of renal and cardiovascular organ damage, and has been the preferred therapeutic target for renal protection for over 30 years. Monotherapy with either an Angiotensin Converting Enzime Inhibitor (ACE-I) or an Angiotensin Receptor Blocker (ARB), together with optimal blood pressure control, remains the mainstay treatment for retarding the progression toward end-stage renal disease. Combining ACE-Is and ARBs, or either one with an Aldosterone Receptor Antagonist (ARA), has been shown to provide greater albuminuria reduction, and to possibly improve renal outcome, but at an increased risk of potentially severe side effects. Moreover, combination therapy has failed to provide additional cardiovascular protection, and large prospective trials on hard renal endpoints are lacking. Therefore this treatment should, at present, be limited to selected patients with residual proteinuria and high renal risk. Future studies with novel agents, which directly act on the RAAS at multiple levels or have a more favourable side effect profile, are greatly needed to further explore and define the potential for and the limitations of profound pharmacologic RAAS inhibition.

Keywords Kidney disease · Renin–Angiotensin–Aldosterone system inhibitors · Treatment · Hypertension · Proteinuria

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Introduction

Since the seminal experimental and clinical work carried out in the seventies and eighties of the previous century demonstrated the key contribution of angiotensin II on the development and progression of hypertension-mediated organ damage [1], and later on with the introduction of Angiotensin Converting Enzime-Inhibitors (ACE-Is) in the therapeutic arena [2], the Renin–Angiotensin–Aldosterone System (RAAS) has been the preferred therapeutic target for renal protection. Over the past 20 years, along with a more detailed understanding of the pathophysiology of the RAAS, and the development of several classes of drugs that effectively interfere with its deleterious effects at the cellular, tissue and systemic level, clinicians have come to rely on the use of RAAS-Inhibitors (RAAS-Is) to curb the progression of renal damage even beyond their blood pressure lowering effects [3]. Thus, pharmacologic blockade of the RAAS has been shown to improve a number of histological and clinical outcomes, ranging from glomerular hypertension to interstitial fibrosis and proteinuria in patients with chronic kidney disease (CKD).

However, the renal protective effects of RAAS-Is, alone or in combinations, has proved so far incomplete in clinical practice, and the number of CKD patients progressing toward end-stage renal disease (ESRD) remains unacceptably high [4]. This issue is even more worrisome when one considers the on-going worldwide rise in the prevalence and incidence of CKD, brought about by longer life expectancy and the dramatic epidemic of diabetes, hypertension and obesity, arguably the main risk factors for kidney diseases [5]. This narrative review will focus on the clinical aspects of renal protection obtained by RAAS inhibition with currently available drugs,as well as those

that will become available soon, either in monotherapy or in different combinations, in patients with CKD (Table 1).

ACE-Is: the mainstay of treatment for CKD patients

ACE-Is were the first class of drugs specifically acting on the RAAS introduced in clinical practice. Since 1993, when the Collaborative Study Group showed the beneficial effect of Captopril on the progression of renal disease in patients with type I diabetes [6], ACE-Is have been used in several large trials in diabetic and non-diabetic patients with CKD. Over the years, the knowledge of the pathophysiology of their numerous mechanisms of action has increased, and their efficacy has been repeatedly proven [7–10]. The ability of ACE-Is to reduce urine protein excretion thereby retarding the progression to ESRD is in part independent of their blood pressure lowering effect. These drugs, although far from being the "magic bullet" of treatment for chronic renal diseases, may provide up to 30 % greater renal protection as compared to standard antihypertensive agents, especially in patients with severe proteinuria [11]. Due also to an unsurpassed clinical record for cardiac protection [12], over the years, ACE-Is have become the standard of treatment for CKD patients.

ARBs: similar protection, greater tolerability?

By directly blocking Angiotensin II Type 1 receptor, these drugs have been shown to attenuate almost all known deleterious effects of the RAAS in vivo [13]. Angiotensin receptor blockers (ARBs) have been repeatedly demonstrated to provide cardiovascular and renal protection at different stages of renal disease, especially in patients with type 2 diabetes. Two independent and concomitant landmark trials, conducted in patients with type 2 diabetes and clinical nephropathy [14, 15], in which the ARBs proved superior to conventional antihypertensive therapy or calcium channel blockers, have contributed to the on-going huge success of these drugs. Despite rather different mechanisms of action, from the clinical practice standpoint, ARBs and ACE-Is seem to convey comparable renal and cardiovascular protection, independentof the severity of renal damage and the presence of diabetes [16, 17]. However, the lack of interaction with bradykinin and its pathway confer to ARBs an undisputed better safety and tolerability profile. Due to this unique feature, ARBs tend to be preferred in highly comorbid patients, and in complex multi-drug regimens where compliance with treatment is often an important issue.

DRIs: the unfulfilled promise

In 2007, the clinical development of Aliskiren, the first in class Direct Renin Inhibitor (DRI), added a new, powerful and much anticipated tool to the therapeutic armamentarium of RAAS-Is. By directly binding to the catalytic site of renin and inhibiting its enzymatic activity, Aliskiren provides a profound, 'upstream' blockade of the RAAS cascade at its very origin. Indeed, a wide, convincing body of in vitro and in vivo experimental data together with superior antihypertensive efficacy and an almost placebo-like tolerability profile support the huge potential for renal and cardiovascular protection of this drug [18]. The clinical development of this drug, however, followed a complicated pathway that eventually led to greatly reduced role in the current therapeutic panorama. Aliskiren was first tested as add-on therapy to Losartan in type 2 diabetic patients with albuminuria in the AVOID study [19], where it delivered greater proteinuria reduction at comparable blood pressure values. Later on, however the same strategy tested in larger prospective trials on hard renal and cardiovascular end points turned out to reach a dead-end, as it became clear that combination therapy may provide too much RAAS inhibition with no further benefit, and possibly greater side effects as compared to monotherapy (see below). Thus, the ALTITUDE study, conducted on patients at high cardiovascular and renal risk with type 2 diabetes mellitus was prematurely stopped, and did not show benefit on renal and cardiovascular hard endpoints by the use of Aliskiren on top of an ACE-I or an ARB [20]. A number of other trials, with similar protocols have shown similar results or only modest benefits on intermediate endpoints. Overall, the subsequent clinical development of Aliskiren and of the entire class of DRIs seems to have been hampered by market and regulatory situations at the global level. Aliskiren, although still on the market, is subject to rather strict prescribing limitations, and it appears that the real clinical potential of the drug in renal and cardiovascular protection has not and probably will never be fully exploited.

ARAs: blocking an important component of the system

Besides its long known role in the maintenance of water and electrolytes balance, aldosterone has been shown to have several unfavourable effects at the tissue and cellular level, which are partly independent of angiotensin II regulation, and may promote the progression of renal damage [21].

Recently elucidated pathophysiologic mechanisms provide a sounding rationale for renoprotective therapies

Table 1 New therapeutic strategies for renal protection with RAAS-Is

Year	Trial name	Drug	Comparator	Population	Mean follow up	Renal endpoints	Results and comments
Combination therapy							
Clinical trials							
ACE-I plus ARB versus ACE-I or ARB							
2000	CALM	Lisinopril 20 mg plus candesartan 16 mg	Lisinopril 20 mg or Candesartan 16 mg	199 patients with type 2 diabetes with microalbuminuria	12 weeks monotherapy with ARB or lisinopril followed by 12 weeks monotherapy or combination treatment	Albuminuria reduction	Significantly larger decrease of albuminuria and larger decrease in BP under dual blockade
2007	IMPROVE	Ramipril 10 mg plus irbesartan 150–300 mg	Ramipril 10 mg	405 hypertensive patients with albuminuria (100 %), diabetes or cardiovascular disease	20 weeks	Albuminuria reduction	Larger decrease of urine albumin excretion and BP under dual blockade
2008	ONTARGET	Telmisartan 80 mg plus ramipril 10 mg	Telmisartan 80 mg or ramipril 10 mg	25,620 patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage	4.7 years	All-cause death, doubling serum creatinine, ESRD	The number of primary outcomes was similar for telmisartan and ramipril but was increased with combination therapy
2011	ORIENT	Olmesartan plus ACE-I	ACE-I	577 patients with diabetic nephropaty and overt proteinuria secondary to type 2 diabetes	3.2 years	Doubling of serum creatinine, ESDR and death	Olmesartan did not improve primary composite renal endpoint on top of ACEI, while it significantly decreased blood pressure, proteinuria and rate of change of reciprocal serum creatinine
2013	VA NEPHRON-D	Losartan 100 mg plus lisinopril 10-40 mg	Losartan 100 mg	1,448 patients with type 2 diabetes and proteinuric CKD (1–3)	2.2 years	GFR decline, ESRD and death	Combination therapy with an ACE-I and an ARB does not provide an overall clinical benefit but is associated with an in-creased risk of adverse events
DRI plus ACE-I or ARB							
2008	AVOID	Aliskiren 150-300 mg plus losartan 100 mg	Losartan 100 mg	599 patients with type 2 diabetes with nephropathy and hypertension	6 months	Albuminuria reduction	Under dual blockade larger decrease of albuminuria and BP

Table 1 continued

Year	Trial name	Drug	Comparator	Population	Mean follow up	Renal endpoints	Results and comments
2012	ALTITUDE	Aliskiren 150-300 mg on top of optimal treatment with an ACE-I or an ARB	Placebo	8,561 patient with type 2 diabetes at high cardiorenal risk	Prematurely stopped after a median follow up of 33 months	All-cause death, doubling serum creatinine, ESRD	Lack of benefit of hard endpoint and potentially harmful side effects
ARA plus ACE-I or ARB versus ACE-I or ACE-I plus ARB							
2006	Epstein et al.	Eplenrenone 50 mg or 100 mg plus enalapril 20 mg	Enalapril 20 mg	268 diabetic patients with macroalbuminuria	12 weeks	Albuminuria reduction and incidence of hyperkalemia	Larger decrease in albuminuria with dual blockade and similar decrease in blood pressure. No difference in hyperkalemia
2009	Mehdi et al.	Spironolactone 25 mg plus lisinopril 80 mg	Lisinopril 80 mg or losartan 100 mg plus lisinopril 80 mg	81 diabetic patients with macroalbuminuria	48 weeks	Albuminuria reduction	Larger decrease of albuminuria with ARA/ACE-I than with ACE-I. Similar decrease in albuminuria with ARB/ACE-I as with ACE-I
METANALYSES							
ACE-I plus ARB versus ACE-I or ARB							
2008	Kunz et al.	ACE-I plus ARB combination	ACE-I or ARB	1,192 patients with or without diabetes and with microalbuminuria and proteinuria	1–4 months 5–12 months	Proteinuria reduction	The ARB and ACE-I combination reduced proteinuria more effectively than either agent alone in the short term, while in the long term this was only true in comparison with ARB
2011	Maione et al.	ACE-I plus ARB combination	ACE-I or ARB	5,442 patients with albuminuria	NA	ESRD and progression to macroalbuminuria	Development of ESRD and progression to macroalbuminuria were reduced significantly with ACEI versus placebo and ARB versus placebo but not with combination therapy versus monotherapy
2013	Susantitaphong et al.	ACE-I plus ARB; ACE-I or ARB plus ARA; ACE-I plus ARB plus DRI; ACE-I plus ARB plus ARA	ACE- I or ARB or ARA or DRI	4,975 CKD patients	NA	GFR and albuminuria variations, doubling serum creatinine, hyperkalemia	Combined RAAS blockade therapy was associated with a significant net decrease in GFR, albuminuria and proteinuria. Combined RAAS blockade therapy was associated with a 9.4 % higher rate of regression to normoalbuminuria and a 5 % higher rate of achieving the BP goal. However, combined RAAS blockade therapy was associated with a significantly greater incidence of side effects

Table 1 continued

Year	Trial name	Drug	Comparator	Population	Mean follow up	Renal endpoints	Results and comments
ARA plus ACE-I or ARB versus ACE-I or ACE-I plus ARB							
2008	Bomback et al.	ARA	ARA on top of ACE-I or ARB	Patients with proteinuria kidney disease	NA	Changes in proteinuria, BP and in GFR; rates of hyperkalemia	Adding ARA to ACE-inhibitor and/or ARB therapy yields significant decreases in proteinuria without adverse effects of hyperkalemia and impaired renal function
2009	Navaneethan et al.	Spironolactone from 25 mg to 50 mg plus ACE-I or ARB Eplenrenone from 50 mg to 200 mg plus ACE-I	ACE-I or ARB	845 CKD patients with albuminuria	NA	Albuminuria reduction, GFR decline	Larger decrease in albuminuria and larger decrease in BP under dual blockade. No difference in renal function decline. More gynecomastia and hyperkalemia with spironolactone but not with eplerenone
2015	Palmer et al.	Any orally administered blood pressure-lowering agent (ACE inhibitor, ARB, calcium-channel blocker, β blocker, α blocker, diuretic, renin inhibitor, aldosterone antagonist, or endothelin inhibitor), alone or in combination	Second blood pressure agent or combination, placebo, or control	43256 patients, mostly with type 2 diabetes and CKD	NA	All-cause mortality and ESRD. Secondary doubling of serum creatinine, regression of albuminuria, acute kidney injury.	ACE-Is and ARBs, alone or in combination, were the most effective strategies against ESRD. The combination of ACE-Is and ARBs has benefits and risks (hyperkalemia and acute kidney injury) that should be carefully considered in clinical practice
Supramaximal dosage							
2007	DROP	Valsartan 320 mg or 640 mg	Valsartan 160 mg	391 hypertensive patients with type 2 diabetes and albuminuria	30 weeks	Albuminuria reduction, regression to normoalbuminuria	Higher valsartan doses were associated with greater reductions in mean albuminuria, independently of BP reductions
2007	ROAD	Individual uptitration of benazepril (median 20 mg/day; range 10–40) or individual uptitration of losartan (median 100 mg/day; range 50–200)	Benazepril 10 mg/die or losartan 50 mg/die	360 non diabetic, CKD patients with proteinuria	3.7 years	Doubling of serum creatinine, ESRD or death	Higher dosages of ACE-I or ARB at comparable BP control led to a reduction of proteinuria and of renal end points
2009	SMART	Candesartan 64 or 128 mg	Candesartan 16 mg	269 CKD patients with persistent proteinuria despite candesartan 16 mg	30 weeks	Proteinuria reduction	Candesartan 128 mg/d results in a further significant reduction in urinary protein excretion independently of BP control. Reductions in BP were not different across the three treatment groups

RAAS renin, angiotensin, aldosterone system, *ACE-I* angiotensin converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *DRI* direct renin inhibitors, *ARA* aldosterone receptor antagonists, *BP* blood pressure, *ESRD* end stage renal disease, *CKD* chronic kidney disease, *GFR* glomerular filtration rate

aimed at blocking Aldosterone receptors at the glomerular and tubular level, thereby reducing profibrotic mechanisms leading to glomerulo-sclerosis and tubule-interstitial fibrosis [21].

Spironolactone has proved very effective as an add-on drug in patients with resistant hypertension, although at the expense of a slight reduction in GFR [22]. Furthermore, relatively short-term studies indicate that treatment with Spironolactone [23] or with the more selective Eplerenone [24] on top of either an ACE-I or an ARB reduces proteinuria as compared to placebo [25]. However, large trials on hard renal endpoints are lacking, and may actually be difficult to perform, mostly because of the risk of hyperkalemia, which increases considerably as GFR decreases below 45 ml/min. More recently, Finerenone, a novel non-steroidal mineral corticoid receptor blocker, with greater receptor affinity than Eplerenone and possibly a better tolerability profile, has been shown to reduce albuminuria on top of another RAAS-I in patients with diabetic nephropathy [26]. For the time being, the use of Aldosterone Receptors Antagonists (ARAs) as add-on drugs in the setting of high residual renal risk is limited to those patients with preserved glomerular filtration rate (GFR) values, and should be avoided altogether in CKD stages 3 or worse [27].

Combination treatment to maximize renal protection: how much is too much?

Simultaneous pharmacologic blockade of the RAAS at multiple sites has a strong pathophysiological rationale, as Angiotensin II may also be generated through ACE-independent pathways, and circulating Angiotensin II levels have been shown to gradually return to pre-treatment values under chronic ACE-I treatment, a phenomenon known as "Angiotensin escape" [28, 29]. As a matter of fact, relatively small preliminary studies suggest additive antiproteinuric effects under combination treatment with an ACE-I and an ARB. This has led to a proposal to use even more complete pharmacological RAAS blockade, sometimes with three drug combination regimens, in order to maximize renal protection and improve patient outcomes [30]. However, two large trials [20, 31] have shown increased harm, and no cardiovascular or renal benefit with combination therapies. In particular, dual RAAS inhibition while reducing albuminuria to a greater extent than monotherapy, has been associated with an excess of hyperkalemia, hypotension, and acute renal impairment. The fact that in the ONTARGET and ALTITUDE trials, renal risk is more often observed among patients without albuminuria led to the hypothesis that long term renal benefit would outweigh the risks associated with combination treatment, at least in the subset of patients with residual proteinuria. This, however, turned out not to be the case, as the recent VA Nepron-D trial [32], carried out in patients with proteinuric diabetic kidney disease, was stopped early because of an increased risk of acute kidney injury and hyperkalemia, and did not show any clinical benefit in terms of renal progression.

According to European and U.S. Drug Regolatory Agencies, combination treatment with either an ACE-I, an ARB or the DRI Aliskiren is currently not recommended due to the lack of benefits on hard end-points and the unfavorable safety profile [33]. Furthermore, dual blockade with Aliskiren and either an ARB or an ACE-I should not be prescribed in patients with diabetes or CKD stage 3 or greater [34].

Of note, these recommendations do not apply to combination treatment with an aldosterone receptor blocking drug, possibly because its use on top of single RAAS inhibiting agent, despite greater risk of hyperkalemia [35, 36], has been shown to reduce morbility and mortality in patients with heart failure [37].

Thus, despite the fact that dual RAAS blockade provides greater proteinuria reduction [36–43], its use in CKD patients has been challenged altogether [44]. On the one hand, while proteinuria is a well-known risk factor for disease progression [45], its reduction under dual blockade treatment has never been associated to hard end-points. Furthermore, the evidence that treatment with dual, sometimes triple RAAS blockade even in the context of individually tailored strategies, remains anecdotal at present, as only small retrospective studies have been published so far [46, 47]. Whether the safety profile of dual RAAS blockade can be improved by patients' selection, careful individualized management and possibly by the use of new potassium lowering agents [48, 49], remains to be established. A few, currently ongoing studies [50, 51] may partially add to our knowledge in this area. In the meantime, a further, unresolved issue that also deserves to be verified by adequately powered studies, is how up-titration of a single RAAS-inhibiting agent compares with combination therapy [52, 53].

Finally, the exact role of add-on therapy with an ARA in patients at high residual renal risk remains to be established. New molecules, with a better safety profile especially with regards to hyperkalemia, have provided encouraging preliminary results [26], and may eventually prove a viable alternative to existing therapeutic strategies.

It appears that although profound RAAS inhibition might yield long term beneficial effects by preventing and reducing organ damage at the tissue level, from a purely hemodynamic perspective there may be a point beyond which further blockade is unsafe rather than useful. For the time being, we believe that multiple RAAS inhibiting therapy should be limited to highly selected, relatively

young patients with fairly maintained GFR values and adequate adherence, in the presence of significant residual proteinuria and long-term renal risk.

A look ahead

As we are expanding our knowledge about RAAS components and their working pathways in both homeostatic and maladaptive mechanisms, the interaction of the system with other endocrine and paracrine systems has become an area of potential therapeutic interest. Thus, an indirect favourable RAAS-inhibitory effect of drugs active on vitamin D metabolism has been claimed to account, at least in part, for the cardiovascular and renal protective effects observed with the use of selective vitamin-D receptor agonist [54]. Similarly, the additive anti-proteinuric effect recently observed by the use of Endothelin-1 Receptor blockers is known to be partly mediated by Angiotensin II inhibition [55].

A more direct and forthcoming therapeutic improvement may be obtained by the use of a new class of drugs, called Angiotensin Receptor Neprilysin Inhibitors (ARNI) [56].

ARNIs have been pharmacologically developed, building on experimental and clinical results with Dual Endopeptidase Inhibitors such as Omapatrilat. Dual ACE and Neprolysin inhibitors (NEP-Is), originally developed for the treatment of heart failure, had previously shown superior antihypertensive efficacy and renal protection [57, 58] as compared ACE-Is, although at the expenses of a worse side-effect profile.

LCZ 696, the first-in-class ARNI, was obtained by chemically replacing the ACE-I in Omapatrilat with Valsartan [56]. Cleverly combining an ARB and a NEP-I allowed researchers to obtain the complementary goals of Angiotensin II blockade together with the vasodilating and natriuretic effects due to the prolonged bioavailability of Natriuretic Peptides, without interfering with the breakdown of bradykinin and therefore with a reduction of potentially dangerous side effects such as angioedema [59].

LCZ, has already proved superior to standard treatment with ACE-I in morbi-mortality trials in chronic heart failure and preliminary evidence [60, 61] suggests that there be beneficial effect on GFR preservation although at the trade-off of a slightly increase in albumin excretion. The potential of this therapeutic strategy is currently being tested in the ongoing UK-HARP study [62], wherein LCZ will be compared to Irbesartan in patients with CKD and proteinuria.

Conclusions

Monotherapy with either an ACE-I or an ARB, together with appropriate, individualized blood pressure control, often in the context of a multiple drug regimen, remains the mainstay treatment for retarding the progression toward ESRD, although long term residual risk remains high in many patients, especially but not solely, in the presence of overt proteinuria. Combining ACE-Is and ARBs or either one with an ARA might provide greater albuminuria reduction and possibly improve renal outcome but at an increased risk of potentially severe side effects, and should therefore, at present, be limited to selected patients' subgroups and carried out under close surveillance in a specialist's setting. Future studies with novel agents, which directly act on the RAAS at multiple levels or have a better side effects profile than current treatments, are much needed to explore the full renoprotective potential and limitations of profound pharmacologic RAAS inhibition.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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