

# RAAS Intervention in Chronic Kidney Disease

## Intervenção no SRAA na Doença Renal Crónica

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### ■ ABSTRACT

Chronic kidney disease (CKD) has usually a progressive nature dependent of multiple factors including blood pressure values and degree of proteinuria. Control of blood pressure to levels below those desirable in the non-CKD population and reduction of proteinuria have been the cornerstone of renoprotection for many years. Blockade of the renin-angiotensin-aldosterone system (RAAS) is the most effective pharmacological strategy for that purpose and has been validated by numerous trials. However, the risk of adverse renal events and of progression for end-stage-kidney disease remains high, which led to the development of several treatment-intensification strategies of RAAS blockade. Among the strategies evaluated, dual-agent blockade has been the target of several long-term trials after promising results in short-term studies more focused on surrogate markers of CKD progression like proteinuria. Unfortunately, the results were disappointing and such dual-agent strategies not only failed to show a significant beneficial effect in slowing CKD progression, but were associated with a worse renal long-term outcome. Among such dual-agent strategies were combinations of an angiotensin-converting enzyme (ACE) inhibitor plus an angiotensin receptor blocker (ARA), ACE inhibitor or an ARB plus the direct renin inhibitor aliskiren. RAAS blockade with an ACE inhibitor and an ARB plus the mineralocorticoid receptor antagonist (MRA) spironolactone is also unproven. Single-agent RAAS blockade intensification with moderate dietary sodium restriction appears promising in retrospective data but currently lacks prospective confirmation. The addition of the vitamin D analogue paricalcitol to single-agent RAAS blockade appears to be beneficial but is still unproven in long-term hard outcome focused trials.

**Key-words:** Progressive chronic kidney disease; proteinuria; renin-angiotensin-aldosterone system; sodium restriction.

### ■ RESUMO

A doença renal crónica (DRC) tem geralmente um carácter progressivo, dependente de múltiplos fatores onde se incluem os valores de tensão arterial e o grau de proteinúria. A principal estratégia renoprotectora inclui o controlo da tensão arterial e a redução da proteinúria. O bloqueio do sistema renina-angiotensina-aldosterona (SRAA) constitui a estratégia mais eficaz para esse objetivo, tendo sido validada em inúmeros ensaios clínicos. Contudo, o risco de eventos adversos renais e de progressão para doença renal crónica

com necessidade de terapêutica de substituição da função renal permanece elevado, o que levou ao desenvolvimento de várias estratégias intensificadoras do bloqueio do SRAA. O bloqueio duplo do SRAA foi alvo de grandes ensaios com longos períodos de seguimento, após resultados favoráveis em ensaios de curta duração. Infelizmente, esses ensaios não só não mostraram um benefício significativo retardando a progressão da DRC, como o bloqueio duplo do SRAA se associou a um pior prognóstico renal. As combinações de duplo bloqueio com resultados desfavoráveis foram a de um inibidor da enzima de conversão da angiotensina (IECA) com um antagonista dos receptores da angiotensina (ARA), e de um IECA ou um ARA com o inibidor directo da renina o aliscireno. O bloqueio duplo com um IECA ou um ARA e um antagonista do receptor dos mineralocorticoides é também uma estratégia que carece de confirmação. A intensificação do bloqueio do SRAA com restrição moderada de sódio parece promissora na análise de dados retrospectivos mas carece de confirmação prospectiva. A adição do análogo da vitamina D paricalcitol ao bloqueio do SRAA é eficaz em pequenos ensaios, sendo necessária confirmação em estudos de longo prazo.

**Palavras-chave:** Doença renal crónica progressiva; proteinúria; restrição salina; sistema renina-angiotensina-aldosterona.

## ■ INTRODUCTION

The decline in glomerular filtration rate (GFR) observed in progressive chronic kidney disease (CKD) ranges from 1 to more than 15 ml/min/1.73m<sup>2</sup> per year, depending upon the degree of proteinuria, blood pressure levels, previous rate of GFR decline and the nature of the specific kidney disease<sup>1-5</sup>. Along with treatment of the underlying disorder (if possible) the cornerstone of renoprotection in CKD patients is the control of blood pressure and proteinuria. Blockade of the renin-angiotensin-aldosterone system (RAAS) is the most effective strategy for this purpose. Accordingly, current guidelines recommend RAAS blockade with an angiotensin-converting-enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB) as first-line therapy for the preservation of renal function in diabetic and non-diabetic CKD patients<sup>6, 7</sup>.

However, the residual risk of adverse renal events and of progression to end-stage-renal disease (ESRD) still remains fairly high with conventional RAAS intervention, which can be partially attributed to insufficient RAAS blockade arising from compensatory feedback mechanisms or to the engagement of signalling pathways not directly affected by RAAS blockade<sup>8</sup>. This led to the development and evaluation of several RAAS focused treatment-intensification strategies that included: dose escalation of a single-

agent, dual-agent blockade, dietary intervention like sodium restriction and the use of other pharmacological agents, such as vitamin D analogues.

In this review, the author provides an overview of the evidence derived from landmark clinical trials concerning several strategies developed and evaluated for improving the outcomes of CKD patients, in the context of RAAS intervention.

## ■ SINGLE-AGENT RAAS BLOCKADE

Angiotensin-converting-enzyme inhibitors and ARBs are more effective than other antihypertensive drugs in reducing proteinuria and in slowing the rate of progression of proteinuric CKD and this effect is independent of the aetiology of renal disease<sup>3</sup>. In contrast with other classes of antihypertensive drugs, ACE inhibitors and ARBs promote the simultaneous dilatation of the afferent and efferent glomerular arterioles, which leads to a greater fall in intraglomerular pressure<sup>9</sup>. Numerous studies have demonstrated that the greater antiproteinuric effect seen with ACE inhibitors and ARBs is related with a greater fall in intraglomerular pressure compared to other types of antihypertensive drugs<sup>9,10</sup>. In fact, when structural disease is present, the excretion of protein varies directly with the degree of intraglomerular pressure<sup>11</sup>.

However, the beneficial antiproteinuric effect of single-agent RAAS blockade with those drugs appears to be not only related with the magnitude of the fall in intraglomerular pressure but also with a direct effect on the permeability characteristics of the glomerular membrane. Such a direct effect could explain the progressive decline in proteinuria over weeks to several months contrasting with the rapid haemodynamic effects of ACE inhibition and the sustained antiproteinuric effect, despite the administration of angiotensin II and the consequential increase in intraglomerular pressure<sup>12-14</sup>. It was also demonstrated that ACE inhibition increases nephrin expression, a major contributor to the glomerular filtration barrier<sup>15</sup>. Finally, ACE inhibitors appear to have a direct antifibrotic effect<sup>16</sup>.

In terms of magnitude, RAAS blockade with an ACE inhibitor generally reduces proteinuria by about 30 to 35% in patients with diabetic and non-diabetic CKD<sup>17-20</sup>.

The role of RAAS blockade with an ACE inhibitor, as a renoprotective strategy in diabetic and non-diabetic CKD patients, is well established in the literature with numerous trials showing a significant benefit that extends beyond its effect in surrogate markers of progression like proteinuria into long-term renal outcomes. The Benazepril trial enrolled 583 patients with non-diabetic CKD<sup>21</sup>. These patients had controlled blood pressure at baseline and were randomly assigned to benazepril or placebo, in addition to their usual antihypertensive regimen. At the end of follow-up, the benazepril group had a significant lower blood pressure and proteinuria was reduced in 25% compared to the placebo group. Also, the relative risk reduction concerning the primary renal end point (doubling the serum creatinine or progression to ESRD) was 53% in the benazepril group (71% in those with baseline clearance above 45 ml/min/1.73 m<sup>2</sup> and 46% in those with baseline clearance inferior to 45 ml/min/1.73m<sup>2</sup>). Of notice, benazepril showed no benefit in patients with proteinuria inferior to 1000mg/day<sup>21</sup>. Regarding diabetic CKD patients, the benefits of ACE inhibition have been proven more than 20 years ago<sup>22</sup>.

RAAS blockade with an ARB is also an effective antiproteinuric therapy in diabetic and non-diabetic CKD patients<sup>17,23</sup>. Regarding the potency of the antiproteinuric effect, a meta-analysis of 49 randomized

studies (most of them small,) published in 2008, showed that ARBs are able to reduce proteinuria, independently of the baseline degree of and of underlying disease. Significantly, the magnitude of the reduction in proteinuria accomplished with ARBs and ACE inhibitors was similar<sup>17</sup>. In terms of long-term outcomes related to the preservation of renal function as opposed to its effects in surrogate markers of progression, RAAS blockade with an ARB has proven to be beneficial in diabetic renal disease<sup>24</sup>. Strong evidence supporting their protective role in disease progression is still lacking in non-diabetic CKD but it seems likely that they will have a similar beneficial effect as ACE inhibitors.

One important finding in many clinical studies dealing with RAAS blockade as a renoprotective strategy is the preferential benefits observed in the subgroups of patients with proteinuria levels above 500 to 1000 mg per day. In fact, there appears to be no renoprotective benefit of implementing RAAS blockade in patients excreting less than 500 mg of protein per day<sup>3,7</sup>.

## ■ SPECIAL SUBPOPULATIONS

There are three subpopulations consistently under-represented in trials that evaluate the renoprotective efficacy of RAAS inhibition: elderly patients, advanced CKD and patients of African origin.

### ■ Elderly patients

The vast majority of trials addressing the potential benefits of RAAS blockade in the preservation of renal function did not include patients over the age of 70<sup>25</sup>. On the other hand, it is well known that older patients are more prone to adverse effects of RAAS blockade, including hyperkalemia and acute renal injury<sup>26</sup>. One important factor concerning RAAS blockade in elderly patients is that they, as a group, are less likely to have proteinuria, which was required in the positive trials of RAAS inhibition. In an analysis of the American registry, the National Health and Nutrition Examination Survey (NHANES) in persons above 70 years of age only 13% had an albumin-to-creatinine ratio greater than 200 mg/g or approximately 300 mg/day<sup>25</sup>. There is no proven benefit of

RAAS inhibition in preserving renal function when protein excretion is below 500 mg/day<sup>3,7,27</sup>. These findings suggest that, as a renoprotection strategy, RAAS inhibition will not benefit the vast majority of elderly patients with CKD and is probably harmful, due to the higher rate of potentially serious side effects<sup>25</sup>. However, in elderly patients with a significant degree of proteinuria, slowing the progression of CKD with RAAS inhibition is likely to outweigh the potential risks.

### ■ Advanced disease

Patients with advanced CKD are at an increased risk of potentially serious side effects arising from RAAS blockade, especially hyperkalemia. To this date, there are only a few studies addressing the potential value of RAAS inhibition in advanced CKD. The benefits of RAAS blockade in advanced disease were best shown in a relatively large, randomized, Chinese study with a follow-up of 3.4 years in which non-diabetic CKD patients were randomly assigned to benazepril or placebo plus other antihypertensive therapy<sup>28</sup>. In the group (n = 281) with a higher baseline serum creatinine concentration (between 3.1 and 5.0 mg/dl), lower mean eGFR (26 ml/min per 1.73 m<sup>2</sup>) and mean proteinuria of 1.6 g/day, significantly fewer patients in the benazepril arm reached the primary end point (41%) versus placebo (60%). The primary end point was the composite of doubling of the serum creatinine level, ESRD or death. Benazepril was also associated with the following benefits, in the more advanced CKD group: lower rate of doubling of the serum creatinine concentration, lower percentage of patients reaching ESRD, greater reduction of proteinuria and a lower rate of decline in GFR. Moreover, the benefits of benazepril were independent of blood pressure values, which were similar in all groups and the incidence of major adverse effects was similar in both arms.

Regarding this study, several factors have been selected to explain the unexpected absence of severe hyperkalemia in the ACE inhibitor treated group: approximately 5% of patients with advanced disease were excluded in the run-in period because of hyperkalemia, intake of potassium was probably lower than in patients on a typical Western diet and diuretics were used in over 80% of patients<sup>29</sup>.

Additional evidence regarding the beneficial effect of RAAS blockade in advanced disease came from a *post hoc* analysis of the data from the REIN trial in which patients with an initial GFR in the lowest group (11 to 33 ml/min/1.73 m<sup>2</sup>) had a reduction in the incidence of ESRD (33%) with ACE inhibition, and from a study of peritoneal dialysis patients in which ACE inhibition slowed the rate of decline of residual renal function<sup>30,31</sup>.

In conclusion, single-agent RAAS inhibition preserves renal function in advanced proteinuric CKD but it must be used with great care, carefully and frequently monitoring for potentially serious adverse events like hyperkalemia.

### ■ Patients of African Origin

In black hypertensive patients, therapy with a calcium channel blocker or a diuretic is generally more effective in lowering blood pressure than RAAS blockade with an ACE inhibitor. Regarding the use of an ACE inhibitor as a renoprotective strategy the results of the AASK trial suggested that the use of ramipril in the subset of black proteinuric CKD patients was associated with a significant reduction in the rate of decline of GFR and also a significant reduction in the composite end point (reduction in GFR of more than 50%, ESRD or death) at three years compared to amlodipine. In the subset of patients with proteinuria below 300 mg/day (approximately two-thirds of patients), there was no significant difference in the mean decline of GFR or in the composite end point<sup>32</sup>.

In conclusion, black CKD patients with proteinuria at least above 300 mg/day are likely to derive renoprotective benefits from RAAS blockade

## ■ TREATMENT-INTENSIFICATION STRATEGIES

### ■ Dose escalation

Regarding dose escalation the majority (but not all) of available studies seem to suggest that the ACE inhibitor dose associated with a maximal anti-proteinuric effect is usually higher than the one

necessary to accomplish a maximal antihypertensive effect<sup>33-36</sup>. As with ACE inhibition, the antiproteinuric effect of ARBs seems to be dose-dependent with a greater reduction of proteinuria at higher doses and also with a different dose-response relationship for blood pressure and proteinuria<sup>33,37-39</sup>. In the SMART trial, for example, patients who received 128 mg/day of candesartan had a 33% more reduction in proteinuria at 30 weeks compared with those who received 16 mg/day. There were no differences in the incidence of hyperkalemia and of blood pressure values between groups<sup>39</sup>.

### ■ Dual-agent RAAS blockade

The main rationale behind the use of multiple agents to block the RAAS simultaneously at different levels is to circumvent the effects of compensatory feedback mechanisms like, for example, those that result in the aldosterone escape. Various permutations have been studied that included combinations of ACE inhibitors with ARBs, ACE inhibitors or ARBs with direct renin inhibitors (DRIs) and ACE inhibitors or ARBs with a mineralocorticoid-receptor antagonist (MRA). Combined blockade of the RAAS have had positive results on surrogate outcomes of CKD progression like proteinuria and favourable short-term outcomes in several studies<sup>40</sup>.

### ■ ACE Inhibitors plus ARBs

Dual therapy with an ACE inhibitor and an ARB appears to have a greater antiproteinuric effect than either agent alone<sup>40-44</sup>. A meta-analysis of 14 trials published in 2008 by Kunz *et al.* found that therapy with an ACE inhibitor and an ARB produced a significant (18 to 25%) greater reduction in proteinuria compared with monotherapy<sup>40</sup>. Despite the relatively small size of those trials the positive results on surrogate markers of CKD progression and on short-term outcomes fuelled the enthusiasm about dual RAAS blockade, with an ACE inhibitor and an ARB, with growing, but unproven, expectations of better long-term renal outcomes.

The ONTARGET trial, a large-scale randomized controlled trial conducted in patients with cardiovascular disease evaluated the efficacy of dual-agent RAAS blockade with the ACE inhibitor ramipril (10 mg/day)

and the ARB telmisartan (40 mg/day). In the ONTARGET trial, combined therapy did not increase cardiovascular protection compared with either agent alone<sup>45</sup>. A *post-hoc* analysis of the results of that trial showed that combined therapy produced a larger reduction in albuminuria and blood pressure but was also associated with an increased risk of adverse renal outcomes compared with monotherapy<sup>46</sup>. Moreover, a *post-hoc* analysis in the subgroup of patients (n = 1786) with an eGFR < 60 ml/min/1.73 m<sup>2</sup> and proteinuria not only failed to demonstrate a benefit of combined RAAS blockade, on renal and cardiovascular outcomes, but such therapy significantly increased the risk of ESRD or doubling of the serum creatinine (4.8% versus 2.8% per year), as well as ESRD alone (2.7 versus 1.6 percent per year)<sup>47</sup>.

Another concern that arises when dual-agent RAAS blockade is compared with single-agent therapy is the relative increase (albeit small) in serum potassium concentration associated with combined therapy<sup>48</sup>.

Summarizing, the lack of proven long-term benefits, on renal and cardiovascular outcomes, along with the possible worsening of renal outcomes, does not support dual-agent RAAS blockade with an ACE inhibitor and an ARB as a valid strategy of renoprotection.

### ■ ACE inhibitors or ARBs plus a DRI (aliskiren)

Dual-agent RAAS blockade with an ACE inhibitor or an ARB and a DRI like aliskiren is associated with a greater decrease in proteinuria than either agent alone<sup>49</sup>. In the AVOID trial, combined therapy with losartan plus aliskiren produced a larger reduction of proteinuria compared with losartan alone, without a significantly greater effect on blood pressure. Moreover, there was a trend for a slower rate of decline of renal function in the dual-agent RAAS blockade group<sup>50</sup>.

The ALTITUDE trial, a large study which randomly assigned type 2 diabetes patients who were at high risk of renal and cardiovascular adverse events, all receiving an ACE inhibitor or an ARB at baseline, to aliskiren or placebo, showed that such dual-agent RAAS blockade did not preserve renal function and increased the risk of adverse events<sup>51</sup>. At baseline, during therapy with an ACE inhibitor or an ARB, the participants had a mean eGFR of 57 ml/min/1.73m<sup>2</sup>,



67.7% had an eGFR below 60 ml/min/1.73m<sup>2</sup>, and 59% had an albumin-to-creatinine ratio of 200mg/g or greater<sup>52</sup>. The safety monitoring board recommended the premature termination of the ALTITUDE trial, based on an interim analysis that showed, in the aliskiren group, an increased incidence of the composite primary end point of ESRD, doubling of serum creatinine, renal death, cardiovascular death, cardiac arrest, heart failure, non-fatal myocardial infarction or non-fatal stroke. The incidence of exclusively renal events (ESRD, doubling of serum creatinine and renal death) at the time of premature termination was similar in both groups. The final efficacy data showed a tendency towards an increase of non-fatal stroke and significantly more acute renal injury, hypotension and hyperkalemia in the aliskiren group<sup>51</sup>.

Thus, current evidence does not support dual-agent RAAS blockade with an ACE inhibitor or an ARB plus aliskiren and such intensification strategy cannot be recommended.

#### ■ ACE inhibitors or ARB plus a MRA (spironolactone)

Several studies have addressed the question of whether combined therapy with an ACE inhibitor or an ARB plus a mineralocorticoid receptor antagonist would have further benefits, reducing proteinuria and retarding the progression of CKD.

A meta-analysis, published in 2009, analyzed the data of eleven small trials. The conclusions were that the addition of a MRA further reduced proteinuria in CKD patients already on an ACE inhibitor or an ARB but greatly increased the risk of hyperkalemia<sup>53</sup>. These trials were very small and had short follow-up periods. Concerns regarding the increased risk of hyperkalemia associated with this therapeutic combination are probably the main reason for the absence of long-term studies. Henceforth, current evidence does not support the addition of an MRA to an ACE inhibitor or an ARB given the very high risk of adverse outcomes, in particular of hyperkalemia.

#### ■ RAAS blockade and dietary sodium restriction

Dietary sodium restriction enhances the effects of RAAS blockade in hypertension and proteinuria. More than 20 years ago it has been shown in an

experimental model that the combination of dietary sodium restriction with RAAS blockade increases the maximal dose response of the pharmacological agents further enhancing its antiproteinuric and antihypertensive effects<sup>54</sup>. The same effect was demonstrated in hypertensive patients<sup>55-57</sup>, in CKD diabetic and non-diabetic patients<sup>58,59</sup> and is further enhanced by the use of diuretics<sup>60</sup>.

Probably, the mechanisms that underlie the augmentation effect of dietary sodium restriction on RAAS blockade are intrarenal as well as effects on blood pressure since enhanced renoprotection occurs even without a significant blood pressure reduction<sup>8</sup>.

Two recent *post hoc* analyses of data from key studies showed a significant beneficial effect on hard renal and cardiovascular end points of dietary sodium restriction in CKD patients during RAAS blockade. The REIN study was a large, randomized trial in patients with CKD and proteinuria that studied the renoprotective effects of RAAS blockade (ramipril) versus other antihypertensive therapy<sup>61</sup>. The *post hoc* analysis grouped patients into tertiles of sodium intake: low (mean 7 g/day), medium (mean 10 g/day) and high (14 g/day). After dose titration, blood pressure values were similar across the tertiles and were maintained throughout follow-up with the expected higher doses of antihypertensive medication in the highest tertile of sodium intake. However, proteinuria was consistently of a higher magnitude in the two upper tertiles of sodium intake. Moreover, after 4 years of follow-up, 60% of patients in the higher tertile versus 20% of those in the lower tertile met the renal end point of the study (dialysis or doubling of serum creatinine values)<sup>62</sup>. The other *post hoc* analysis looked at the pooled data from the RENAAL and IDNT trials and pointed in the same direction extending the above results to diabetic CKD patients<sup>63</sup>. The RENAAL and IDNT trials explored the effects of RAAS blockade on renal and cardiovascular outcomes versus other antihypertensive therapy. In the *post hoc* analysis, patients were once again grouped in tertiles of sodium intake: low (8 g of salt per day), medium (10 g of salt per day) and high (12 g of salt per day). The number of renal and cardiovascular events was approximately double in patients in the higher tertile compared to those in the lower tertile. The increased rate of renal and cardiovascular events in the higher tertile group correlated strongly with the proteinuria level. Furthermore, in this analysis,

the benefit of RAAS blockade over other types of antihypertensive therapy was not evident, or even tended to be reversed in patients in the higher tertile of sodium intake<sup>63</sup>.

These results need long-term prospective validation but moderate sodium restriction appears to be an effective and feasible intensification strategy of RAAS blockade increasing its renoprotective effects. Furthermore, the lower tertiles of sodium intake in those analyses represented a relatively high salt intake, surpassing the amount recommended by the WHO of approximately 5 g per day. Not only is this moderate restriction more inductive of patient compliance making it more feasible in clinical practice, but an overzealous salt restriction in the context of RAAS blockade appears to have a detrimental effect. In fact, analyses of data from large clinical trials show a J-shaped curve for the relationship between dietary sodium intake and mortality, with increased risk at a daily salt intake below 3 g per day<sup>63</sup>. Also, a *post hoc* analysis of pooled data from the ONTARGET and TRANSCED studies revealed that very high, but also very low, dietary sodium intake were associated with an increased risk of cardiovascular death and hospitalization<sup>64</sup>. Of note, average daily salt intake in Portugal is about 12.3 g per day, as determined by urinary sodium excretion<sup>65</sup>.

### ■ RAAS blockade and vitamin D

Beyond mineral metabolism, vitamin D appears to be renoprotective through several mechanisms including anti-inflammatory and antifibrotic effects. Specifically in the context of RAAS intervention, interaction of the vitamin D receptor with the renin gene inhibits renin release<sup>66</sup>. Thus, intensification of RAAS blockade with vitamin D supplementation or vitamin D analogues administration might prevent the associated reactive rise in renin increasing the efficacy of RAAS intervention. Treatment with the vitamin D analogue paricalcitol (2 mcg/day), in combination with RAAS blockade allowed for a greater reduction (18 to 28%) in proteinuria compared with an ACE inhibitor or an ARB plus placebo in a recent randomized controlled trial<sup>67</sup>. The incidence of hypercalcaemia, adverse events and serious adverse events was similar between groups receiving paricalcitol versus placebo<sup>67</sup>. The VIRTUE study is an ongoing trial that aims to address whether the addition of paricalcitol

can further improve the renoprotective effect of RAAS blockade plus dietary sodium restriction. Patients will be randomly assigned to paricalcitol versus placebo and to either a liberal sodium diet or a low sodium diet. All patients will receive a standard dose of the ACE inhibitor ramipril.

## ■ CONCLUSIONS

The RAAS intervention using an ACE inhibitor or an ARB is the most effective strategy for the preservation of renal function and prevention of complications associated with progressive proteinuric chronic renal disease in diabetic and non-diabetic patients. However, the risk of adverse renal and cardiovascular events still remains high and several treatment intensification strategies were developed and evaluated. In spite of its favourable short-term results, current evidence does not support long-term dual-agent RAAS blockade in patients with CKD, at least for the combination of agents and populations included in the ONTARGET (ACE inhibitor plus ARB) and ALTITUDE (ACE inhibitor or ARB plus aliskiren) trials. The lack of long-term studies and concern regarding adverse events also makes single-agent (ACE inhibitor or ARB) RAAS blockade with supra-maximal doses and combined therapy consisting of an ACE inhibitor or an ARB plus a MRA (spironolactone) still unproven and potentially harmful strategies for the preservation of renal function. The RAAS intervention can also be intensified by dietary changes like sodium restriction. The putative beneficial effects of moderate dietary sodium restriction during single-agent RAAS blockade on renal and cardiovascular outcomes still require long-term prospective confirmation. However, current evidence seem to support that single-agent RAAS blockade combined with a reduction in dietary sodium is an effective and safe treatment intensification strategy for the preservation of renal function. Regarding vitamin D renoprotective effects, the addition of the vitamin D analogue paricalcitol to single-agent RAAS blockade increases the antiproteinuric effect. We will have to wait for the results of ongoing long-term studies to see whether or not combination therapy with paricalcitol can improve the renoprotective efficacy of single-agent RAAS blockade.

**Conflict of interest statement.** None declared.

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